Spartan

'06 for Windows, Macintosh and Linux

Tutorial
and
User's Guide

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Scope of this Guide

This guide provides a general reference for both ***Spartan'06*** for Windows, Macintosh and Linux and the Essential Edition of **Spartan'06** for Windows and Macintosh. It is divided into 19 chapters grouped into three sections, along with several appendices.

Section I (**Introduction**, **Chapter 1**) introduces ***Spartan*** as a tool for exploring organic, bioorganic, inorganic and organometallic chemistry by way of molecular mechanics and quantum chemical calculations, together with an array of graphical models for conveying the results of these calculations. The section ends with a brief discussion of new capabilities in ***Spartan'06*** as well as improvements to previous versions.

Section II (**Getting Started**, **Chapters 2** to **9**) describes the overall operating environment of ***Spartan***, and then provides an extensive set of "hands-on" tutorials. Most of the tutorials can be completed with the Essential Edition, and sections which can not be completed are marked as such. This section is the place to start for new users of the program, and should also be perused by users of previous versions of ***SPARTAN***.

Section III (**Features and Functions**, **Chapters 10** to **19**) describes in detail the functions available from the menus and dialogs incorporated into the graphical user interface for ***Spartan***. The focus is on graphical input and manipulation of structure, input of other required information, and text, spectral and graphical output resulting from molecular mechanics and quantum chemical calculations. This section is intended as a general reference to ***Spartan***.

What this guide ***does not do*** is document the performance and cost (in computation time) of the different molecular mechanics and quantum chemical models available in ***Spartan***, or recommend specific models or combinations of models for use on "real" chemical problems. Neither does it show the utility of graphical models in presenting and interpreting the results of the calculations. These topics are covered in depth in ***A Guide to Molecular Mechanics and Quantum Chemical***

Calculations available from Wavefunction, which also provides a collection of illustrative examples.

Appendices provide an overview of the program's overall architecture as well as its present capabilities and limitations (**A**), a directory of functions under its menus (**B**), a listing of commonly-used options (**C**), a listing of units (**D**), the proper citation for the program (**E**), instructions for installing the Cambridge Structural Database (**F**), directions for making databases from ***Spartan*** calculations (**G**), directions for pharmacophore input (**H**) and directions for installing a network HASP (**I**). Several of these appendices are included as part of the program's Help facilities.

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Section I

Introduction

Molecular mechanics calculations and quantum chemical calculations play an ever-increasing role in modern chemistry. Traditionally, they have served to supply information about structures, relative stabilities and other properties of isolated molecules. Because of their inherent simplicity, molecular mechanics calculations on complex molecules have spread widely throughout the chemical community. Quantum chemical calculations, including Hartree-Fock molecular orbital calculations, but especially calculations that take account of electron correlation, are much more time demanding. Only recently, have fast enough computers become widely available to make their application routine among mainstream chemists.

Quantum chemical calculations may also be called on to furnish information about the mechanisms and product distributions of chemical reactions, either directly by calculations on transition states, or indirectly by modeling the steric and electronic demands of the reactants. Quantitative calculations, leading directly to information about the geometries of transition states, and about reaction mechanisms in general, are becoming more and more common, while qualitative models are still needed for systems that are too large to be subjected to the more rigorous treatments. Finally, quantum chemical calculations may be asked to supply information to complement existing experimental data or to replace it altogether, for example, atomic charges for QSAR analyses, and intermolecular potentials for molecular mechanics and molecular dynamics calculations.

Spartan has been designed to address the ever increasing role that calculations play in chemistry and related fields. It represents a continued collaboration between Wavefunction, Inc., and Q-Chem, Inc. Q-Chem codes supplement and extend the traditional strengths of ***Spartan*** as an easy to learn and use tool for molecular mechanics and semi-empirical and Hartree-Fock molecular orbital calculations, and a wide range of graphical models, with a full range of density functional models as well as a selection of important post-Hartree-Fock models. All models have been implemented using what we believe are the most robust algorithms currently available, and have been tuned for high performance on Intel processors.

Spartan is intended to be utilized by chemists, not only computational chemists who are already familiar with the capabilities of molecular mechanics and quantum chemical methods, but also experimental chemists who may have little or no prior experience, but who want to use calculations much in the same way as experimental techniques such as NMR spectroscopy. This ambitious goal is directly reflected in the program's overall design criteria: "convenient access to a full range of modern molecular mechanics and quantum chemical models", and clearly distinguishes ***Spartan*** from other molecular modeling packages.

Spartan'06 is supported under Windows (2000, XP, XP 64 and Vista), Macintosh (OS 10.4.x and higher), Linux (Linux Kernel 2.6 or later). The Linux version (only) may be used in a server mode with Windows, Macintosh or Linux acting as a front end. It is also able to perform calculations locally.

Spartan has been compiled with the latest version (9.0) Intel compilers. This has led to an overall speed increase of ≈20-25% (relative to previous releases), independent of algorithm changes.

1. **Integrals.** ***Spartan's*** integral code has been improved resulting in a speed increase of ≈30% over ***Spartan'04***. This affects Hartree-Fock, density functional and all wavefunction-based correlation methods.

2. **Gradients.** ***Spartan's*** gradient code has been improved resulting in a speed increase of a factor of ≈2 over ***Spartan'04***. This affects structure and transition-state structure optimization for Hartree-Fock, density functional and all wavefunction-based correlation methods.

3. **RI-MP2.** A new RI-MP2 code has been implemented. This provides structures and energies that are nearly identical to

those from MP2 with an ***order of magnitude speed increase*** for energy calculations, and a speed increase of a factor of ≈3 for structure calculations. This makes RI-MP2 calculations competitive with density functional calculations for moderate sized molecules.

4. **Dual Basis Sets.** A procedure has been implemented that allows the effects of basis set extension (small basis set to large basis set) to be accurately approximated using perturbation theory. Depending on the choice of large and small basis sets, this can result in an ***order of magnitude speed increase*** over a conventional large basis set calculation. Dual basis sets may be used with Hartree-Fock, density functional and MP2 calculations.

5. **NMR.** NMR chemical shift calculations have been extended to density functional models. The Hartree-Fock chemical shift code has been improved resulting in a speed increase of ≈20%.

6. **Heats of Formation.** A new procedure, termed T1, that provides heats of formation within 2 kJ/mol (RMSD) of G3(MP2) values has been formulated. It is based on the G3(MP2) recipe with several changes. It requires an HF/6-31G* structure instead of an MP2/6-31G* structure, and an RI-MP2 energy calculation using a very large and flexible basis set instead of a comparable MP2 calculation. Additionally, the basis set RI-MP2 calculation makes use of dual basis set techniques. An empirical correction based on atom counts and Mulliken bond orders replaces the QCISD(T), zero-point energy and temperature correction terms in the G3(MP2) model. This scheme, which is restricted to uncharged, closed-shell molecules comprising H, C, N, O, F, S, Cl and Br that can be well represented by conventional Lewis structures ("normal" organic molecules), is ***2-3 orders of magnitude faster than G3(MP2)***. This permits accurate thermochemical calculations to be routinely carried out on organic molecules up to molecular weight of ≈400 amu.

7. **Conformer Library Generation.** A new capability has been added to provide generation of libraries of diverse conformers.

This is based on a systematic search of conformation space using MMFF molecular mechanics, followed by a procedure to eliminate conformers that occupy similar space. Conformer libraries are intended for use in similarity analysis. Conformer libraries corresponding to common drugs (≈5,000 molecules) and to the Maybridge compendium, ***Compounds for Drug Discovery Chemistry*** (≈70,000 molecules), the Life Chemicals collection (≈240,000 molecules), are available from Wavefunction as options to ***Spartan***.

8. **Chemical Function Descriptors (CFD's).** Descriptors indicating possible chemical functionality are automatically generated based on structure. These identify possible hydrogen-bond acceptors or donors, positive or negative ionizable sites, and aromatics and other hydrophobes. Default CFD definitions and sizes (precision) may be adjusted. CFD's are intended for use in alignment and similarity analysis.

9. **Alignment.** ***Spartan's*** alignment procedure has been extended to include both structures and chemical functionality (CFD's), and to allow alignment of one or more molecules to a pharmacophore. A scoring function based on rms deviations between selected atomic centers or between CFDs (automatically adjusted to account for unfavorable intramolecular interactions) has also been provided.

10. **Similarity Analysis.** A new capability has been developed for assessing and quantifying the similarity of one or more templates (either molecules or pharmacophores), to one or more libraries (including libraries of diverse conformers). Similarity between molecules may either be based on structure or on CFD's, whereas similarity between molecules and pharmacophores is based solely on CFD's. A scoring function based on rms deviations between selected atomic centers or between CFDs (automatically adjusted to account for unfavorable intramolecular interactions) has also been provided.

11. **Spartan Molecular Database (SMD).** The Spartan Molecular Database has grown from ≈50,000 to ≈150,000 molecules each

available at up to 5 theoretical models: HF/3-21G, HF/6-31G*, EDF1/6-31G*, B3LYP/6-31G*, and MP2/6-31G*. In addition, calculations using the HF/6-311+G**, B3LYP/6-311G+G** and MP2/6-311+G** models for ≈2,000 molecules have been added, as well as ≈1,200 G3(MP2) calculations. Each data entry corresponds to an optimized structure at the lowest-energy conformer determined from MMFF molecular mechanics and includes the geometry, gas-phase energy, estimated (aqueous) solvation energy, HOMO and LUMO energies, dipole moment and Mulliken, NBO and electrostatic-fit atomic charges. Calculated infrared spectra are available for ≈40,000 molecules, NMR chemical shifts for ≈15,000 molecules and calculated UV/visible spectra for ≈1,500 molecules. Approximate van der Waals surfaces and electrostatic potential maps may be instantly generated for all database entries. In addition to substructure searching, SMD may now be searched by name, molecular weight, formula or isomer.

12. **Transition States and the Spartan Reaction Database (SRD).** The library of structures previously forming the basis of ***Spartan's*** automatic transition state guessing procedure has been extended to ≈1500 organic and organometallic reactions, and has been made available for substructure searching. The transition states in the Spartan Reaction Database (SRD) are each available at one or more of the following models: AM1, PM3, HF/3-21G, HF/6-31G*. Each data entry contains the optimized (transition-state) structure and the vibrational frequencies. Access to SRD is from the reactant (or product) structure together with appropriate reaction arrows. ***Spartan's*** automatic transition-state guessing procedure remains available.

13. **Access to Web-based Spectra Libraries.** Experimental spectral data may now be retrieved on-line and displayed in addition to or in lieu of calculated spectra. The IR and UV/visible spectra collections from NIST and the NMR carbon chemical shift collection from the University of Cologne are available.

14. **Retrieval of PDB files.** PDB files can be retrieved from via PDB website from within ***Spartan***. Bound ligands can be extracted and associated with chemical function descriptors (designating hydrogen bonds, electrostatic interactions and hydrophobic regions) as well as the peptide/nucleotide base residues comprising the active site environment, and excluded volume centers (indicating the space occupied by the protein/nucleotide). A database of ≈1250 small molecules bound to proteins/nucleotides in the PDB is included as part of Spartan Molecular Database and may be searched by substructure.

15. **Support for Unassisted 3D Stereo Visualization (Windows Only).** ***Spartan*** supports the Sharp 3D LCD monitor as well as the Sharp Actius AL3D notebook. These allow unassisted 3D stereo visualization of molecular structure and graphics.

16. **Substituent Builder.** A new builder for generation of substituted molecules has been included.

17. **Access to ChemDraw (Windows Only).** ChemDraw may now be directly accessed from within ***Spartan***. The resulting 2D drawings are automatically converted to 3D structures. ChemDraw must be licensed from CambridgeSoft and installed on the same machine as ***Spartan***.

18. **New Graphical Displays and Capabilities.** Graphical calculations are now performed in ***Spartan's*** user interface and no longer need to be submitted. Graphical display of accessible surface area (electron density or on any property map based on the electron density) has been provided. The area on the electron density for which the absolute value of the electrostatic potential is greater than a user-specified amount is reported. This provides an alternative property to polar surface area (PSA).

19. **Enhanced Copy/Paste Operations.** Text may now be pasted from a ***Spartan*** spreadsheet or from an external source (MS® Excel, for example) into a ***Spartan*** spreadsheet.

20. **New Semi-Empirical Parameterization.** RM1 (Recife Model 1; G.B. Rocha, R.O. Freire, A. Simas and J.J.P. Stewart,

J.Computational Chem., **27**, 1101 (2006)) has been added to the semi-empirical molecular orbital procedures available in ***Spartan***. RM1 is a reparameterization of AM1, using a much larger training set of molecules than was previously practical. For the elements supported (H, C, N, O, F, P, S, Cl, Br and I), RM1 yields lower mean absolute errors than either AM1 or PM3 for bond lengths, heats of formation, dipole moments and ionization potentials (comparisons with MNDO were not provided). Only the mean absolute error for bond angles was (slightly) larger than that for AM1 (but smaller than that for PM3).

21. **Database of Experimental Heats of Formation.** A database of heats of formation at 298K for ≈2,000 molecules in the gas phase has been assembled from several sources. Where available, data are provided in the **Molecule Properties** dialog and may be entered into the spreadsheet. This database will probably not expand significantly in the future.

22. **CAS Numbers.** A library of CAS numbers has been provided. Where available, these are provided in the **Molecule Properties** dialog. This library will greatly expand in the future.

Since the release of ***Spartan'04***, ***Spartan*** users have reported a number of bugs via ***support@wavefun.com***. These bugs have been addressed. Wavefunction would like to thank our customers for their help in making ***Spartan*** a better program.

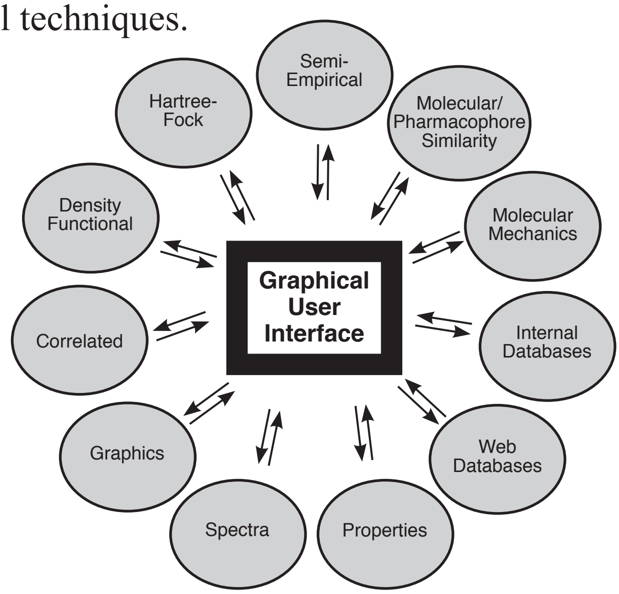
Chapter 1

Spartan'06

This chapter describes the architecture of ***Spartan'06****, focusing on the connectivity of graphics, database and computational components. Available molecular mechanics and quantum chemical methods are enumerated, and their overall role suggested.*

Spartan'06 is a cross-platform application. In most cases, Spartan's features are identical between Windows, Mac and Linux versions. In some cases, features are necessarily platform specific. The following nomenclature will be used throughout this manual to indicate when a feature is not available: **NAL**: Not Available Linux, **NAM**: Not Available Mac and **NAW**: Not Available Windows.

Spartan'06 ("***Spartan***") comprises a series of independent modules tightly connected via a graphical user interface, that is highly functional yet rather simple and uncluttered. It has been designed not only to greatly reduce the drudgery and possibility of human error associated with the preparation of input, but also to guide the interpretation of output. The interface is perhaps best viewed as an interactive and intuitive window into a full range of modern computational techniques.


Semi-Empirical
Hartree-Fock
Molecular/ Pharmacophore Similarity
Density Functional
Molecular Mechanics
Graphical User Interface
Correlated
Internal Databases
Graphics
Web Databases
Spectra
Properties

Included in the interface are builders for organic, inorganic and organometallic molecules, polypeptides and polynucleotides, as well as for creating lists of substituted molecules, and a procedure for guessing transition states. In addition, access to ChemDraw[*] is provided without having to exit ***Spartan's*** interface. Also included is the Spartan Molecular Database, a collection of over 140,000 calculated structures for molecules, each obtained from as many as eight different theoretical models, as well as a collection of approximately 1,200 small molecules bound to proteins and nucleotides from the PDB[**]. Also provided is an interface to the Cambridge Structural Database, comprising over 350,000 experimental X-ray crystal structures[***], and the Spartan Reaction Database (SRD), a collection of transition states for approximately 1,500 organic and organometallic reactions. Finally, ***Spartan*** allows for import of a variety of data files, most important among them being PDB (protein structures) and SDF (structure drawings). Thus, it is not only possible to construct molecules from scratch, but also to access existing structures.

Spartan's interface also provides the gateway into a range of modern computational methods, including molecular mechanics models, semi-empirical and Hartree-Fock molecular orbital models, and a variety of so-called correlated models including density functional models. None of these models is likely to be ideal for every application[****].

---

[*] ChemDraw is not included with ***Spartan***, but may be obtained from CambridgeSoft (www.cambridgesoft.com). **NAL**, **NAM**. While all versions of ***Spartan*** are able to read ChemDraw files, seamless access is presently available only in the Windows version.

[**] Additional databases comprising sets of diverse conformers of pharmaceuticals and pharmaceutical candidates as well as Maybridge and Life Chemicals collections of organic molecules are available from Wavefunction.

[***] The Cambridge Structural Database is not included with ***Spartan***, but rather is available on a subscription basis from the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk) or one of its distributors (**NAM**).

[****] Full discussion and assessment of the specific molecular mechanics and quantum chemical models available in ***Spartan*** is provided in: W.J. Hehre, ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***, Wavefunction, Irvine, 2003. See also: W.J. Hehre, L. Radom, P.v.R. Schleyer and J.A. Pople, ***Ab Initio Molecular Orbital Theory***, Wiley, New York, 1986; Y. Shao, L.F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S.T. Brown, A.T.B. Gilbert, L.V. Slipchenko, S.V. Levchenko, D.P. O'Neill, R.A. DiStasio Jr., R.C. Lochan, T. Wang, G.J.O. Beran, N.A. Besley, J.M. Herbert, C.Y. Lin, T. Van Voorhis, S.H. Chien, A. Sodt, R.P. Steele, V.A. Rassolov, P.E. Maslen, P.P. Korambath, R.D. Adamson, B. Austin, J. Baker, E.F.C. Byrd, H. Dachsel, R.J. Doerksen, A. Dreuw, B.D.

While the most sophisticated quantum chemical models may yield excellent results, they will likely be too time consuming for routine application, and it will usually be necessary to contend with lesser treatments. ***Spartan's*** interface facilitates mixing and matching different molecular mechanics and quantum-chemical models. Results from one model may easily be passed on for further analysis with another (better) model.

The simplest computational methods in ***Spartan*** are molecular mechanics models using the SYBYL and MMFF force fields, with aqueous energy corrections available for the latter (MMFFaq). These are available to determine equilibrium geometries and conformations of molecules comprising upwards of several thousand atoms. Molecular mechanics models are at present the only computational techniques that are applicable to biopolymers including proteins. Calculations involving very large molecules and conformational analysis on smaller but conformationally-flexible molecules, including assignment of the lowest-energy conformer, identification of collections of reasonable low-energy conformers and creation of libraries of diverse conformers, are perhaps the most important roles of molecular mechanics.

Quantum chemical models are required to account for the geometries of transition states as well as to obtain reaction energies (thermodynamics) and activation energies (kinetics). The simplest of these, semi-empirical molecular orbital models, can be routinely applied to systems with one to two hundred atoms. Supported in ***Spartan*** are the MNDO model (with extensions for second-row and heavier main-group elements), the AM1 model, the PM3 model with parameters for most transition metals and the recently introduced RM1 model (a complete reparameterization of AM1).

**** *con't.* Dunietz, A.D. Dutoi, T.R. Furlani, S.R. Gwaltney, A. Heyden, S. Hirata, C-P. Hsu, G. Kedziora, R.Z. Khalliulin, P. Klunzinger, A.M. Lee, M.S. Lee, W.Z. Liang, I. Lotan, N. Nair, B. Peters, E.I. Proynov, P.A. Pieniazek, Y.M. Rhee, J. Ritchie, E. Rosta, C.D. Sherrill, A.C. Simmonett, J.E. Subotnik, H.L. Woodcock III, W. Zhang, A.T. Bell, A.K. Chakraborty, D.M. Chipman, F.J. Keil, A.Warshel, W.J. Hehre, H.F. Schaefer, J. Kong, A.I. Krylov, P.M.W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.,* **8**, 3172 (2006).

Hartree-Fock molecular orbital models remain a mainstay of quantum chemical techniques, in particular, for equilibrium and transition-state structure determination, and for thermochemical comparisons. The models available in ***Spartan*** may be routinely applied to molecules with fifty to one hundred atoms.

Hartree-Fock models are, however, not adequate for thermochemical comparisons where bonds are broken or formed, nor do they provide a proper account of the geometries of molecules incorporating transition metals. So-called correlated models are required. Several classes of correlated models are available in ***Spartan***[*]: density functional models, Møller-Plesset models, coupled cluster models and quadratic configuration interaction (QCI) models. Density functional models may be applied as widely as Hartree-Fock models. On the other hand, the simplest Møller-Plesset model (MP2) is limited to molecules comprising thirty or fewer atoms. An approximate RI-MP2 model has been introduced in ***Spartan'06***. It is nearly an order of magnitude faster than MP2 for energy calculations and 2-3 times faster for equilibrium and transition-state geometry calculations, but provides nearly identical results.

Higher order (MP3 and MP4) Møller-Plesset, coupled cluster and QCI models are available for energy calculations only. They are limited in practice to molecules incorporated less than 10-20 heavy (non-hydrogen) atoms.

Hartree-Fock and correlated models may be used with a variety of all-electron Gaussian basis sets. Hartree-Fock models are often quite successful with split-valence basis sets, while correlated models require at the very least polarization basis sets, and in some situations basis sets incorporating diffuse functions as well. Introduced in ***Spartan'06*** is the ability to (accurately) approximate changes in energy and wavefunction as a result of extension from a small basis set to a large basis set. This may lead to order of magnitude performance enhancement over previous large basis set calculations.

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[*] Not available in the Essential Edition.

Pseudopotentials are available for use with both Hartree-Fock and correlated models for calculations on molecules incorporating heavy elements.[*]

A series of recipes (combinations of different methods) are available to estimate thermochemical quantities[*]. G2, G3 and G3 (MP2) recipes, while applicable only to very small systems, have been shown to yield heats of formation in excellent accord with experiment and, therefore, provide benchmarks against which other calculations may be judged. Introduced in ***Spartan'06*** is a new recipe, termed T1, designed to provide accurate heats of formation. It is based on the G3 (MP2) model but requires 2-3 orders of magnitude less computation time.

Quantum chemical calculations are most commonly performed on molecules in their electronic ground state. Only recently have practical and reliable methods for excited-state species become available. ***Spartan*** provides singles configuration interaction (CIS) techniques[*] for energies, equilibrium and transition-state geometries and conformations. In addition, energy calculations (only) on excited states with the CIS (D) model as well as a range of density functional models may be performed.[*]

Spartan provides access to several common spectral quantities, in particular infrared spectra (molecular mechanics, semi-empirical, Hartree-Fock, density functional and MP2 models), NMR spectra[*,**] (Hartree-Fock and density functional models) and UV/visible spectra[*] (CIS, CIS(D) and density functional models). These are available both as numerical data (vibrational frequencies, chemical shifts, etc.) as well as spectral plots. Internet connections to IR, NMR and UV/visible databases are available allowing direct comparison of calculated and experimental spectra.

Introduced in ***Spartan'06*** is a powerful set of tools to quantify both the similarity of molecular structures and of chemical environments characteristic of these structures[*]. Also available is the ability to identify molecules that fit into a specific chemical environment (a so-called pharmacophore). Finally, pharmacophores may be extracted from small molecules bound to proteins and nucleotides in the PDB (and more generally in PDB file format).

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[*] Not available in the Essential Edition.

[**] Chemical shifts only.

Spartan'06 provides a variety of graphical tools to assist chemists in interpreting the results of molecular mechanics and quantum chemical calculations as well as similarity analyses. Not only do these include the usual variety of structure models, including structure models appropriate for biopolymers, but also molecular orbitals, electron and spin densities, local ionization potentials and electrostatic potentials that can be displayed as surfaces, slices and property maps. Introduced in ***Spartan'06*** is the ability to distinguish accessible and inaccessible regions on a density surface and on property maps based on this surface.

All graphical models may be manipulated in real time. As many quantities as desired can be displayed simultaneously, and visual comparisons easily made among them both for single molecules and among different molecules. Animation files may be made, based either on structural models alone or in combination with any graphical models, and these in turn are used to depict conformational change or chemical reaction.

Section II

Getting Started

The chapters in this section provide a brief introduction to the graphical user interface for ***Spartan'06*** and, following this, a series of tutorials. The objective of the latter is to provide hands on experience and, in doing so, illustrate the way in which molecular mechanics and quantum chemical calculations as well as similarity analyses may be set up, performed and interpreted. This is the place to start for new users. Users of previous versions of ***Spartan*** are also advised to peruse this section.

No attempt has been made to illustrate all of ***Spartan's*** capabilities. For this, the reader should consult **Section III** of this guide. Focus is on the use of ***Spartan*** to calculate equilibrium and transition-state geometries, to search conformation space, to align molecules and evaluate the similarities of molecules, to evaluate reaction thermochemistry and activation energetics and to obtain infrared, UV/visible and NMR spectra. Likewise, no attempt has been made to assess the performance of the various molecular mechanics and quantum chemical models. The majority of tutorials make use of only molecular mechanics models, semi-empirical and Hartree-Fock molecular orbital models[*]. In some cases these may not lead to acceptable results. Thorough assessment of all models available in ***Spartan*** is provided in ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***.

Graphical models are illustrated in several of the tutorials that follow, and connections between specific models and chemical observables are pointed out, for example, between electrostatic potential maps and electrophilic character. A more complete account is provided in the aforementioned guide. ***Spartan'06*** provides greatly enhanced capabilities over previous versions for display and manipulation of structure models for biopolymers, and these too are illustrated.

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[*] This is a deliberate decision, as it minimizes the time required to complete the tutorials and allows nearly all tutorials to be completed using only the Essential Edition of ***Spartan*** (that lacks density functional, MP2 and other correlated calculations). Tutorials or sections of tutorials that cannot be completed with the Essential Edition are indicated as such.

Operating ***Spartan*** **(Chapter 2)** outlines the basic workings of ***Spartan's*** graphical user interface. It should be perused before starting the tutorials and referred to as needed. The tutorials, that make up the bulk of this section, are divided across seven chapters: *Basic Operations*, *Organic Molecules*, *Groups of Organic Molecules*, *Organic Reactions*, *Medicinal Chemistry, Polypeptides to Proteins* and *Inorganic/Organometallic Molecules*. The first three of these cover a number of important general features and should be completed first, and in order. The remaining chapters cover more specialized topics.

Estimates for required computer time (in minutes, assuming a 2GHz mobile Pentium) are indicated at the top of the first page of each tutorial.

5 mins

Where two times are provided, the second corresponds to the total time including the optional parts of the tutorial.

Chapter 2

Operating ***Spartan***

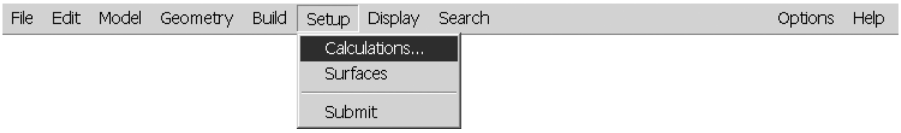
*This chapter describes the general operating features of **Spartan'06**. It should be read prior to starting the tutorials.*

Starting and Quitting *Spartan*

To start on Windows, *click* on the **Start** button, then *click* on **Programs**, and finally *click* on ***Spartan'06*** (or *double click* on the ***Spartan*** icon on your desktop). To start on Linux, bring up a terminal and *type* **spartan**. To start on Macintosh, *double click* on the ***Spartan'06*** icon in the Applications Folder. To quit, select **Exit** from the **File** menu.

Menus

Program functions may be accessed using pull-down menus under the headings in the menu bar, for example, the **Setup** menu.



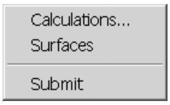
File	Allows you to create a new molecule or read in a molecule that you have previously created and to print text and graphics.
Edit	Allows you to transfer information to and from the clipboard, to undo the last operation and to find text strings and molecule fragments.
Model	Allows you to control the style of your model and to display hydrogen bonds and chemical function descriptors.
Geometry	Allows you to measure bond lengths and angles, define points and planes, setup constraints and frozen atoms, select conformational degrees of freedom and align molecules.

Build	Allows you to build and edit molecules and to create lists of substituted molecules. Provides access to ChemDraw™. (**NAL**, **NAM**)
Setup	Allows you to specify the task to be performed and the theoretical model to be employed, to specify graphical surfaces and property maps and to submit jobs for calculation.
Display	Allows you to display text output, molecular and atomic properties, surfaces and property maps and infrared, UV/visible and NMR spectra, as well as to access experimental IR, UV/visible and NMR spectra over the internet. Also allows you to present data in a spreadsheet and make plots from and perform regression analysis on these data and to access the results of a similarity analysis.
Search	Allows you to search the Cambridge Structural Database (CSD) of experimental X-ray crystal structures, the Spartan Molecular Database (SMD) of calculated structures, properties and spectra, the Spartan Reaction Database (SRD) of calculated transition-state structures and to retrieve structures and extract ligands from the Protein Data Bank (PDB). Allows you to guess a transition-state geometry based on a library of reactions and to identify tautomers.
Options	Allows you to set display standards, specify databases, assign compute servers and monitor executing jobs.

A complete listing of menu functions is provided in **Appendix B**.

Keystroke Equivalents

Keystroke equivalents for menus are designated by the underlined letter: **File**, **Edit**, **Model**, **Geometry**, **Build**, **Setup**, **Display**, **Search**, **Options** and **Help**. To access a menu, *press* the **Alt** key and the appropriate letter key (case insensitive), for example, **Alt S** to access the **Setup** menu.



Each menu entry is designated by an underlined letter. To access the entry, *press* the appropriate letter key, for example, *press* the **C** key to access the **Calculations** dialog.

Icons

Icons provide convenient access to selected functions under the **File**, **Build, Geometry** and **Search** menus.

- New
- Open
- Close
- Save As
- View
- Add Fragment
- Delete
- Make Bond
- Break Bond
- Minimize
- Measure Distance
- Measure Angle
- Measure Dihedral
- Freeze Center
- Set Torsions
- Set Similarity Centers
- Constrain Distance
- Constrain Angle
- Constrain Dihedral
- Define Point
- Define Plane
- Define CFD
- Align
- Databases
- Ligands
- Transition States
- Tautomers

Mouse and Keyboard Operations

The following functions are associated with the mouse.

	button	
keyboard	**left**	**right**
–	selection, X/Y rotate, exchange[a]	X/Y translate
Shift	range selection, Z rotate	scaling[b]
Ctrl	global X/Y rotate[c]	global X/Y translate
Ctrl + **Shift**	multiple selection, global Z rotate[c]	scaling[b]
Ctrl (add fragment mode)	fragment X/Y rotate chirality invert[a]	fragment X/Y translate
Ctrl + **Shift** (add fragment mode)	fragment Z rotate absolute configuration invert[a]	scaling[b]
Alt (Windows)	group selection, bond rotation	bond stretching
Ctrl + **Shift**[d] (Mac & Linux)	bond rotation absolute configuration invert[a]	bond stretching

a) Requires *double clicking*.
b) Scaling is always applied to all open molecules and all fragments. The center mouse wheel will also scale molecules (**NAW**).
c) Global rotations can be either molecule or screen centered. This is controlled by **Global Rotate** in the **Miscellaneous Preferences** dialog (**Preferences...** under **Options** menu).
d) In **Add Fragment** mode with bond selected (red arrow visible).

Mouse/keyboard operations may be broadly separated into two categories: selection (picking) and manipulation (translation/rotation).

Selection. The left button is used for selection of objects on screen and/or of menu items. Left and right buttons together are used to define a selection box for copying/cutting to the clipboard, as well as for multiple model selection. Together with the **Shift** key, the left button allows for selection over a range. Together with the **Ctrl** (**Control**) key, the left button allows for multiple selection. Both range and multiple selection apply not only to text items in lists, but to atoms and bonds in molecules as well. Together with the **Alt** key, the left button allows for selection of an entire group (detached molecular fragment). In add fragment mode, *double clicking* the left button leads to atom or group exchange while *double clicking* on an atom with the **Ctrl** key depressed leads to inversion in chirality of the atom and *double clicking* on an atom with both **Ctrl** and **Shift** keys depressed inverts the absolute configuration of the molecule.

Manipulation. The left button is used for rotation and the right button is used for translation and scaling of objects on screen. With no keys depressed, the left mouse button gives rise to rotation about the X and Y (screen) axes, while the right mouse button gives rise to translation in the X and Y (screen) directions. Together with the **Shift** key, the left mouse button gives rise to rotation about the Z direction and the right mouse button gives rise to scaling.

The **Ctrl** key in conjunction with the left or right mouse buttons and (optionally) the **Shift** key, signifies a change in focus away from the default for the purpose of rotations and translations. Outside of add fragment mode, the default is focus on a single molecule (the selected molecule). Use of the **Ctrl** key changes focus to the entire set of molecules on screen, meaning that rotations and translations are carried out globally. In add fragment mode, the default is focus on the full set of fragments that make up the molecule being constructed, and rotations and translations refer to this set of fragments as a whole. Use of the **Ctrl** key changes focus to a single fragment (the selected fragment), and rotations and translations now refer only to this fragment.

In add fragment mode, use of the **Alt** key in addition to the left mouse button allows for rotation about a selected bond and, in addition to the right mouse button, for stretching of the selected bond.

Additional keys control various ***Spartan*** functions.

3, 4	**3** selects red-cyan and **4** selects hardware interlaced stereo display (**NAL**, **NAM**). Pressing **3/4** again returns to non-stereo display.
Page Up, Page Down **Home, End**	Moves "up" (**Page Up**), "down" (**Page Down**), to the "top" (**Home**) and to the "bottom" (**End**) of the set of open molecules. Also, moves up and down pages in the **Output** dialog.
Insert	In add fragment mode only, inserts a new fragment on screen. This is accomplished by selecting the fragment from the model kit, holding down the **Insert** key and *clicking* on screen. **Alt** key for Macintosh.
Delete	Deletes a fragment, free valence, CFD, reaction arrow, the contents of a selection box, spectrum, curve, or plot. This is accomplished by holding down the **Delete** key and *clicking* on the fragment, etc.

Selecting Molecules, etc.

Two or more molecules may be simultaneously displayed in ***Spartan's*** window. However, only one molecule may be selected. The selected molecule has access to all capabilities (molecule building, job setup and submission and text and graphical display and manipulation), while non-selected molecules may only be displayed as static images. The exceptions involve scaling and the use of the **Ctrl** key.

Selection of a molecule occurs by *clicking* on its structure model or on any of its associated graphical surfaces. This results in deselection of the previously selected molecule. Molecular properties for the selected molecule are available in the **Properties** dialog (**Display** menu). Atom, bond, substituent and surface display properties, pharmacophores and group descriptors, as well as information about geometrical constraints may be accessed by subsequent *clicking* on an atom, bond, etc., associated with the selected molecule, that are then highlighted (colored gold). *Clicking* on the selected atom, bond etc. resets the display to molecular properties. *Clicking* on another molecule results in display of molecular properties for that molecule. Information about plots (including spectra) and changes to plot style and range are also available from this dialog.

Where the molecule belongs to a list with more than a single member, selection from among the different members in the list may be made using either the ◀ and ▶ buttons or the scroll bar at the bottom left of the screen. Alternatively, if the spreadsheet for the list is open on screen (see **Chapter 16**), selection can be made by *clicking* on the molecule label at the left of the spreadsheet. *Clicking* on ▶ at the bottom left of the screen animates the display of molecules in the list, that is, steps through them sequentially. This is useful for displaying a progression of graphical surfaces along a reaction coordinate. *Clicking* on ⏸ (that replaces ▶) stops the animation.

Two or more molecules from the same list may be displayed at once (although only one may be selected). Molecules are marked for display by *checking* the box immediately to the right of the molecule label in the spreadsheet (**Chapter 16**).

Dialogs

Dialogs are either modal (as indicated by **...** following their reference in a menu) or non-modal. Modal dialogs need to be dismissed before program operation can continue, while non-modal dialogs may be kept open on screen. Only one modal dialog may be open on screen, while several different non-modal dialogs and/or several copies of the same non-modal dialog (each copy referring to a different molecule or list of molecules) may be open on screen.

3-Dimensional Displays

Spartan supports both red-cyan and hardware-interlaced stereo.[*] Red/blue glasses (supplied with ***Spartan***) must be worn in the case of the former while the latter requires a Sharp™ 3D LCD monitor or Sharp 3D notebook.

Changing Colors and Setting Preferences

Colors and **Preferences...** under the **Options** menu (**Chapter 18**) allows for changing default background and graphical object colors, and for setting (and resetting) program defaults, respectively. Further control of color is discussed in **Chapter 16**.

Monitoring and Killing Jobs

Monitor under the **Options** menu (**Chapter 18**) allows for monitoring of executing jobs as well as for killing jobs.

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[*] Hardware-interlaced stereo mode (**NAL**, **NAM**).

Chapter 3

Basic Operations

This tutorial introduces a number of basic operations in ***Spartan*** *required for molecule manipulation, property query and spectra and graphics display. It should be completed by new* ***Spartan*** *users, but can probably be skipped by those who have used earlier versions. Specifically it shows how to: i) open molecules, ii) view different models and manipulate molecules on screen, iii) measure bond distances, angles and dihedral angles, iv) display energies, dipole moments, atomic charges and infrared, UV/visible and NMR spectra, and v) display graphical surfaces and property maps. Spreadsheet operations are not illustrated, no molecules are built and no calculations are performed.*

1. Start ***Spartan***. *Click* (left mouse button) on **File** from the menu bar that appears at the top of ***Spartan's*** main window. *Click* on **Open...** from the **File** menu that appears. Alternatively, *click* on the 📂 icon at the top of the screen. A file browser appears.

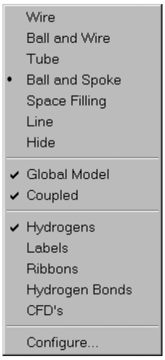
   Move to the ***tutorials*** directory*, *click* on ***basic operations***and *click* on **Open** (or *double click* on ***basic operations***). Ball-and-spoke models for ***ethane***, ***acetic acid dimer***, ***propene***, ***ammonia***, ***hydrogen peroxide***, ***acetic acid***, ***water***, ***cyclohexanone***, ***6-phenylazulene***, ***ethylene***, ***benzene***, ***aniline*** and ***cyclohexenone*** appear on screen.

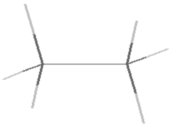
2. Identify ***ethane*** on the screen, and *click* on it (left button) to make it the selected molecule. Practice rotating (*move* the mouse while holding down the left button) and translating (*move* the mouse while holding down the right button) ***ethane***. *Click* on a different molecule, and then rotate and translate it.

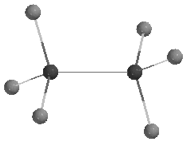
3. Return to ***ethane***. *Click* on **Model** from the menu bar.

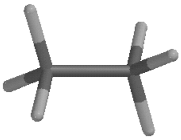
---

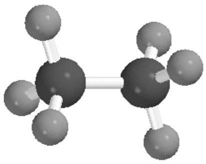
* For Windows, this is found in ***Program Files/Wavefunction/Spartan06***. For Linux, this is found in the directory where ***Spartan*** was installed. For Macintosh, this is located in the Spartan.06.full folder on the installation CDROM.


Wire
Ball and Wire
Tube
• Ball and Spoke
Space Filling
Line
Hide
✓ Global Model
✓ Coupled
✓ Hydrogens
Labels
Ribbons
Hydrogen Bonds
CFD's
Configure...


Wire


Ball-and-Wire

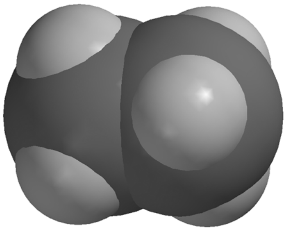

Tube


Ball-and-Spoke

One after the other, select **Wire**, **Ball and Wire**, **Tube** and finally **Ball and Spoke** from the **Model** menu. All four models for ***ethane*** show roughly the same information. The wire model looks the most like a conventional line formula. It uses color to distinguish different atoms, and one, two and three lines between atoms to indicate single, double and triple bonds, respectively.

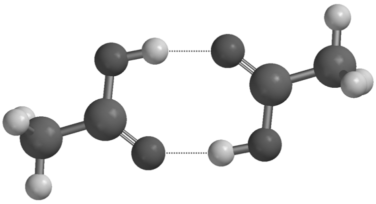
The ball-and-wire model is identical to the wire model, except that atom positions are represented by small spheres, making it easy to identify atom locations. The tube model is identical to the wire model, except that bonds are represented by solid cylinders. The tube model is better than the wire model in conveying three-dimensional shape. The ball-and-spoke model is a variation on the tube model; atom positions are represented by colored spheres, making it easy to see atom locations.

Select **Space Filling** from the **Model** menu.


Space-Filling

The space-filling model is different from the other models in that bonds are not shown. Rather, each atom is displayed as a colored sphere that represents its approximate size. Thus, the space-filling model for a molecule provides a measure of its size. While lines between atoms are not drawn, the existence (or absence) of bonds can be inferred from the extent to which spheres on neighboring atoms overlap. If two spheres substantially overlap, then the atoms are almost certainly bonded, and conversely, if two spheres hardly overlap, then the atoms are not bonded. Intermediate overlaps suggest weak bonding, for example, hydrogen bonding.

Select ***acetic acid dimer***. Switch to a space-filling model and look for overlap between the (OH) hydrogen on one acetic acid molecule and the (carbonyl) oxygen on the other. Return to a ball-and-spoke model and select **Hydrogen Bonds** from the **Model** menu.



Ball-and-Spoke model for acetic acid dimer
with hydrogen bonds displayed

The two hydrogen bonds, that are responsible for holding the acetic acid molecules together, will be drawn.

Use the **3** key to toggle between red-cyan stereo 3D and regular display.* To view in 3D you will need to wear the red/blue glasses provided with ***Spartan***.

4. Distances, angles, and dihedral angles can easily be measured with ***Spartan*** using **Measure Distance**, **Measure Angle**, and **Measure Dihedral**, respectively, from the **Geometry** menu.

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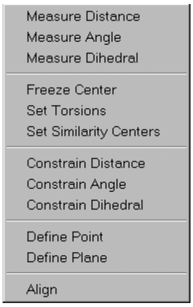
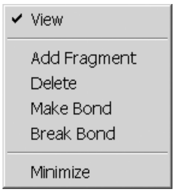
* If you have a Sharp™ LCD stereo display (**NAL**, **NAM**), use the **4** key instead of the **3** key. No glasses are needed.


Measure Distance
Measure Angle
Measure Dihedral
Freeze Center
Set Torsions
Set Similarity Centers
Constrain Distance
Constrain Angle
Constrain Dihedral
Define Point
Define Plane
Align

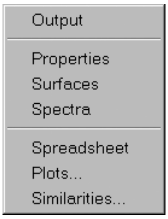
a) **Measure Distance**: This measures the distance between two atoms. First select ***propene*** from the molecules on screen, and then select **Measure Distance** from the **Geometry** menu (or *click* on the ‹?› icon at the top of the screen). *Click* on a bond or on two atoms (the atoms do not need to be bonded). The distance (in Ångstroms) will be displayed at the bottom of the screen. Repeat the process for several atoms. When you are finished, select **View** from the **Build** menu (or *click* on the V icon at the top of the screen).


✓ View
Add Fragment
Delete
Make Bond
Break Bond
Minimize

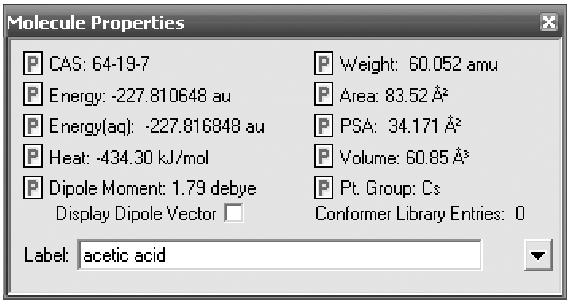
b) **Measure Angle**: This measures the angle around a central atom. Select ***ammonia*** from the molecules on screen, and then select **Measure Angle** from the **Geometry** menu (or *click* on the ∠? icon at the top of the screen). *Click* first on H, then on N, then on another H. Alternatively, *click* on two NH bonds. The HNH angle (in degrees) will be displayed at the bottom of the screen. *Click* on V when you are finished.

c) **Measure Dihedral**: This measures the angle formed by two intersecting planes, one containing the first three atoms selected and the other containing the last three atoms selected. Select ***hydrogen peroxide*** from the molecules on screen, then select **Measure Dihedral** from the **Geometry** menu (or *click* on the ? icon at the top of the screen) and then *click* in turn on the four atoms (HOOH) that make up hydrogen peroxide. The HOOH dihedral angle will be displayed at the bottom of the screen. *Click* on V when you are finished.

5. Energies, dipole moments and atomic charges among other calculated properties, are available from **Properties** under the **Display** menu.



a) **Energy:** Select ***acetic acid*** from the molecules on screen and then select **Properties** from the **Display** menu. The **Molecule Properties** dialog appears.



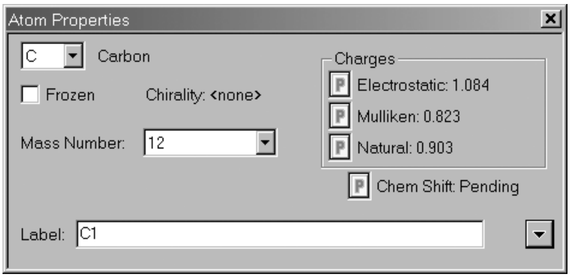
CAS: 64-19-7
Energy: -227.810648 au
Energy(aq): -227.816848 au
Heat: -434.30 kJ/mol
Dipole Moment: 1.79 debye
Display Dipole Vector ☐
Weight: 60.052 amu
Area: 83.52 Å²
PSA: 34.171 Å²
Volume: 60.85 Å³
Pt. Group: Cs
Conformer Library Entries: 0
Label: acetic acid

This provides the energy for acetic acid in atomic units (au). Also provided is an estimate of the energy in water (also in au).

b) **Dipole Moment:** The magnitude of the dipole moment (in debyes) is also provided in the **Molecule Properties** dialog. A large dipole moment indicates large separation of charge. You can attach the dipole moment vector, +⟶ where the lefthand side + refers to the positive end of the dipole, to the model on the screen, by *checking* the box to the right of **Display Dipole Vector** near the bottom of the dialog.

The vector will not be displayed if the dipole moment is zero. Also, the dipole moment will not be reported if the molecule is charged, because in this case it depends on the location and orientation of the molecule in space.

c) **Atomic Charges:** To display the charge on an atom, *click* on it with the **Molecule Properties** dialog on the screen. The **Atom Properties** dialog replaces the **Molecule Properties** dialog.



Atom Properties

C Carbon

☐ Frozen

Chirality: <none>

Mass Number: 12

Charges

Electrostatic: 1.084

Mulliken: 0.823

Natural: 0.903

Chem Shift: Pending

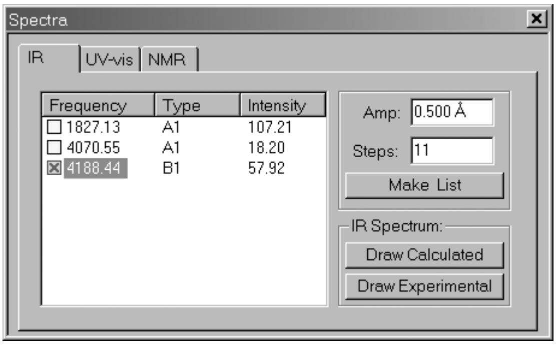
Label: C1

Three different atomic charges are given in units of electrons. A positive charge indicates a deficiency of electrons on an atom and a negative charge, an excess of electrons. Repeat for other atoms. Confirm that the positively-charged atom(s) lie at the positive end of the dipole moment vector. When you are finished, close the dialog by *clicking* on the ☒ in its top right-hand corner.

The three sets of atomic charges for acetic acid are different because the charge on an atom in a molecule is not a property. It cannot be measured, nor can it be uniquely defined. The different calculated charges correspond to different ways of distributing charge among the atoms.

d) **Infrared Spectra:** Molecules vibrate (stretch, bend, twist) even if they are cooled to absolute zero. This is the basis of infrared spectroscopy, where absorption of energy occurs when the frequency of a particular molecular motion matches the frequency of the light. Infrared spectroscopy is important for identifying molecules as different functional groups vibrate at noticeably different and characteristic frequencies.

Select ***water*** from the molecules on screen. To animate a vibration, select **Spectra** from the **Display** menu and *click* on the **IR** tab. This leads to the **IR Spectra** dialog.



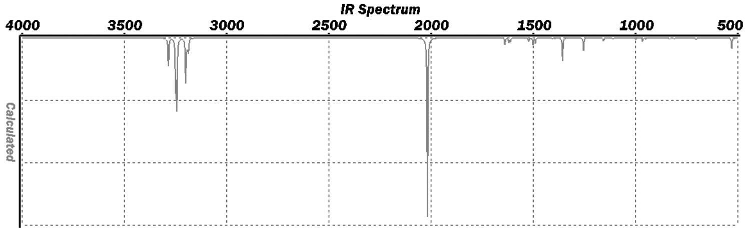
Frequency	Type	Intensity
☐ 1827.13	A1	107.21
☐ 4070.55	A1	18.20
☒ 4188.44	B1	57.92

Amp: 0.500 Å

Steps: 11

This displays the three vibrational frequencies for the water molecule, corresponding to bending and symmetric and antisymmetric stretching motions. One after the other, *click* on each frequency and examine the motion. Turn “off” the animation when you are finished.

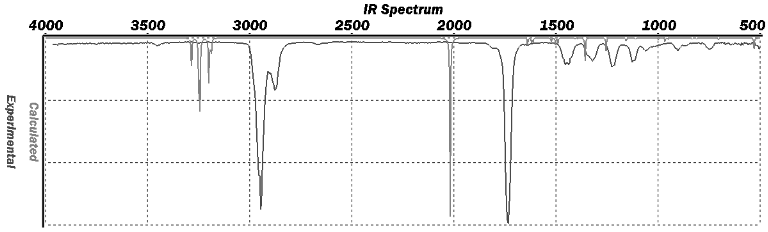
Select ***cyclohexanone***. The **Spectra** dialog now lists its 45 vibrational frequencies. Examine each in turn (*click* on the entry in the dialog) until you locate the frequency corresponding to the CO (carbonyl) stretch. Next, *click* on **Draw Calculated** at the bottom of the dialog. The infrared spectrum of cyclohexanone appears.



You can move the spectrum around the screen by first *clicking* on it to select it and then *moving* the mouse while holding down the right button. You can size it by *moving* the mouse up and down while holding down both the **Shift** key and the right button.

Identify the line in the spectrum associated with the C=O stretch (a small gold ball moves from line to line as you step through the frequencies in the **Spectra** dialog). Note that this line is isolated and that it is very intense, making it easy to find.

If your computer is connected to the internet, you can draw the experimental IR spectrum for cyclohexanone on top of the calculated spectrum. *Click* on **Draw Experimental**.

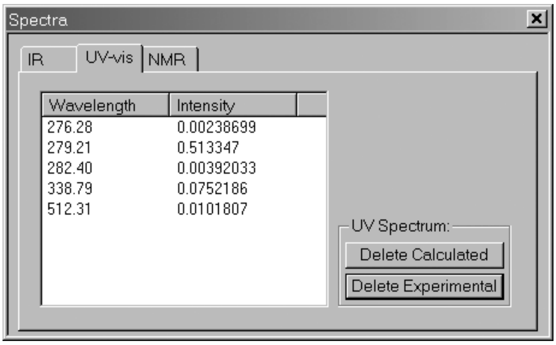


Note that the two spectra are broadly similar, but that the lines in the calculated spectrum are consistently of higher frequency. To see this more clearly, *click* on the calculated spectrum, hold down both the **Shift** and **Alt** keys (**Shift** and **Alt/Option** on Macintosh) and move the mouse up and down. The calculated spectrum will be uniformly scaled and it will be possible to bring it into close agreement with the experimental spectrum.

You can remove the plot by *clicking* on both **Delete Calculated** and **Delete Experimental** in the **Spectra** dialog.

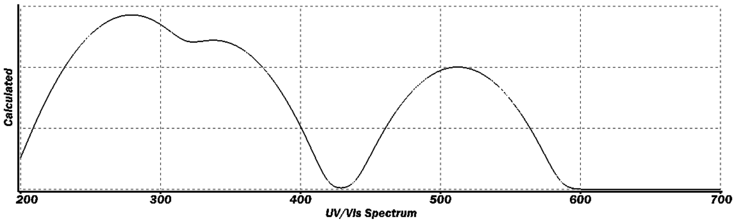
e) **UV/visible Spectra:** Absorption of light in the visible or ultraviolet range of the electromagnetic spectrum leads to electronic excitation from the ground-state to excited-states and (in the case of absorption in the visible), is responsible for a molecule’s color. UV/visible spectroscopy not only offers a valuable fingerprint but is also an important screen to identify molecules that may be damaged by exposure to light.

Select ***6-phenylazulene*** from the molecules on screen. Bring up the **Spectra** dialog and *click* on the **UV/vis** tab. This leads to the **UV/vis Spectra** dialog.

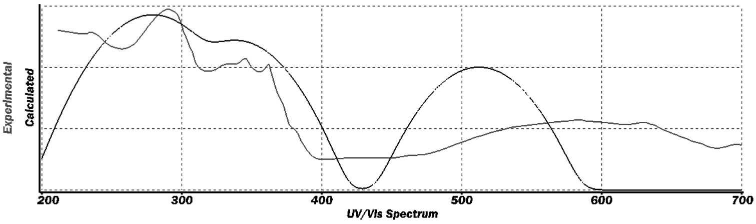


Wavelength	Intensity
276.28	0.00238699
279.21	0.513347
282.40	0.00392033
338.79	0.0752186
512.31	0.0101807

Click on **Draw Calculated** to show the calculated spectrum.



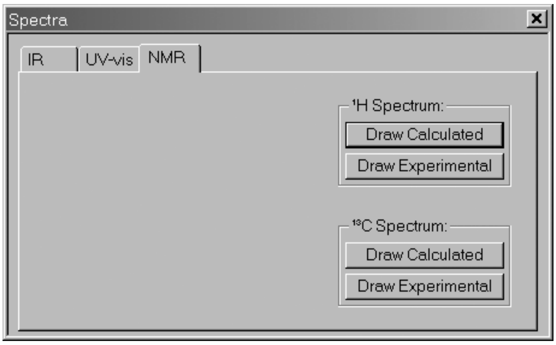
This shows a strong absorption peak around 510 nm. If you are on the internet, *click* on **Draw Experimental** to superimpose the experimental spectrum onto the calculated one.



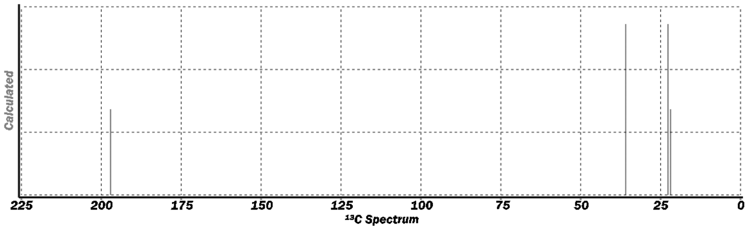
This also shows absorption in the visible. Remove the spectra by *clicking* on **Delete Calculated** and **Delete Experimental**.

f) **NMR Spectra:** Along with mass spectrometry, NMR spectroscopy is the most powerful tool available with which to assign molecular structure. Most nuclei exhibit NMR spectra, but proton and ^{13}C are by far the most important.

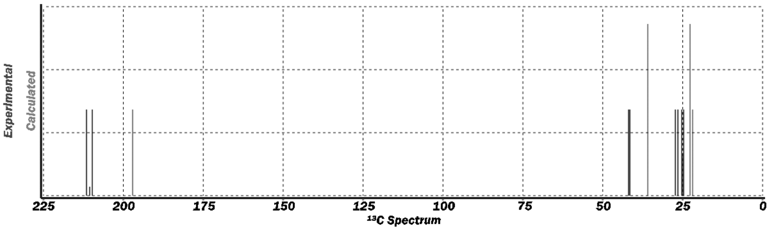
Again select ***cyclohexanone*** from the molecules on screen. Bring up the **Spectra** dialog and *click* on the **NMR** tab. This leads to the **NMR Spectra** dialog.


Spectra
IR
UV-vis
NMR
¹H Spectrum:
Draw Calculated
Draw Experimental
¹³C Spectrum:
Draw Calculated
Draw Experimental

Click on **Draw Calculated** under **^{13}C Spectrum** to show the calculated ^{13}C spectrum.



This comprises four lines, corresponding to the four distinct carbons. If you are connected to the internet, *click* on **Draw Experimental** (under **^{13}C Spectrum**) to superimpose the experimental spectrum onto the calculated one.

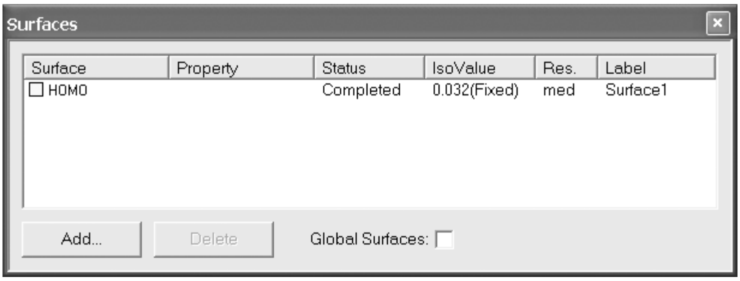


Remove the spectra by *clicking* on **Delete Calculated** and **Delete Experimental**.

6. ***Spartan*** permits display, manipulation and query of a number of important graphical quantities resulting from quantum chemical calculations. Most important are the electron density (that reveals how much space a molecule actually takes up), the bond density (that reveals chemical bonds), and key molecular orbitals (that provide insight into both bonding and chemical

reactivity). In addition, the electrostatic potential map, an overlaying of the electrostatic potential (the attraction or repulsion of a positive charge for a molecule) onto the electron density, is valuable for describing overall molecular charge distribution as well as anticipating sites of electrophilic addition. Another indicator of electrophilic addition is provided by the local ionization potential map, an overlaying of the energy of electron removal (ionization) onto the electron density. Finally, an indicator of nucleophilic addition is provided by the LUMO map, an overlaying of the lowest-unoccupied molecular orbital (the LUMO) onto the electron density.

Select ***ethylene*** from the molecules on screen, and then select **Surfaces** from the **Display** menu. The **Surfaces** dialog appears.



Surface	Property	Status	IsoValue	Res.	Label
☐ HOMO		Completed	0.032(Fixed)	med	Surface1

Click inside the box to the left of the line ***homo...*** (select ***homo...***) inside the dialog. This will result in the display of ethylene's highest-occupied molecular orbital as an opaque solid. This is a π orbital, equally concentrated above and below the plane of the molecule. The colors (red and blue) give the sign of the orbital. Changes in sign correlate with bonding or antibonding character. You can if you wish, turn "off" the graphic by again selecting ***homo...***.

Next, select ***benzene*** from the molecules on screen and select ***density potential...*** inside the **Surfaces** dialog. An electrostatic potential map for benzene will appear. *Click* on the map. The **Style** menu will appear at the bottom right of the screen. Select **Transparent** from this menu. Making the map transparent allows you to see the molecular skeleton underneath. The surface is colored red in the π system (by convention, indicating negative potential and the fact that this region is attracted to a positive charge), and blue in the σ system (by convention, indicating positive potential and the fact that this region is repelled by a positive charge).

Select ***aniline*** from the molecules on screen, and select ***density ionization...*** inside the **Surfaces** dialog. The graphic that appears, a so-called ***local ionization potential map***. By convention, red regions on the density surface indicate areas from which electron removal (ionization) is relatively easy, meaning that they are subject to electrophilic attack. These are easily distinguished from regions where ionization is relatively difficult (by convention, colored blue). Note that the *ortho* and *para* ring carbons are more red than the *meta* carbons, consistent with the known directing ability of the amino substituent.

Finally, select ***cyclohexenone*** from the molecules on screen, and select ***lumo...*** in the **Surfaces** dialog. The resulting graphic portrays the lowest-energy empty molecular orbital (the LUMO) of cyclohexenone. This orbital is delocalized onto several atoms and it is difficult to tell where exactly a pair of electrons (a nucleophile) will attack the molecule.

A clearer portrayal is provided by a ***LUMO map***, that displays the (absolute) value of the LUMO on the electron density surface. By convention, the color blue is used to represent maximum value of the LUMO and the color red, minimum value. First, remove the LUMO from your structure (select ***lumo...*** in the **Surfaces** dialog) and then turn on the LUMO map (select ***density lumo...*** in the dialog). Note that there are two blue regions, one directly over the carbonyl carbon and the other over the β carbon. This is entirely consistent with known chemistry. Enones may either undergo carbonyl addition or conjugate (Michael) addition.

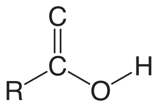
7. When you are finished, close all the molecules on screen by selecting **Close** from the **File** menu or alternatively by *clicking* on the 📂 icon at the top of the screen.

Chapter 4

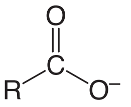
Organic Molecules

This chapter shows how to: i) construct organic molecules from atomic fragments, functional groups and rings, ii) carry out molecular mechanics and quantum chemical calculations, iii) calculate and draw infrared and NMR spectra and iv) calculate and interpret graphical models. It also illustrates use of the Spartan Molecular Database of calculated structures, energies and molecular properties as well as ***Spartan's*** *interface to the Cambridge Structural Database.*

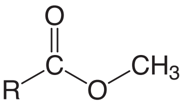
The simplest building blocks incorporated into ***Spartan's*** organic model kit are atomic fragments. These constitute specification of atom type, for example, carbon, and local environment, for example, tetrahedral. However, much of organic chemistry is organized around functional groups, collections of atoms the structure and properties of which are roughly the same in every molecule. The organic model kit also incorporates a small library of functional groups that can easily be extended or modified. For example, the carboxylic acid group may be modified to build a carboxylate anion (by deleting a free valence from oxygen), or an ester (by adding tetrahedral carbon to the free valence at oxygen).



carboxylic acid

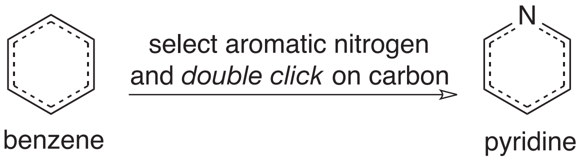


carboxylate anion



ester

Polyatomic rings are also common components in organic molecules, and the organic model kit incorporates a library of commonly-encountered hydrocarbon rings, that can easily be modified by atom replacement. For example, pyridine may be built starting from benzene by selecting aromatic nitrogen from the list of atomic fragments, and then *double clicking* on one of the carbons.

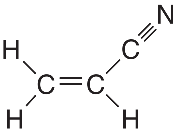


Functional groups may also be modified in this manner.

The tutorials in this chapter illustrate construction of organic molecules using atomic fragments, functional groups and rings. They also illustrate the way in which molecular mechanics and quantum chemical calculations are set up, their results examined and interpreted, and infrared and NMR spectra computed and displayed. A variety of graphical models are introduced and illustrated. Finally, examples of the use of the Spartan Molecular Database of calculated molecular structures, energies and properties and of the Cambridge Structural Database of experimental X-ray crystal structures are provided.

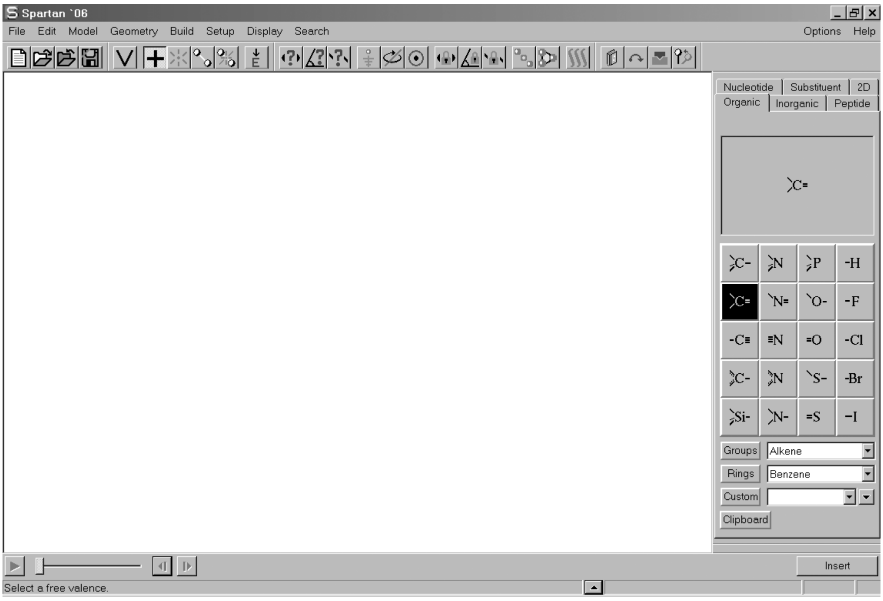
1 min

Acrylonitrile



Acrylonitrile provides a good opportunity to illustrate the basics of molecule building in ***Spartan***, as well as the steps involved in carrying out and analyzing a quantum chemical calculation.

1. *Click* with the left mouse button on **File** from the menu bar. Then *click* on **New** from the menu that appears (or *click* on the 🗋 icon at the top of the screen). The organic model kit appears.


Spartan '06
File
Edit
Model
Geometry
Build
Setup
Display
Search
Options
Help
Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
C=
C-
N
P
-H
C=
N=
O-
-F
-C≡
≡N
=O
-Cl
C-
N
S-
-Br
Si-
N-
=S
-I
Groups
Alkene
Rings
Benzene
Custom
Clipboard
Insert

Select a free valence.

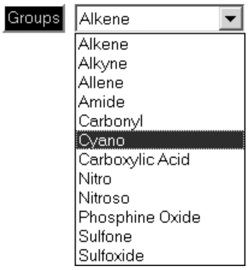
Among other things, it contains a library of atomic fragments. *Click* on trigonal planar sp^2 hybridized carbon C= from the fragment library. The atom icon is shown in reverse video to indicate that it is active. In addition, a model of the fragment appears at the top of the model kit. Bring the cursor anywhere on screen and *click*. Rotate the carbon fragment (*drag* the mouse while holding down the left button) so that you can clearly see both the double free valence (=) and the two single free valences (–).

> ***Spartan's*** model kits connect atomic fragments (as well as groups, rings and ligands) through free valences. Any remaining free valences will automatically be converted to hydrogen atoms.

2. sp^2 carbon is still selected. *Click* on the double free valence. The two fragments are connected by a double bond, leaving you with ethylene. If you make a mistake and *click* instead on the single free valence, select **Undo** from the **Edit** menu. You can also start over by selecting **Clear** from the **Edit** menu.

> ***Spartan's*** model kits allow only the same type of free valences to be connected, for example, single to single, double to double, etc.

3. *Click* on **Groups** in the model kit, and select **Cyano** from the functional groups available from the menu.



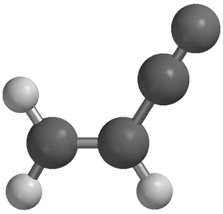
Click on any of the four single free valences on ethylene (they are all the same). This bonds the cyano group to ethylene, leaving you with acrylonitrile.*

4. Select **Minimize** from the **Build** menu (or *click* on the E icon at the top of the screen). The final molecular mechanics strain energy (36.2 kJ/mol) and symmetry point group (C_s) are provided at the bottom right of the screen.

---

* You could also have built acrylonitrile without using the **Groups** menu. Starting from scratch (**Clear** from the **Edit** menu), first build ethylene as above, then select sp hybridized carbon -C≡ from the model kit and then *click* on one of the free valences on ethylene. Next, select sp hybridized nitrogen ≡N from the model kit and *click* on the triple free valence on the sp carbon. Alternatively, you could have built the molecule entirely from groups. Starting from scratch, *click* on **Groups**, select **Alkene** from the menu and *click* anywhere on screen. Then select **Cyano** from the menu of functional groups and *click* on one of the free valences on ethylene. In general, molecules can be constructed in more than one way.

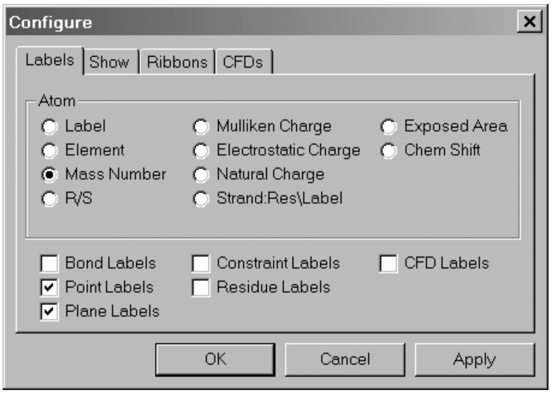
5. Select **View** from the **Build** menu (or *click* on the V icon at the top of the screen). The model kit disappears, leaving only a ball-and-spoke model of acrylonitrile on screen.



ball-and-spoke model

This model can be manipulated (rotated, translated and zoomed) by using the mouse (if necessary, in conjunction with keyboard functions). To rotate the model, *drag* the mouse while holding down the left button; to rotate in the plane of the screen also hold down the **Shift** key. To translate the model, *drag* the mouse with the right button depressed. To zoom the model (translation perpendicular to the screen), hold down the **Shift** key in addition to the right button while *dragging* the mouse up (zoom in) or down (zoom out).

6. Select **Configure...** from the **Model** menu, and *check* **Mass Number** under **Atom** in the **Configure** dialog that appears.



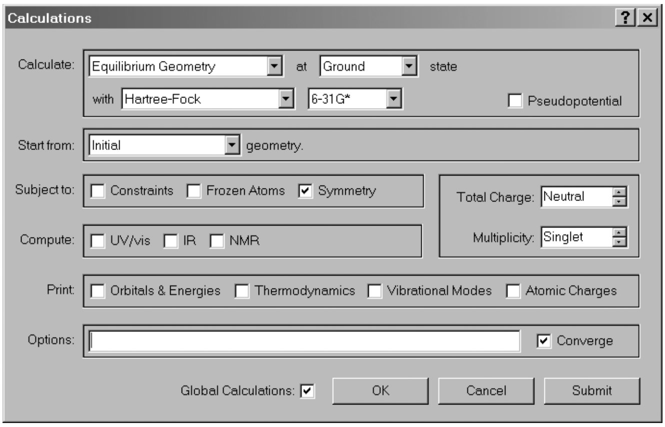
Configure

Atom
○ Label ○ Mulliken Charge ○ Exposed Area
○ Element ○ Electrostatic Charge ○ Chem Shift
● Mass Number ○ Natural Charge
○ R/S ○ Strand:Res\Label

☐ Bond Labels ☐ Constraint Labels ☐ CFD Labels
☑ Point Labels ☐ Residue Labels
☑ Plane Labels

Click on **OK** to remove the dialog. Mass numbers will appear next to the individual atoms. Remove the atom labels by selecting **Labels** from the **Model** menu.*

7. Select **Calculations...** from the **Setup** menu, and perform the following operations in the **Calculations** dialog which appears.



Calculations

Calculate: Equilibrium Geometry at Ground state

with Hartree-Fock 6-31G* ☐ Pseudopotential

Start from: Initial geometry.

Subject to: ☐ Constraints ☐ Frozen Atoms ☑ Symmetry

Total Charge: Neutral

Multiplicity: Singlet

Compute: ☐ UV/vis ☐ IR ☐ NMR

Print: ☐ Orbitals & Energies ☐ Thermodynamics ☐ Vibrational Modes ☐ Atomic Charges

Options: ☑ Converge

Global Calculations: ☑

   a. Select **Equilibrium Geometry** from the top menu to the right of **Calculate**. This specifies optimization of equilibrium geometry.

   b. Select **Hartree-Fock** and then **3-21G** from the two bottom menus to the right of **Calculate**. This specifies a Hartree-Fock calculation using the 3-21G split-valence basis set.

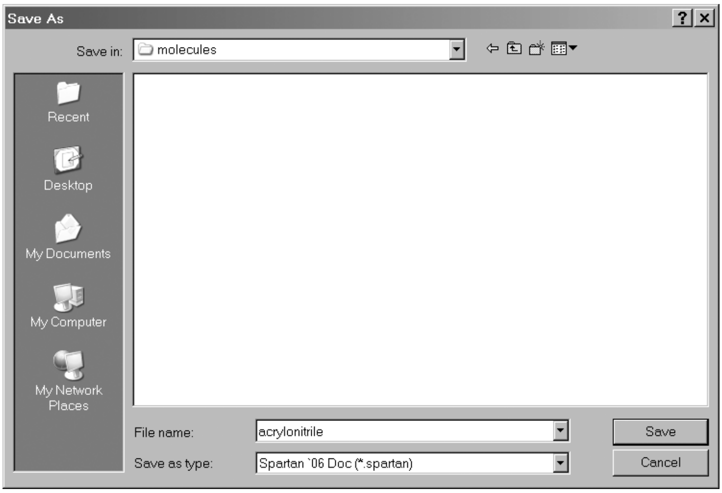
   When you finish, *click* on **OK** to remove the dialog.

8. Select **Submit** from the **Setup** menu.** A file browser appears.

---

* **Labels** from the **Model** menu is automatically selected (turned "on") following a change in the **Configure** dialog by choosing **OK** or **Apply**.

** You could also have *clicked* on **Submit** inside the **Calculations** dialog.

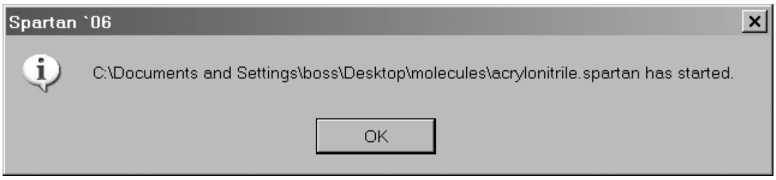

Save As
Recent
Desktop
My Documents
My Computer
My Network Places
Save
Cancel

Save in: molecules

File name: acrylonitrile

Save as type: Spartan `06 Doc (*.spartan)

Type the name ***acrylonitrile*** in the box to the right of **File name**, and then *click* on **Save**.* You will be notified that the calculation has been submitted.

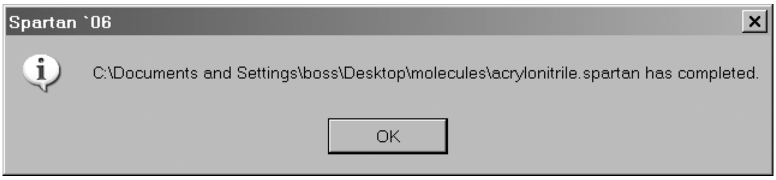

Spartan `06
OK

C:\Documents and Settings\boss\Desktop\molecules\acrylonitrile.spartan has started.

Click on **OK** to remove the message from the screen.

After a molecule has been submitted, and until the calculation has completed, you are not permitted to modify any dialogs or other information associated with it.

9. You will be notified when the calculation has completed.

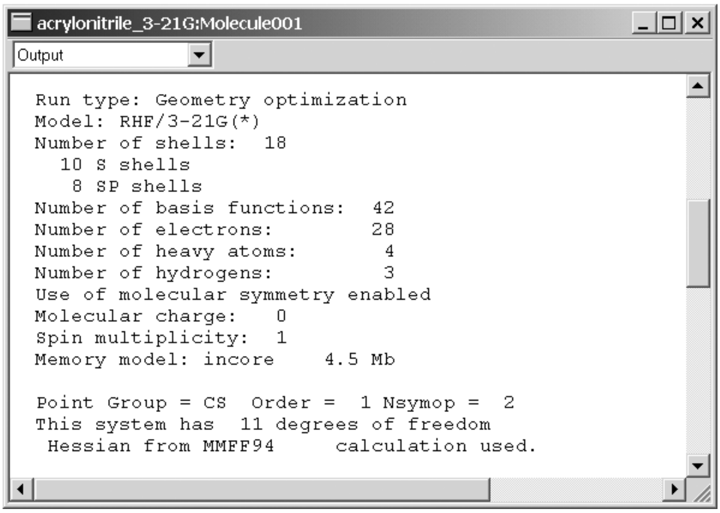

Spartan `06
OK

C:\Documents and Settings\boss\Desktop\molecules\acrylonitrile.spartan has completed.

---

* You can use default names (spartan1, spartan2, . . .) simply by *clicking* on **Save**. The Macintosh version will automatically name the molecule if it is recognized from the Spartan Molecular Database (**NAW**, **NAL**).

Click on **OK** to remove the message from the screen. Select **Output** from the **Display** menu. A window containing text output for the job appears.



```
Run type: Geometry optimization
Model: RHF/3-21G(*)
Number of shells:  18
  10 S shells
   8 SP shells
Number of basis functions:  42
Number of electrons:        28
Number of heavy atoms:       4
Number of hydrogens:         3
Use of molecular symmetry enabled
Molecular charge:   0
Spin multiplicity:  1
Memory model: incore    4.5 Mb

Point Group = CS  Order =  1 Nsymop =  2
This system has  11 degrees of freedom
 Hessian from MMFF94     calculation used.
```

You can scan the output from the Hartree-Fock calculation by using the scroll bar at the right of the window. The information at the top of the dialog includes the task, basis set, number of electrons, charge and multiplicity, as well as further details of the calculation. Below this is the symmetry point group of the molecule that was maintained during the optimization.

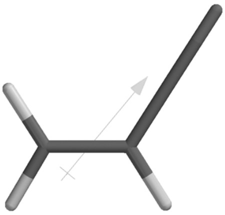
Eventually, a series of lines appear, each beginning with “Cycle no:”. These tell the history of the optimization process. Each line provides results for a particular geometry. Ideally, the energy will monotonically approach a minimum value for an optimized geometry. If the geometry was not optimized satisfactorily an error message, such as: “Optimization has exceeded N steps – Stop”, will be displayed following the last optimization cycle. In this case, you would have been notified that the job had failed, rather than seeing the “completed” message dialog.

Near the end of the output is the final energy* (-168.82040 atomic units for acrylonitrile with the 3-21G basis set), and the computation time. *Click* on ☒ in the top right-hand corner of the dialog to close the dialog.

---

* See **Calculations...** (**Setup** menu; **Chapter 15**) for a discussion of how energy relates to the more familiar quantities, heat of formation and strain energy.

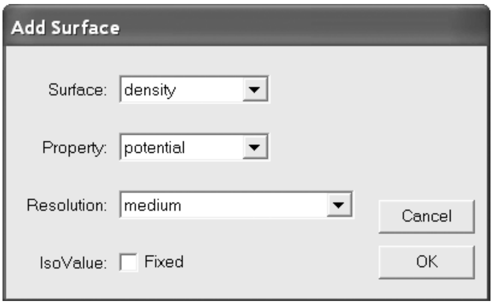
You may examine the total energy and dipole moment without having to go through the output. Select **Properties** from the **Display** menu to bring up the **Molecule Properties** dialog. To see the dipole moment vector (indicating the sign and direction of the dipole moment), *check* the box to the right of **Display Dipole Vector**. (A tube model is best for this display.)



Uncheck the box to remove the dipole moment vector.

Click on an atom. The (**Molecule Properties**) dialog will be replaced by the **Atom Properties** dialog. Among other things, this provides three different sets of atomic charges: **Electrostatic**, **Mulliken** and **Natural**. To obtain the charge on another atom, simply click on it. Inspect all the atomic charges on acrylonitrile (by *clicking* on the appropriate atoms). When you are done, *click* on ☒ at the top right of the **Atom Properties** dialog to close it.

10. Select **Surfaces** from either the **Setup** or **Display** menu. *Click* on **Add...** (at the bottom of the **Surfaces** dialog that results) to bring up the **Add Surface** dialog.


Add Surface

Surface: density

Property: potential

Resolution: medium

IsoValue: ☐ Fixed

Select **density** from the **Surface** menu and **potential** from the **Property** menu.[*] This requests an electrostatic potential map (an electron density surface onto which the value of the electrostatic potential will be mapped). *Click* on **OK**. A line ***density potential...*** appears at the top of the dialog. If you make a mistake, *click* on this line (select ***density potential...***) and then *click* on **Delete** at the bottom of the dialog.

11. The graphics calculation will run automatically (without needing to submit the job)[**] following your request. When it has completed (a few seconds), select ***density potential...***. The surface itself corresponds to the electron density and provides a measure of the overall size and shape of acrylonitrile. The colors indicate values of the electrostatic potential on this surface; by convention, colors toward red correspond to negative potential (stabilizing interaction between the molecule and a positive charge), while colors toward blue correspond to positive potential. The nitrogen (the most electronegative atom) is red and the hydrogens (the most electropositive atoms) are blue.

14. Select **Close** from the **File** menu (or *click* on 📂) to remove acrylonitrile from the screen.[***] Also, close any dialogs that may be open.

---

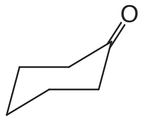
[*] In this and other tutorials, **Resolution** will be set to **medium**. Both lower and higher resolution images may be requested. The former provides rough images that require significantly less computer time to generate. The latter provides production quality images that require significantly more computer time. Computer time can also be reduced by *checking* **Fixed** to the right of **Isovalue** in the **Add Surface** dialog. This results in static surfaces that cannot be changed.

[**] Automatic generation of graphics is currently available only for Windows. Macintosh and Linux customers will need to submit the calculation.

[***] While ***Spartan*** permits as many molecules as desired on screen at a given time, it will be less confusing for first-time users to handle a single molecule at a time.

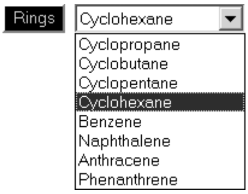
2 mins

Cyclohexanone



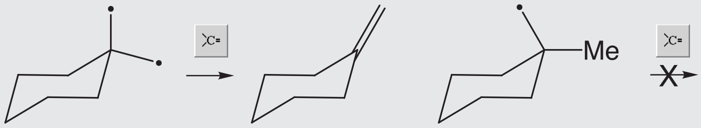
Cyclohexanone provides the opportunity to illustrate additional building features as well as graphical models for investigation of the stereoselectivity of an important class of organic reactions.

1. *Click* on 🗎 to bring up the organic model kit. *Click* on **Rings** and select **Cyclohexane** from the menu of rings.


Rings
Cyclohexane
Cyclopropane
Cyclobutane
Cyclopentane
Cyclohexane
Benzene
Naphthalene
Anthracene
Phenanthrene

Click anywhere on screen and cyclohexane will appear. Select sp^2 carbon >C= from the model kit. *Double click* on any carbon (not free valence). The sp^3 hybridized center will be replaced by an sp^2 hybridized carbon.

> ***Spartan's*** organic model kit allows replacement of fragments, subject both to the usual valence rules and to the availability of free valences. For example, replacement of an sp^3 carbon by an sp^2 carbon requires that at least two free valences be available. This is possible for cyclohexane (above), but would not have been allowed for the substituted ring carbon in methylcyclohexane.



Select sp^2 oxygen =O from the model kit. *Click* on the double free valence on the sp^2 carbon. You have made cyclohexanone. *Click* on E to produce a final structure with C_s symmetry, and then on V to remove the model kit.

2. Select **Calculations...** from the **Setup** menu. Specify **Equilibrium Geometry** from the top menu to the right of **Calculate**, and **Hartree Fock** and **3-21G** from the two bottom menus to the right of **Calculate**. *Click* on **OK**.

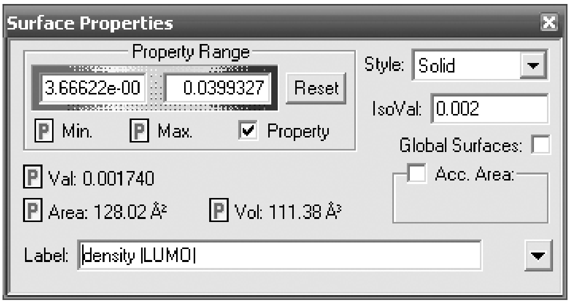
3. Cyclohexanone undergoes nucleophilic attack at the carbonyl carbon, and it is reasonable to expect that the molecule's lowest-unoccupied molecular orbital (the LUMO) will be localized here. To visualize the LUMO, enter the **Surfaces** dialog (**Setup** or **Display** menu). *Click* on **Add...**, and select **LUMO** from the **Surface** menu (**none** from the **Property** menu). *Click* on **Apply**. Also request an electron density surface onto which the (absolute) value of the LUMO has been mapped in color (a so-called LUMO map). Select **density** from the **Surface** menu and **|LUMO|** from the **Property** menu. C*lick* on **OK**. Submit the job (**Submit** from the **Setup** menu) with the name ***cyclohexanone***.

> Graphical displays may either be requested at the time of geometry calculation (as in the present example), or, under Windows, at anytime after (as in the previous example). In the latter case, it is not necessary to submit the job. ***Spartan*** keeps track of what has been done and will not perform unnecessary calculations. (**NAL**, **NAM**)

4. After the calculations have completed, reenter the **Surfaces** dialog and select ***LUMO...***. The LUMO of cyclohexanone appears. As expected, this is a π* orbital primarily localized on the carbonyl group.

5. Inside the **Surfaces** dialog, turn "off" the display of the LUMO (select ***LUMO...***). Next, select ***density |LUMO|...*** to display the electron density surface onto which the (absolute) value of the LUMO has been mapped. By convention, colors toward red indicate small (absolute) values of the LUMO (near zero), while colors toward blue indicate large (absolute) values of the LUMO. Note the blue spot directly over the carbonyl carbon. This corresponds to the maximum value of the LUMO and is where nucleophilic attack will occur.

6. You will see that the blue spot over the *axial* face of the carbonyl carbon is bigger than that over the *equatorial* face. This indicates preferential attack by nucleophiles onto the *axial* face. Quantify the difference by measuring the (absolute) value of the LUMO on these two faces. Bring up the (**Molecule**) **Properties** dialog (**Display** menu) and *click* anywhere on the LUMO map. The **Surface Properties** dialog appears.



Property Range: 3.66622e-00 to 0.0399327
☑ Property
Style: Solid
IsoVal: 0.002
Global Surfaces: ☐
☐ Acc. Area:
Val: 0.001740
Area: 128.02 Å²
Vol: 111.38 Å³
Label: density |LUMO|

Turn the map such that you can clearly see the *axial* face of the carbonyl carbon, and *click* on the area of maximum blue. The (absolute) **Value** of the LUMO at the surface point you have selected is provided in the dialog. Note the value, and then turn the map over such that you can now see the *equatorial* face of the carbonyl carbon, and *click* on the region of maximum blue on this face*. Do these values support your qualitative conclusions from viewing the image?

7. Remove ***cyclohexanone*** and any remaining dialogs from the screen.

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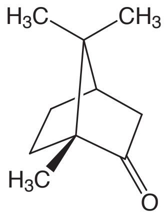
* *Click* on the background to return to the **Molecule Properties** dialog.

Camphor



Camphor illustrates how one molecule may be used as the starting point for another. It also illustrates a search on the Cambridge Structural Database (CSD).[*] No calculations are involved in this example.

1. Bring ***cyclohexanone*** (previous example) back onto the screen. Select **Open...** from the **File** menu (or *click* on 📂) and *double click* on ***cyclohexanone*** in the dialog which results. Next select **Save As...** from the **File** menu (or *click* on the 💾 icon at the top of the screen), supply the name ***camphor*** and *click* on **Save**.

2. Select **Add Fragment** from the **Build** menu (or *click* on the + icon at the top of the screen) to bring up the organic model kit. *Click* on sp^3 carbon >C- from the model kit and then *click* on the *axial* free valence two positions removed from the carbonyl carbon. You have made *axial* 3-methylcyclohexanone.

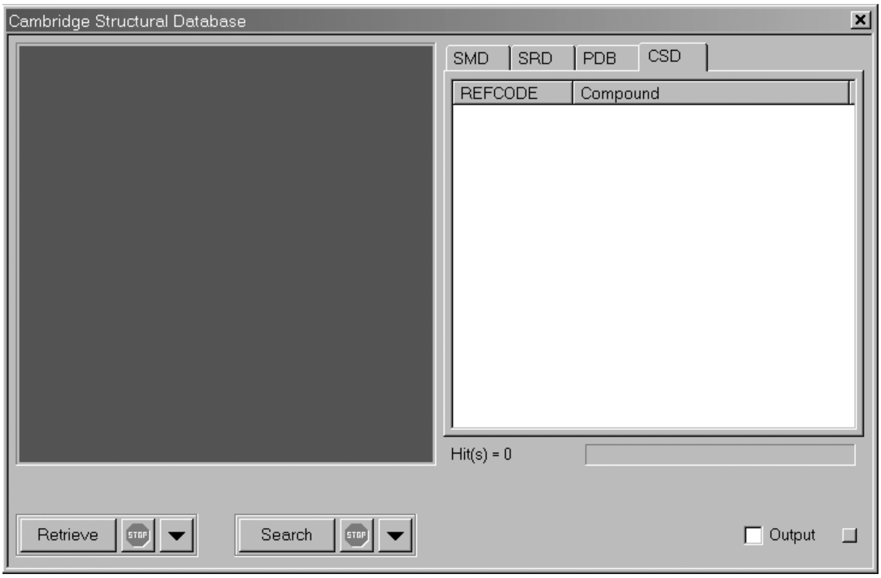
3. Select **Make Bond** from the **Build** menu (or *click* on the ⚯ icon at the top of the screen). *Click* on one of the free valences of the sp^3 carbon which you have just added and then on the *equatorial* free valence on the opposite side of the six-membered ring (adjacent to the carbonyl group). A bond will be drawn. *Click* on ↓E to produce a refined (intermediate) structure. Finish the structure by adding three methyl groups (*click* on >C- from the model kit and, one after the other, *click* on the three appropriate free valences). Finally, *click* on ↓E to give a minimized camphor geometry with C_1 symmetry. *Click* on V to remove the model kit.

---

[*] In order to complete this tutorial, CSD will need to be licensed and installed. For information refer to the CCDC website (www.ccdc.cam.ac.uk). For installation instructions, see **Appendix F** (**NAM**).

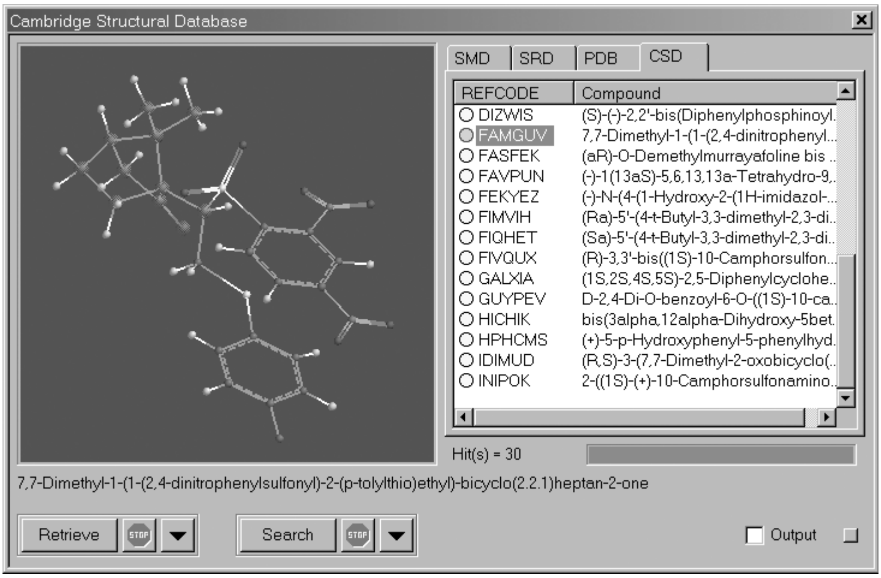
4. Select **Configure...** from the **Model** menu. *Check* **R/S** under **Atom** in the dialog that results, and *click* on **OK**. R/S labels now appear (only) on the two bridgehead carbons. Both should be R (or both S), depending on which enantiomer you have built. You can if you wish turn “off” the labels by selecting **Labels** from the **Model** menu.

5. Move the molecule to the far right of the screen. Then, select **Databases** from the **Search** menu (or *click* on the icon at the top of the screen). *Click* on the **CSD** tab at the top of the **Databases** dialog that results. This brings up the **CSD** dialog.



Click on one of the free valences on the methyl group that you added to the bridgehead carbon adjacent to the carbonyl group. The free valence is replaced by an orange cone. This signifies that the search is to be restricted to molecules that derive from substitution of camphor at this carbon.

6. *Click* on the **Search** button at the bottom of the dialog. Hits will appear in the text box at the right of the **CSD** dialog.



REFCODE	Compound
○ DIZWIS	(S)-(-)-2,2'-bis(Diphenylphosphinoyl.
● FAMGUV	7,7-Dimethyl-1-(1-(2,4-dinitrophenyl...
○ FASFEK	(aR)-O-Demethylmurrayafoline bis ..
○ FAVPUN	(-)-1(13aS)-5,6,13,13a-Tetrahydro-9,.
○ FEKYEZ	(-)-N-(4-(1-Hydroxy-2-(1H-imidazol-...
○ FIMVIH	(Ra)-5'-(4-t-Butyl-3,3-dimethyl-2,3-di..
○ FIQHET	(Sa)-5'-(4-t-Butyl-3,3-dimethyl-2,3-di..
○ FIVQUX	(R)-3,3'-bis((1S)-10-Camphorsulfon...
○ GALXIA	(1S,2S,4S,5S)-2,5-Diphenylcyclohe..
○ GUYPEV	D-2,4-Di-O-benzoyl-6-O-((1S)-10-ca..
○ HICHIK	bis(3alpha,12alpha-Dihydroxy-5bet.
○ HPHCMS	(+)-5-p-Hydroxyphenyl-5-phenylhyd.
○ IDIMUD	(R,S)-3-(7,7-Dimethyl-2-oxobicyclo(..
○ INIPOK	2-((1S)-(+)-10-Camphorsulfonamino..

Hit(s) = 30

7,7-Dimethyl-1-(1-(2,4-dinitrophenylsulfonyl)-2-(p-tolylthio)ethyl)-bicyclo(2.2.1)heptan-2-one

7. Wait for the search to complete, or terminate it at any time by *clicking* on STOP to the right of the **Search** button. Hits for which structural data are available are indicated by filled yellow circles.* *Click* on any one of these. Its name will be highlighted and a structure model will appear in the window at the top of the dialog. This model can be manipulated in the usual way.** (You need to position the cursor inside the window.)

8. When you are done, remove the **CSD** dialog (*click* on ☒ at the top right) and close ***camphor***.

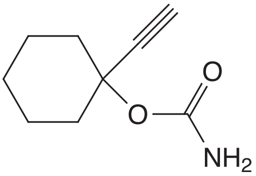
---

* Unfilled circles correspond to entries for which structural data are unavailable.

** One (or more) structures may be transfered to ***Spartan's*** file system using the **Retreive** button. Full discussion is provided in **Chapter 17**.

1 min

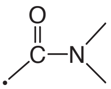
Ethinamate



Acrylonitrile, cyclohexanone and camphor are examples of molecules that can adopt only a single conformation. Much more common are molecules that can adopt more than one conformation, usually due to rotation about single bonds or puckering of rings. The sedative ethinamate is not atypical, and presents an interesting question of whether the alkyne or the carbamate occupies the favored *equatorial* position on the six-membered ring.

This tutorial and the one immediately following, illustrate the simplest approach to dealing with conformationally-flexible molecules, that is, finding the lowest-energy conformer (the global minimum). Tutorials in later chapters address the more difficult problem of identifying all reasonable low-energy conformers.

1. Bring up the organic model kit (🗎). *Click* on **Rings**, select **Cyclohexane** from the menu and *click* anywhere on screen. *Click* on sp^3 oxygen (O) in the model kit and add to either an *equatorial* or *axial* free valence on cyclohexane. *Click* on **Groups** and select **Amide** from the menu. Make certain that free valence on the amide group to be used for bonding is associated with carbon and not with nitrogen. This is indicated by a • on the icon at the top of the model kit.

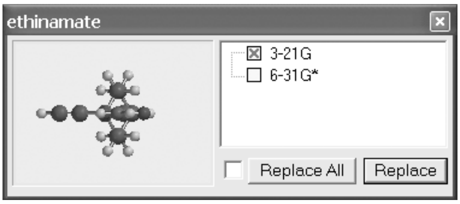
   

   You can move the bonding position by repeatedly *clicking* on the icon. When you are satisfied, add the amide to oxygen to make the carbamate functionality. Finally, select **Alkyne** from the **Groups** menu and add to the same carbon on the cyclohexane ring as occupied by the carbamate group (using the remaining *axial* or *equatorial* free valence). *Click* on ↓E and then on V to remove the model kit.

2. Bring up the **Calculations** dialog (**Setup** menu). Select **Equilibrium Conformer** from the top menu to the right of **Calculate** and **Molecular Mechanics** and **MMFF** from the two bottom menus. You have requested that ***Spartan*** examine all possible conformers*, but then select only the most stable conformer (according to the MMFF model). *Click* on **Submit** at the bottom of the dialog. Name the molecule ***ethinamate***.

3. When completed, the preferred conformer will replace the initial conformer (just like a calculated equilibrium geometry replaces a starting geometry). Which group, alkyne or carbonate, occupies the *equatorial* position?

4. Note that the name "ethanimate" appears at the bottom of the screen. This indicates that it is already available in the Spartan Molecular Database (SMD) of molecular structures and properties. *Click* on ▲ immediately to the left of the name. This brings up the **SMD Preview** dialog.



Listed at the right are theoretical models for which ethanimate is available, while a ball-and-spoke model of the selected SMD entry is displayed at the left. It can be manipulated using the mouse. Is the conformation of ethanimate in the database entries the same as you have found?

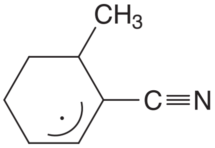
5. Close ***ethinamate*** as well as any open dialogs.

---

* This system is small, and the possible conformers will be systematically examined. This is not practical for molecules with a large number of degrees of conformational freedom. Here Monte-Carlo methods need to be employed.

1 min

3-Cyano-4-methylcyclohexenyl Radical



This tutorial illustrates how different models may be combined to achieve a desired result with minimum computation cost. MMFF molecular mechanics will be employed to establish equilibrium conformation, the semi-empirical AM1 model to establish equilibrium geometry and the Hartree-Fock 3-21G model to provide a basis for graphical calculations.

1. Build 3-cyano-4-methylcyclohexene. Start with **Cyclohexane** from the **Rings** menu, *click* on ⚬⚬, and then *click* on *axial* free valences on any two adjacent carbons. Add **Cyano** from the **Groups** menu to one of the *equatorial* free valences on a carbon adjacent to the double bond. Finally, add a methyl group (C-) to the appropriate ring position using either the *equatorial* or *axial* free valence.

2. Select **Delete** from the **Build** menu (or *click* on the ⁙ icon at the top of the screen), and *click* on the (*axial*) free valence on the carbon to which the cyano group is attached. *Click* on ↓E to produce a refined geometry with C_1 symmetry. *Click* on V to remove the model kit.

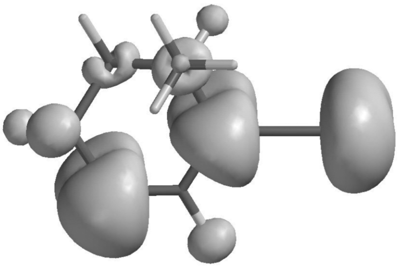
3. Select **Calculations...** (**Setup** menu). Specify **Energy** from the top menu to the right of **Calculate**, **Hartree-Fock** and **3-21G** from the two bottom menus. Next, specify **MMFF Conformer** from the **Start from** menu and **AM1** from the menu which then appears to the right. You have requested that a Hartree-Fock energy is to be obtained using an AM1 geometry, which in turn is to be based on the best conformation according to MMFF.

   This molecule has one unpaired electron. It is necessary to change **Multiplicity** from **Singlet** to **Doublet**. *Click* on **OK**.

4. Select **Surfaces** (**Setup** or **Display** menu). *Click* on **Add...**. Select **spin** from **Surface** menu and **none** from the **Property**

menu, and *click* on **Apply**. Select **density** from the **Surface** menu and **spin** from the **Property** menu. *Click* on **Apply**. You have requested two different representations of spin distribution. The first presents spin density as a surface of constant value, while the second color maps the value of the spin density onto an electron density surface. Also, request the singly-occupied molecular orbital (SOMO). Select **SOMO** from the **Surface** menu (**none** from the **Property** menu) and *click* on **OK**.

5. Submit the job. Name it ***3-cyano-4-methylcyclohexenyl radical*** When completed, examine the conformation. Is the methyl group *equatorial* or *axial*? Next, enter the **Surfaces** dialog. Select ***spin...*** to display the spin density surface. Note that the spin density is delocalized over two of the ring carbons and onto the cyano group.



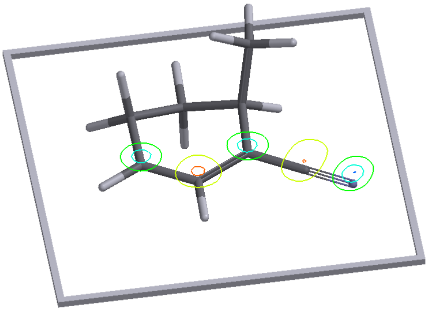
6. Again enter the **Surfaces** dialog. First, remove the spin density surface. Then, display the spin density map. Select ***density spin...***. Note that the areas of maximum spin (colored blue) exactly match those where the surface is large in the previous image.

   Select **Properties** (**Display** menu) and *click* anywhere on the spin density map. This brings up the **Surface Properties** dialog. **Range** provides the range of spin density values. Note, in particular, that negative values of the spin density are possible.

7. Enter the **Surfaces** dialog, turn “off” display of the spin density map and then select ***SOMO...*** to turn “on” display of the SOMO. Note that the singly-occupied molecular orbital is nearly identical to the previously-displayed image of the spin.

8. Turn "off" display of the SOMO. Next, *click* on **Add...** at the bottom of the (**Surfaces**) dialog, and select **Slice** from the **Surfaces** menu and **spin** from the **Properties** menu. *Click* on **OK**. A new line ***Slice spin...*** appears in the window at the top of the dialog.* Select it.

9. A plane (a slice of spin density) surrounded by a frame appears in the middle of the model on screen. *Click* on the frame (or inside of it) to select. It will now be surrounded by a gold frame. Position the cursor outside the frame, then *press* both the **Shift** key and right button and move the mouse up and down. This will zoom the plane. You can also translate and rotate the plane independently of the molecule using the usual mouse operations. Alternatively, you can move the molecule and plane together by first *clicking* on the molecule (the frame will now turn white) and then using the mouse. For all operations, be certain to keep the cursor positioned outside of the frame. Size and orient the slice as you wish.**



10. Remove ***3-cyano-4-methylcyclohexenyl radical*** and any remaining dialogs from the screen.

---

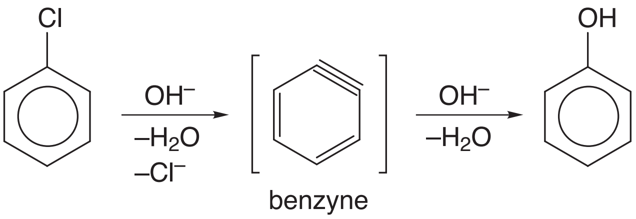
* No further calculations are involved as this is just another way of representing the spin density.

** You can change the display style from **Contours** to **Solid** or **Transparent** using the **Style** menu at the bottom right of the screen. This will appear only when the slice is selected.

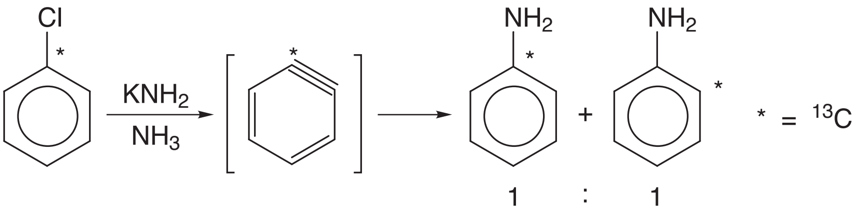
5 mins

Infrared Spectrum of Benzyne

Benzyne has long been implicated as an intermediate in nucleophilic aromatic substitution, e.g.



While the geometry of benzyne has yet to be conclusively established, the results of a ^{13}C labeling experiment leave little doubt that two (adjacent) positions on the ring are equivalent.



Benzyne has reportedly been trapped in a low-temperature matrix and its infrared spectrum recorded.* Furthermore, a line in the spectrum at 2085 cm^{-1} has been assigned to the stretching mode of the incorporated "triple bond".

Here you will calculate the structure of benzyne using the Hartree-Fock 3-21G model and, following this, obtain an infrared spectrum for the molecule. Comparison with the experimental spectrum (specifically the line at 2085 cm^{-1} attributed to the C≡C stretch) should allow you to comment one way or another about the report.

1. Bring up the organic model kit, select **Benzene** from the **Rings** menu and *click* anywhere on screen. *Click* on ⁜ and *click* on two adjacent free valences on benzene. (Alternatively, hold down the **Delete** key while you *click* on the two free valences.) *Click* on ↓E and then on V.

---

* O. Chapman *et al*, *J. Am. Chem. Soc.*, **95**, 6134 (1973).

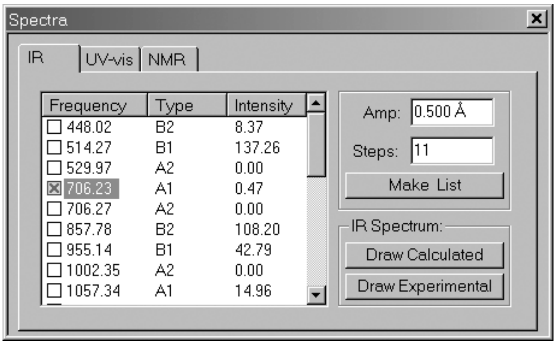
2. Enter the **Calculations** dialog (from the **Setup** menu). Select **Equilibrium Geometry** from the top menu to the right of **Calculate** and **Hartree-Fock** and **3-21G** from the two bottom menus. *Check* **IR** to the right of **Compute** in the center of the dialog. You have requested that an infrared spectrum be computed following optimization of geometry. *Click* on **Submit** and provide the name ***benzyne***.

3. While you are waiting for the calculation to complete, build 2-butyne, optimize its geometry with the same Hartree-Fock model and compute its infrared spectrum. Name the molecule ***2-butyne***. 2-butyne will serve as a standard with which to adjust the infrared spectrum of the benzyne.

4. When both calculations have completed, examine the geometry of benzyne. Does it incorporate a triple bond? Compare the length with that in 2-butyne.

> You should have two molecules on screen, benzyne and 2-butyne. Go between them by *clicking* on them in turn. All manipulations (except scaling) pertain only to the selected molecule. Likewise, all dialog operations pertain only to the selected molecule.

5. Select (*click* on) benzyne and then select **Spectra** from the **Display** menu. *Click* on the **IR** tab in the dialog that results to bring up the **IR Spectra** dialog.



Frequency	Type	Intensity
☐ 448.02	B2	8.37
☐ 514.27	B1	137.26
☐ 529.97	A2	0.00
☒ 706.23	A1	0.47
☐ 706.27	A2	0.00
☐ 857.78	B2	108.20
☐ 955.14	B1	42.79
☐ 1002.35	A2	0.00
☐ 1057.34	A1	14.96

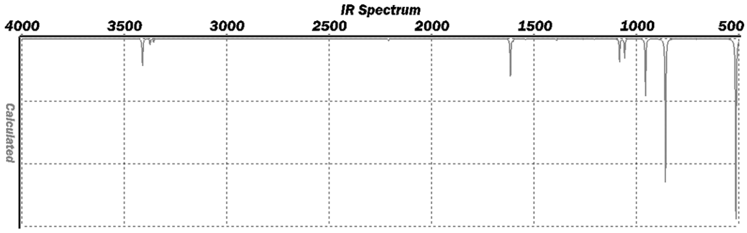
Amp: 0.500 Å

Steps: 11

One after the other, *check* the yellow boxes to the left of the frequencies in the dialog. In response, the vibrational motion associated with this frequency will be animated. Find the frequency which best fits the description of a C≡C stretch, and record its value. Do not close the **IR Spectra** dialog.

6. Select 2-butyne and find and record the frequency corresponding to the C≡C stretch. It should be on the order of 12% larger than the experimental frequency (2240 cm^{-1}) at this level of calculation.* Compute a scaling factor based on the ratio of measured to calculated frequencies, and apply this to the calculated frequency in benzyne. Is your (scaled) frequency in reasonable accord with the reported experimental value of 2085cm^{-1}?

7. Again, select benzyne and *click* on **Draw IR Spectrum** inside the **IR Spectra** dialog. The resulting spectrum is like any other graphical object in that it can be translated and zoomed using the usual mouse commands. (It cannot be rotated.) You need to *click* on the spectrum to select it. Locate the line corresponding to the C≡C stretch in the spectrum. Having done so, can you further comment one way or the other about the validity of the experimental result?



8. Close both molecules on screen together with any open dialogs.

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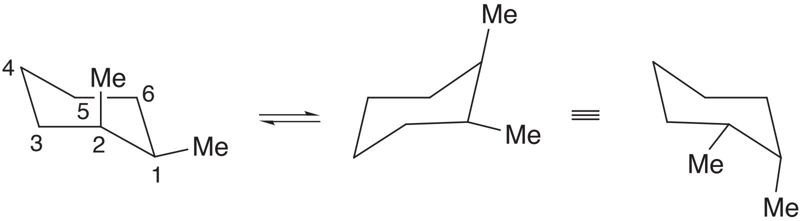
* Rationalization of this behavior together with performance statistics for a number of theoretical models available in ***Spartan*** is found in ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***.

^{13}C Spectrum of *cis*-1,2-Dimethylcyclohexane *(cannot be completed with the Essential Edition)*

At normal temperatures, the NMR spectrum of a conformationally-flexible molecule represents a (Boltzmann-weighted) average of the NMR spectra of all accessible conformers. Only when the temperature is lowered will the spectrum reveal its components, and its complexity. A particularly simple example is *cis*-1,2-dimethylcyclohexane, where there are only two equivalent conformers.



The room temperature ^{13}C spectrum contains only four lines at 34.9, 31.9, 24.2 and 16.4 ppm relative to TMS, corresponding to an equal weighting of C_1 and C_2, C_3 and C_6, and C_4 and C_5 and the two methyl carbons, respectively. Only when the sample is cooled sufficiently does the spectrum reveal eight distinct lines.

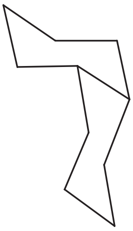
Here, you will calculate the (static) ^{13}C NMR spectrum of *cis*-1,2-dimethylcyclohexane, and then average chemical shifts for the three pairs of equivalent ring carbons to yield the observed (room temperature) spectrum. You will use the carbon shifts in cyclohexane as a standard (instead of TMS). Optionally, you will obtain a ^{13}C spectrum for *cis*-decalin to see to what extent it serves a model for static *cis*-1,2-dimethylcyclohexane.

1. Build and minimize *cis*-1,2-dimethylcyclohexane. Inside the **Calculations** dialog, specify calculation of equilibrium geometry using the Hartree-Fock 6-31G* model. *Check* **NMR** to the right of **Compute**, and submit the job. Name it ***cis-1,2-dimethylcyclohexane***.
2. Perform the same calculation (6-31G* equilibrium geometry and NMR spectrum) on cyclohexane (name it ***cyclohexane***). This will be used (in place of TMS) as the reference compound for the ring carbons in dimethylcyclohexane.

3. After the calculations have completed, record chemical shifts for all ring carbons in *cis*-1,2-dimethylcyclohexane, either from the **Atom Properties** dialog (select **Properties** from the **Display** menu and *click* on a carbon) or by labeling the model (select **Configure...** from the **Model** menu and *check* **Chem Shift** under **Atom** in the dialog which results). In the latter case, you may want to remove the hydrogens (select **Hydrogens** from the **Model** menu) to simplify the display. Also, obtain the ^{13}C shift in cyclohexane and compute a correction factor based on its difference to the measured shift (27.6 ppm) to be added to the *cis*-1,2-dimethylcyclohexane shifts. Finally, average the calculated chemical shifts to obtain a room temperature ^{13}C spectrum. How do the averaged ^{13}C shifts compare with measured values?

4 to 6 optional

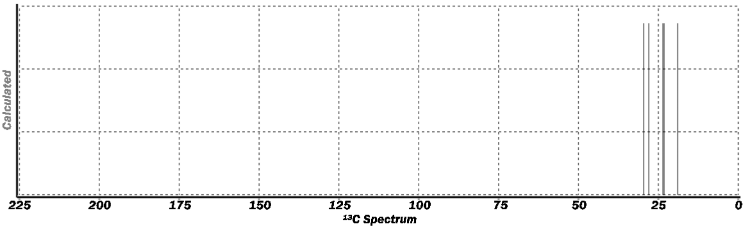
4. *cis*-Decalin is a reasonable model for static *cis*-1,2-dimethylcyclohexane, in that it is unable to undergo (rapid) ring inversion.



Build *cis*-decalin. Start with cyclohexane, add sp^3 carbons at adjacent *cis* free valences and connect these carbons by two additional sp^3 groups. Instead of calculating its equilibrium geometry, get it from the Spartan Molecular Database (SMD). *Click* on ▲ to the right of the name (***cis-decalin***) at the bottom of the screen to bring up the **SMD Preview** dialog. *Check* **6-31G*** and *click* on the **Replace** button at the bottom of the dialog. The SMD entry will replace the structure you built.

5. Enter the **Calculations** dialog. It should be set up for a single-point-energy calculation using the Hartree-Fock 6-31G* model. *Check* **NMR** to the right of **Compute** and *click* on **Submit** and supply the name ***cis-decalin***.

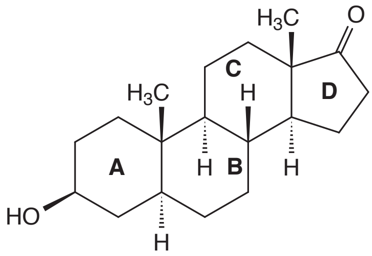
6. The calculation will require several minutes. When completed, select **Spectra** from the **Display** menu and *click* on the **NMR** tab. *Click* on **Draw ^{13}C Spectrum**. Because of the (C_2) symmetry of *cis*-decalin, your spectrum will contain only five lines, all of equal intensity. Relate these to the six lines corresponding to the ring carbons in static *cis*-1,2-dimethylcyclohexane. Pay particular attention to the differences in chemical shifts between carbons which average in the equilibrating molecule. Is *cis*-decalin a good model?



7. Close all molecules and any open dialogs.

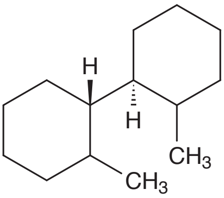
5 mins

Androsterone



Construction of the steroid androsterone illustrates a number of tactics involved in building complex organic molecules. It also provides a good opportunity to compare space-filling models and electron density surfaces as measures of molecular size and shape.

1. *Click* on 🗎. Select **Cyclohexane** from the **Rings** menu, and *click* anywhere on screen to create the A ring.
2. **Cyclohexane** is still selected. The icon at the top of the model kit should indicate **eq** (*equatorial*) rather than **ax** (*axial*); attachment needs to be made using an *equatorial* free valence. If not, *click* on the icon to switch to **eq**. *Click* on an *equatorial* free valence of the **A** ring to join it to the **C** ring. You have made bicyclohexane.
3. Rotate around the bond connecting the **A** and **C** rings to position the *axial* free valences on the connecting carbons opposite (180°) to each other. (This bond should be encircled by a red marker. If it is not, *click* on the bond.) To do so, hold down both the **Alt** key and the left button and *drag* the mouse up and down. *Equatorial* free valences on the cyclohexane carbons adjacent to those that connect the two rings are now positioned to form the **B** ring (in a chair geometry).
4. Select sp^3 carbon (>C-) and *click* on the two opposing *equatorial* free valences on the rings you have just joined. The resulting structure should appear as follows.



Click on ⚯ and, one after another, *click* on the (*equatorial*) free valences that nearly overlap to create the **B** ring. *Click* on ↓E. Check to see that all rings are chairs and that the stereochemistry is as in the figure in the previous page. If not, then you have probably made an error. You can start over (select **Clear** from the **Edit** menu), or undo the last operation you performed (**Undo** from the **Edit** menu).

5. Next, form the **D** ring starting from the carbon that will become a carbonyl group. Select **Carbonyl** from the **Groups** menu and *click* on the appropriate free valence on the **C** ring. Select sp^3 carbon (C-) from the model kit and *click* first on the single free valence on the carbonyl carbon and then on a free valence of the sp^3 carbon just added.

6. Form a five-membered ring (the **D** ring) by first *clicking* on ⚯ and then joining the free valence from the second sp^3 carbon added in the previous step and the appropriate *equatorial* free valence on the **C** ring. *Click* on ↓E.

7. Add two methyl groups. Select sp^3 carbon (C-) from the model kit. *Click* on the *axial* free valence at the appropriate juncture of the **C** and **D** rings, and then on the *axial* free valence at the proper juncture of the **A** and **B** rings.

8. Add the hydroxy group. Select sp^3 oxygen (O-) from the model kit, and *click* on the appropriate *axial* position on the **A** ring. *Click* on ↓E and then on V.

9. Androsterone incorporates several chiral centers. To assign them as R or S, select **Configure...** (**Model** menu) and *check* **R/S** under **Atom** in the dialog that appears. *Click* on **OK**. R/S labels will appear next to each of the chiral centers. (To remove the labels, select **Labels** from the **Model** menu.)

11. Select **Calculations...** from the **Setup** menu and specify calculation of an equilibrium geometry at the AM1 level. *Click* on **OK**. Submit. Name it ***androsterone***.

Compare the surface area and volume of a space-filling model to that obtained from an electron density surface.

12. Select **Properties** (**Display** menu). The **Molecule Properties** dialog provides both the surface area and the volume of a space-filling (CPK) model. Write down both values. Leave the **Molecule Properties** dialog on screen.
13. Select **Surfaces** (**Setup** or **Display** menu). *Click* on **Add**. Select **density** from the **Surface** menu and **none** from the **Property** menu, and *click* on **OK**. Leave the **Surfaces** dialog on screen. If you are using Macintosh or Linux versions, you need to select **Submit** from the **Setup** menu.
14. Graphical surface requests will be processed without having to submit the job. When completed, *click* on ***density...*** in the **Surfaces** dialog. *Click* on any portion of the density surface. The **Surface Properties** dialog which replaces the **Molecule Properties** dialog provides both the surface area and the volume of the electron density surface. How do these compare with quantities from the CPK model?
15. Remove ***androsterone*** and any remaining dialogs from the screen.

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* Windows only, **NAL**, **NAM**.

Chapter 5

Groups of Organic Molecules

This chapter introduces and illustrates a number of basic operations involved in processing groups of molecules, as well as the associated spreadsheet for organizing and fitting data and facilities for making plots.

Computational investigations like experimental investigations are rarely restricted to single molecules, but rather may involve a series of related molecules. Here, it may be of interest to compare geometries, energies or other calculated properties, or to compare trends in calculated and measured properties. ***Spartan*** provides facilities for these purposes. In particular, it allows molecules to be grouped, either manually, or automatically as a result of a conformational search, from following a particular vibrational motion, or from a scan of one or more geometrical variables. Once put into a group, molecules may be aligned based either on their structures or chemical functionalities. Calculations may be performed either on individual molecules or, just as simply, on the complete group of molecules.

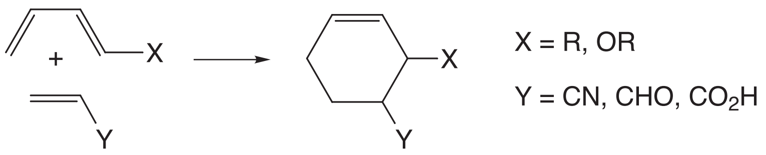
Associated with a group (including a group of one molecule) is a spreadsheet. This allows convenient access to virtually any calculated quantity. Additionally, data may be entered manually into the spreadsheet or transferred from another application such as Excel. Data in the spreadsheet may be manipulated, linear regression analyses performed and both 2D and 3D plots constructed. Alternatively, the data in a ***Spartan*** spreadsheet may be transferred to Excel for further analysis.

The tutorials in this chapter introduce a number of the basic group operations available in ***Spartan***. These include building a group from scratch, and processing groups resulting from a conformational search and from varying a torsion angle. Also provided is an example of fitting an experimental observable to one or more calculated properties by way of linear regression.

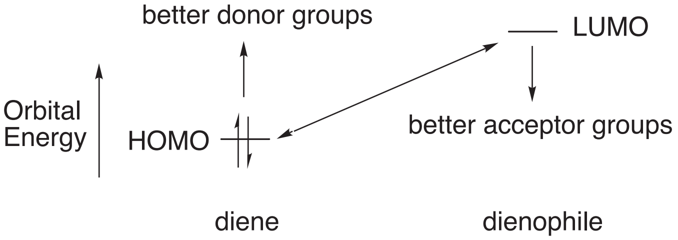
2 mins

Dienophiles in Diels-Alder Cycloadditions

The most common Diels-Alder reactions involve electron-rich dienes and electron-deficient dienophiles.



The rate of these reactions generally increases with increasing π-donor ability of the diene substituent, and with increasing π–acceptor ability of the dienophile substituent. This can be rationalized by noting that donor groups raise the energy of the highest-occupied molecular orbital (HOMO) on the diene, while acceptor groups lower the energy of the lowest-unoccupied molecular orbital (LUMO) on the dienophile. Thus, the HOMO-LUMO gap is reduced, leading to enhanced stabilization.



To test such an hypothesis, you will examine the extent to which experimental relative rates of Diels-Alder cycloadditions involving cyclopentadiene and a variety of cyanoethylenes correlate with dienophile LUMO energies.

1. Bring acrylonitrile that you previously constructed onto the screen. Select **Open...** from the **File** menu (or *click* on 📂), and *double click* on ***acrylonitrile*** in the file browser which results.* Place acrylonitrile onto the clipboard, by first drawing a selection box. Position the cursor slightly above and slightly to the left of the molecule then, while holding down on both left and

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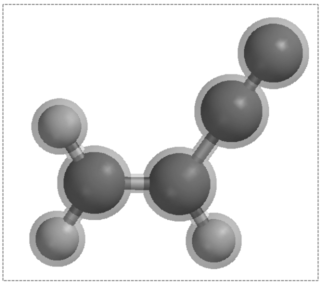
* If the electrostatic potential map is displayed, enter the **Surfaces** dialog (**Display** menu) and *click* on the line ***density potential...*** to turn it "off".

right buttons, *drag* the mouse to a position slightly below and slightly to the right of the molecule. Finally, release both buttons. Acrylonitrile will be surrounded by dotted lines (a selection box).



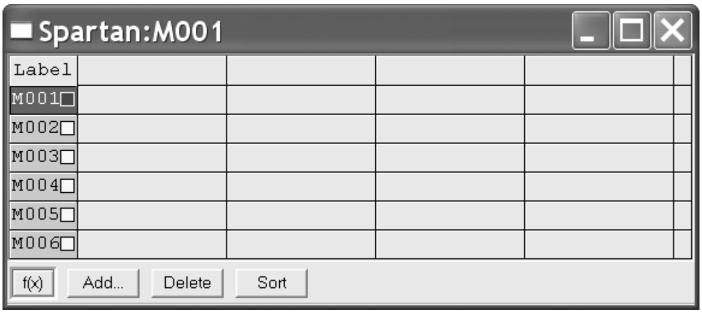
Select **Copy** from the **Edit** menu. Close acrylonitrile (📂).

2 Bring up the organic model kit (📄). *Click* on **Clipboard** at the bottom of the model kit. The structure of acrylonitrile that you copied to the clipboard will appear in a box at the top of the model kit. (You can manipulate this structure by positioning the cursor inside the box and using the usual mouse/keyboard commands.) *Click* anywhere on screen and acrylonitrile (the contents of the clipboard) will be drawn. *Click* on ↓E to produce a refined structure.

3. Select **New Molecule** from the **File** menu. This requests that a molecule that has yet to be built is to be appended onto the end of a group of molecules in which the currently selected molecule (acrylonitrile) is a member. The screen will be cleared. *Click* on **Clipboard** at the bottom of the model kit and *click* on screen. Acrylonitrile will appear. *Click* on **Groups** in the model kit, select **Cyano** and add to the appropriate free valence on acrylonitrile to make 1,1-dicyanoethylene. *Click* on ↓E.

4. Repeat this procedure (**New Molecule**, followed by **Clipboard**, followed by **Groups**, followed by ↓E) four more times to build *cis* and *trans*-1,2-dicyanoethylene, tricyanoethylene and tetracyanoethylene. When you are all done (six molecules in total), *click* on V to remove the model kit.

5. The molecules have been put into a single group, allowing calculated properties to be accessed via a spreadsheet. Select **Spreadsheet** from the **Display** menu.



To select individual molecules, *click* on their labels (**M001**, **...**) in the left hand column, or use the ◀ and ▶ keys at the bottom left of the screen. You may change the default labels to proper names (***acrylonitrile***, **...**) by directly typing in new names into cells under the **Label** column. *Press* the **Enter** key (**return** key on Mac) following each entry.

6. Enter the **Calculations** dialog (**Setup** menu), and specify an energy calculation using the Hartree-Fock 3-21G model. Select **AM1** from the **Start from** menu. This indicates that the 3-21G energy calculation is to be preceded by calculation of geometry using the AM1 model. Note, that **Global Calculations** is *checked*. This ensures that the calculations are to be applied to all members of the group (and not just the selected member).

7. Submit the job. Name it ***Diels-Alder dienophiles***. While you are waiting for it to complete, enter the experimental relative rates from the table below into the spreadsheet.

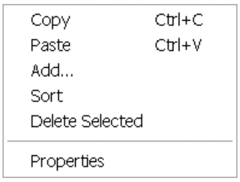
Experimental relative rates for Diels-Alder cycloadditions of cyclopentadiene[*]

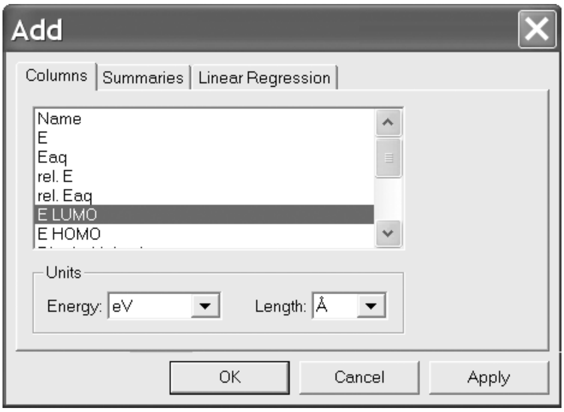
dienophile	**$\log_{10}$ (relative rate)**	**dienophile**	**$\log_{10}$ (relative rate)**
acrylonitrile	0	1,1-dicyanoethylene	4.64
trans-1,2-dicyanoethylene	1.89	tricyanoethylene	5.66
cis-1,2-dicyanoethylene	1.94	tetracyanoethylene	7.61

[*] J. Sauer, H. Weist and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).

First, type a title **Log(rate)=** into the header cell at the top of a blank column in the spreadsheet and *press* the **Enter** (**return**) key. Then enter the rate data in the appropriate cells. *Press* the **Enter** (**return**) key after each entry. Sort the group according to relative rate. *Click* on the column header **Log(rate)**, and then *click* on **Sort** at the bottom of the spreadsheet.

8. After all calculations are complete, *click* on a header cell at the top of a blank column. Then, *click* on **Add...** at the bottom of the spreadsheet. Alternatively, hold down the right mouse button while the cursor is positioned inside the spreadsheet, and select **Add...** from the menu which results.

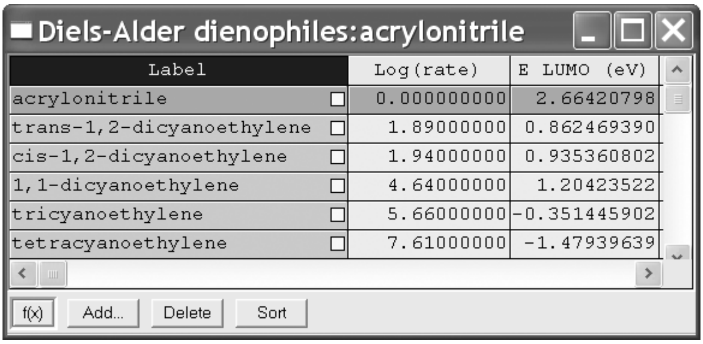

Copy Ctrl+C
Paste Ctrl+V
Add...
Sort
Delete Selected
Properties


Add
Columns
Summaries
Linear Regression
Name
E
Eaq
rel. E
rel. Eaq
E LUMO
E HOMO
Units
OK
Cancel
Apply

Energy: eV

Length: Å

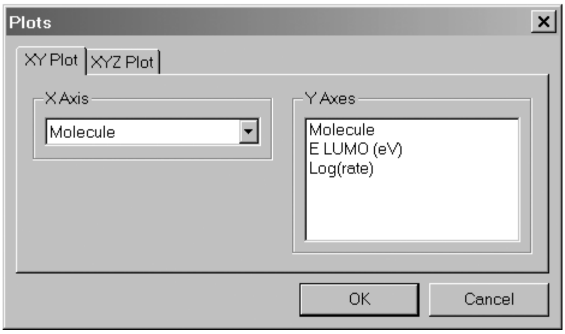
Select **E LUMO** from the list in the dialog that results and **eV** from the **Energy** menu. *Click* on **OK**.


Diels-Alder dienophiles:acrylonitrile
f(x)
Add...
Delete
Sort

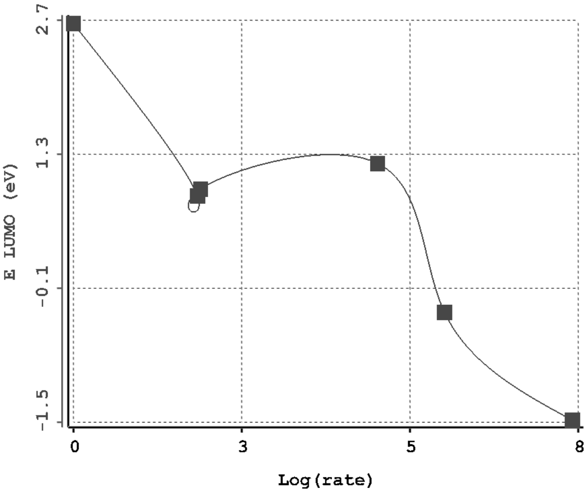
Label		Log(rate)	E LUMO (eV)
acrylonitrile	☐	0.000000000	2.66420798
trans-1,2-dicyanoethylene	☐	1.89000000	0.862469390
cis-1,2-dicyanoethylene	☐	1.94000000	0.935360802
1,1-dicyanoethylene	☐	4.64000000	1.20423522
tricyanoethylene	☐	5.66000000	-0.351445902
tetracyanoethylene	☐	7.61000000	-1.47939639

The spreadsheet has now served its purpose by collecting both calculated (LUMO energy) and experimental (relative rate) data for all six dienophiles. You can, if you wish, now remove it from the screen (*click* on ☒ at the top right).

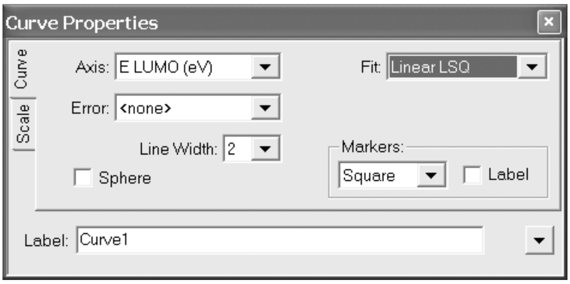
9. Select **Plots...** from the **Display** menu. This leads to the **Plots** dialog.



Make certain that the **XY Plot** tab at the top of the dialog is selected. Select **Log(rate)** from the list of items in the **X Axis** menu and **E LUMO(eV)** from the **Y Axes** list. *Click* on **OK** to remove the dialog and show the plot.



The default curve, a so-called cubic spline, smoothly connects the data points, but is of little value in establishing a correlation. A better representation is provided by a simple linear least-squares fit. Select **Properties** from the **Display** menu and *click* anywhere on the curve that you have just drawn. The **Curve Properties** dialog appears.


Curve Properties

Axis: E LUMO (eV)

Error: <none>

Line Width: 2

☐ Sphere

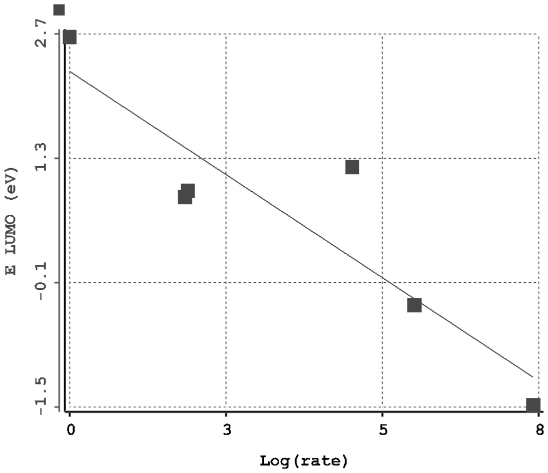
Fit: Linear LSQ

Markers: Square

☐ Label

Label: Curve1

Select **Linear LSQ** from the **Fit** menu. A new plot appears.

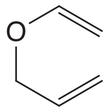


Note that there is a correlation between relative rates and LUMO energy.

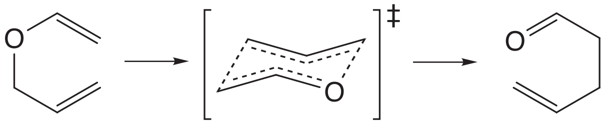
10. Remove all molecules and any remaining dialogs from the screen.

5 mins

Allyl Vinyl Ether



Allyl vinyl ether undergoes Claisen rearrangement, the mechanism for which demands a chair arrangement of the reactant.



Is this the lowest-energy conformer (global minimum) or is additional energy required to properly orient the molecule for reaction? To find out, you need to locate all the conformers of allyl vinyl ether, identify the best chair structure and evaluate its energy relative to that of the actual global minimum. You will first carry out a conformational search using the MMFF molecular mechanics model, and then obtain relative conformer energies using single-point 6-31G* Hartree-Fock calculations based on AM1 equilibrium geometries.

1. Bring up the organic model kit and construct allyl vinyl ether (in any conformation) from a sequence of sp^2 and sp^3 carbons and an sp^3 oxygen. *Click* on ↓E to produce a refined geometry. *Click* on ✓.
2. Bring up the **Calculations** dialog and select **Conformer Distribution** from the top menu to the right of **Calculate** and **Molecular Mechanics** and **MMFF** from the two bottom menus. *Click* on **OK**.
3. Submit the job. Name it ***allyl vinyl ether***. When completed, it will give rise to a series of low-energy conformers* placed in a new file ***allyl vinyl ether.M001***.** Open this file.*** Select

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* By default, only conformers within 40 kJ/mol of the global minimum will be kept. This can be changed (see **Conformational Search** in **Appendix C**).

** **M001** is the default label of the molecule you built. You can change it by altering the **Labels** field in the **Molecule Properties** dialog (**Properties** under the **Display** menu; **Chapter 15**).

*** The Macintosh version automatically opens the resulting file (**NAW**, **NAL**). To avoid confusion, it is a good idea to close the original file ***allyl vinyl ether***.

Spreadsheet from the **Display** menu.

Size the spreadsheet such that all rows (corresponding to different conformers) are visible at one time. *Click* on **Add...** at the bottom of the spreadsheet. Select **E** from the list at the top of the dialog which appears, **kJ/mol** from the **Energy** menu and *click* on **OK**. Energies for each of the different conformers will be added to the spreadsheet. Examine the lowest-energy conformer (the top entry). Is it in a chair conformation suitable for Claisen rearrangement? If not, identify the lowest-energy conformer which is suitable. You can keep two or more conformers on screen at the same time by *checking* the boxes immediately to the right of the molecule labels (the leftmost column) in the spreadsheet. To get a clearer idea of structural similarities and differences, align the conformers. Select **Align** from the **Geometry** menu (or *click* on the icon at the top of the screen) and select **Structure** from the **Align by** menu at the bottom right of the screen. A message will appear at the bottom left of the screen.

Select atoms.

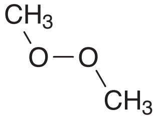
Click on the two carbons of the vinyl group and on the oxygen to designate them as alignment centers. Each will be marked by a red circle. If you make a mistake, *click* on the circle and it will disappear. When you are done, *click* on the **Align by** button at the bottom right of the screen. *Click* on ✓.

4. To obtain a better estimate of conformational energy differences, perform 6-31G* energy calculations using AM1 geometries. Make a copy of ***allyl vinyl ether.M001*** (💾), and name it ***allyl vinyl ether Hartree-Fock***. Using the copy, delete all conformers except the global minimum and the lowest-energy conformer poised for Claisen rearrangement. Select each conformer to be discarded, and then select **Delete Molecule** from the **File** menu. Alternatively, *click* on the cell in the spreadsheet containing the label for the molecule to be deleted, and then *click* on **Delete** at the bottom of the spreadsheet. When you are done, the spreadsheet should contain only two entries.

5. Enter the **Calculations** dialog, and specify calculation of an energy using the Hartree-Fock 6-31G* model. Also, specify **AM1** from the **Start from** menu. Make certain that **Global Calculations** at the bottom of the dialog is checked to specify that the dialog settings apply to both conformers.
6. Submit the job. When completed, examine the conformer energies. How much energy is needed to go from the global minimum to a conformer poised to undergo Claisen rearrangement?
7. Remove all molecules and any remaining dialogs from the screen.

30 mins/40 mins

Internal Rotation in Dimethylperoxide



Quantum chemical calculations, in particular, Hartree-Fock molecular orbital calculations, density functional calculations and MP2 calculations, may be called on to furnish data to parameterize empirical energy functions for use in molecular mechanics and/or molecular dynamics calculations. Most important are data relating to torsional motions, for it is here that experimental data are most scarce. Note that the empirical energy function needs to reflect the inherent periodicity. One suitable choice is a truncated Fourier series.

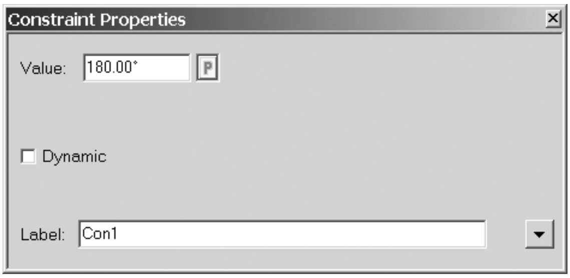
$$E^{torsion}(\omega) = k^{torsion1}(1 - \cos(\omega - \omega^{eq})) + k^{torsion2}(1 - \cos 2(\omega - \omega^{eq})) + k^{torsion3}(1 - \cos 3(\omega - \omega^{eq}))$$

Here, ω^{eq} is the ideal dihedral angle and $k^{torsion1}$, $k^{torsion2}$ and $k^{torsion3}$ are parameters. The first (one-fold) term accounts for the difference in energy between *syn* and *anti* conformers, the second (two-fold) term for the difference in energy between planar and perpendicular conformers, and the third (three-fold) term for the difference in energy between eclipsed and staggered conformers.

In this tutorial, you will generate a potential energy function for rotation about the oxygen-oxygen bond in dimethylperoxide using 6-31G* Hartree-Fock calculations (and optionally from B3LYP/6-31G* density functional calculations) and then fit this potential to a truncated Fourier series.

1. Build dimethylperoxide. If the molecule is not already in an *anti* conformation, *click* on ? and set the COOC dihedral angle to **180** (180°) by *typing* **180** in the box at the lower right of the screen and *pressing* the **Enter** key (**return** key on Mac). ***Do not minimize***.
2. Select **Constrain Dihedral** from the **Geometry** menu (or *click* on the 🔒 icon at the top of the screen). Select the COOC torsion, and then *click* on 🔓 at the bottom right of the screen.

The icon will change to 🔒 indicating that a dihedral constraint is to be applied. Select **Properties** (**Display** menu) and *click* on the constraint marker on the model on screen. This leads to the **Constraint Properties** dialog.

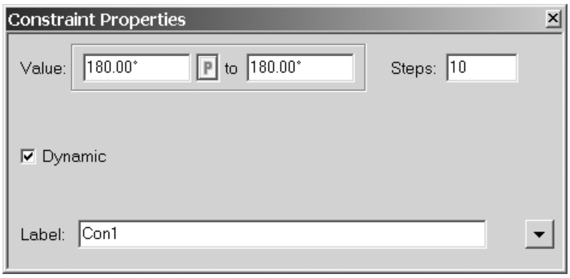


Value: 180.00°

☐ Dynamic

Label: Con1

3. *Check* **Dynamic** inside the dialog. This leads to an extended form of the **Constraint Properties** dialog that allows the single (dihedral angle) constraint value to be replaced by a sequence of constraint values.



Value: 180.00° to 180.00° Steps: 10

☑ Dynamic

Label: Con1

Leave **180** (180°) in the box to the right of **Value** alone, but change the contents of the box to the right of **to** to **0** (0°). You need to *press* the **Enter** key after you type in the value. **Steps** should be **10**. (If it is not, *type* **10** and *press* the **Enter** key.) What you have specified is that the dihedral angle will be constrained first to 180°, then to 160°[*], etc. and finally to 0°. *Click* on ☒ to dismiss the dialog.

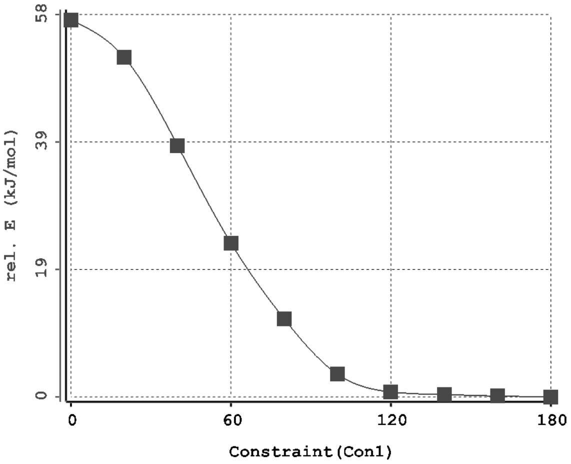
4. Bring up the **Calculations** dialog and select **Energy Profile** from the top menu to the right of **Calculate**, and **Hartree-Fock** and **6-31G*** from the two bottom menus. *Click* on **OK** and submit the job. Name it ***dimethylperoxide***.

---

[*] The difference between constraint values is given by: (final-initial)/(steps-1).

5. When the calculations have completed, they will go into a file named ***dimethylperoxide.M001***. Open this file.* Align the conformers. *Click* on ≋, select **Structure** from the **Align by** menu at the bottom right of the screen and, one after the other, *click* on both oxygens and on one of the carbons. Then *click* on the **Align by** button at the bottom right of the screen. Bring up the spreadsheet (**Display** menu), and enter both the energies relative to the 180° conformer, and the COOC dihedral angles. First *click* on the label (**M001**) for the top entry in the spreadsheet (the 180° conformer), then *click* on the header cell for the leftmost blank column, and finally, *click* on **Add...** at the bottom of the spreadsheet. Select **rel. E** from the quantities in the dialog that results, **kJ/mol** from the **Energy** menu and *click* on **OK**. To enter the dihedral angle constraints, *click* on 🔒, *click* on the constraint marker attached to dimethylperoxide and *click* on P at the bottom of the screen (to the right of the value of the dihedral angle). *Click* on ✓.

6. Select **Plots...** (**Display** menu). Select **Constraint(Con1)** from the **X Axis** menu and **rel. E(kJ/mol)** from the **Y Axes** list. *Click* on **OK**.

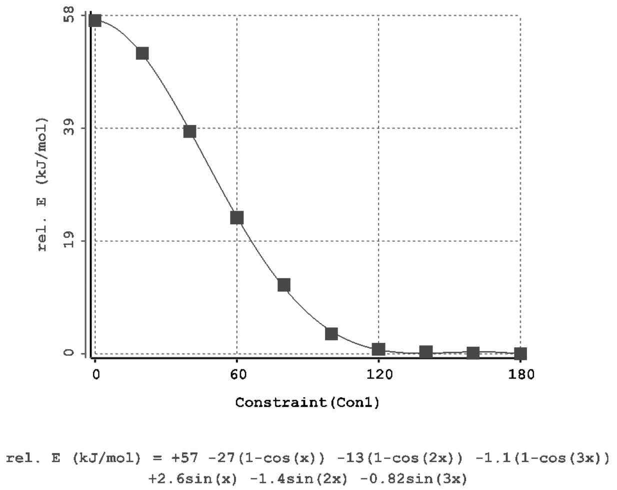


The curve (a so-called cubic spline) smoothly connects the data points. To fit the points to a Fourier series, bring up the

---

* The Macintosh version automatically opens the resulting file (**NAW**, **NAL**).

Properties dialog (**Display** menu) and *click* anywhere on the plot. Select **Fourier LSQ** from the **Fit** menu and *click* on ☒ to remove the dialog. A new plot appears.



rel. E (kJ/mol) = +57 -27(1-cos(x)) -13(1-cos(2x)) -1.1(1-cos(3x)) +2.6sin(x) -1.4sin(2x) -0.82sin(3x)

The actual fit expression appears at the bottom of the plot.

7 and 8 optional ***(cannot be completed with the Essential Edition)***

7. Use energies from B3LYP/6-31G* density functional calculations, together with the Hartree-Fock geometries to provide a better fitting function. First, make a copy of ***dimethylperoxide.M001***. Name it ***dimethylperoxide density functional***. Next, enter the **Calculations** dialog and specify calculation of energies using the B3LYP/6-31G* density functional model. Make certain that **Global Calculations** (at the bottom of the dialog) is *checked* to signify that energy calculations are to be performed on all conformers.

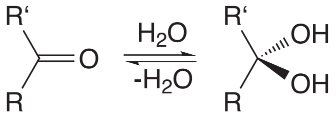
8. Submit the job. It will require several minutes to complete. When it is done, draw a new energy plot and compare it to the energy plot produced earlier.

9. Remove all molecules and any remaining dialogs from the screen.

30 mins

Hydration of Carbonyl Compounds

The hydration of carbonyl compounds has been extensively studied primarily because it serves as a model for a number of important reactions, nucleophilic addition to carbonyl compounds among them.



$$K_{eq} = \frac{[\text{hydrate}]}{[H_2O]\,[\text{carbonyl}]} = \frac{[\text{hydrate}]}{55.5\,[\text{carbonyl}]}$$

Experimental K_{eq} for hydration of carbonyl compounds[*]

	$\log(k_{eq}/55.5)$		$\log(k_{eq}/55.5)$
$PhCOCH_3$	-6.8	CF_3COCH_3	-0.2
CH_3COCH_3	-4.6	$PhCOCF_3$	0.1
PhCHO	-3.8	H_2CO	1.6
t-BuCHO	-2.4	CF_3CHO	2.7
CH_3CHO	-1.7	CF_3COCF_3	4.3

[*] J.P. Guthrie, Can. J. Chem., **53**, 898 (1975); **56**, 962 (1978).

In this tutorial, you will use ***Spartan's*** linear regression analysis tool to correlate calculated properties of carbonyl compounds with measured equilibrium constants for their hydration.

1. Build the compounds[*] listed above. Use **Carbonyl** (**Groups** menu) as a starting point for each to ensure consistent atom numbering. Put in one list; select **New Molecule** following construction of each molecule, that is, build and minimize acetophenone, select, **New Molecule**, build and minimize acetone, select **New Molecule**, etc. *Click* on V.
2. Enter the **Calculations** dialog and specify calculation of equilibrium geometry using the Hartree-Fock 3-21G model.[**]

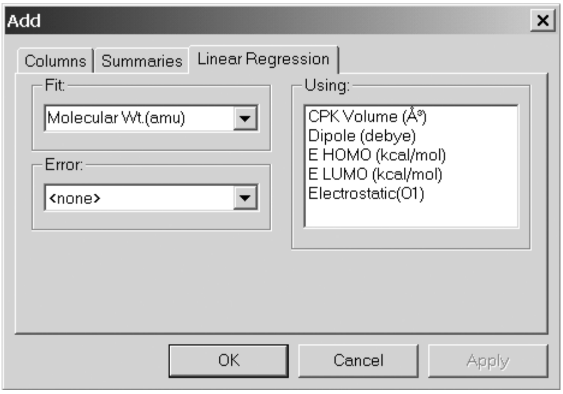
---

[*] Keep the phenyl ring and the carbonyl group coplanar for benzaldehyde, acetophenone and trifluoroacetophenone.

[**] You can save computer time by specifying calculation of an energy using the Hartree-Fock 3-21G model, and then selecting AM1 from the **Start from** menu. This requests a semi-empirical AM1 geometry in place of the 3-21G geometry. As all of these molecules are in SMD, you can save even more time by bringing up the **SMD Preview** dialog (*click* on ▲ at the bottom right of the screen), *clicking* on the yellow square to the left of 3-21G and then *clicking* on **Replace All** at the bottom of the dialog. In this case, skip the calculation step as all the results you require are already available.

Make certain that **Global Calculations** is *checked*. *Click* on **Submit**. Name the job ***carbonyl compounds***.

3. While you are waiting for the calculations to complete, bring up the spreadsheet. *Click* inside the header cell of an empty column, *type* **Log(Keq)** and *press* the **Enter** key (**return** key on Mac). Then enter the experimental equilibrium constants into the appropriate cells. You need to *press* the **Enter** (**return**) key following each data entry. Sort the list according to the value of Log(Keq). *Click* inside the header cell **LogKeq** and then *click* on **Sort** at the bottom of the spreadsheet. If you like, replace the labels in the spreadsheet (***M001***, ...) by correct names (***acetophenone***, ...).
4. After the calculations have completed, *click* inside the header cell for an empty column, and then *click* on **Add...** at the bottom of the spreadsheet. Select (*click* on) the following quantities in the dialog: **E LUMO**, **E HOMO**, **Dipole**, **CPK Volume** and **Molecular Weight**. *Click* on **OK**.
5. Select **Properties** (**Display** menu) and *click* on the oxygen atom for whatever compound is displayed. *Click* on P to the left of **Electrostatic** (under **Charges**) in the **Atom Properties** dialog (that has replaced the **Molecular Properties** dialog), to place oxygen charges into the spreadsheet.
6. *Click* on **Add...** at the bottom of the spreadsheet, and then *click* on the **Linear Regression** tab at the top of the dialog that results. This brings up the **Add Linear Regression** dialog.

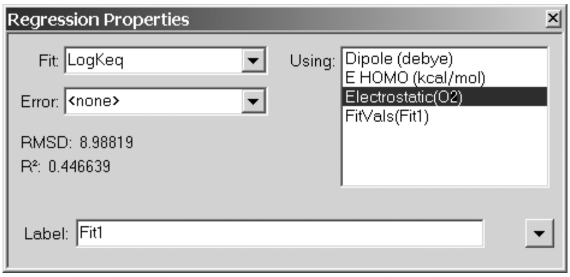


Fit: Molecular Wt.(amu)

Error: <none>

Using:
CPK Volume (Å^3)
Dipole (debye)
E HOMO (kcal/mol)
E LUMO (kcal/mol)
Electrostatic(O1)

Select **Log(Keq)** from the **Fit** menu and **Electrostatic (OX)**[*] from the **Using** list. *Click* on **OK**. Two new rows will be added at the bottom of the spreadsheet. With a **Properties** dialog on screen, *click* anywhere on the row in the spreadsheet labelled **Fit1** (the first fit performed on this data set). The **Regression Properties** dialog appears.


Regression Properties

Fit: LogKeq

Error: <none>

RMSD: 8.98819

R²: 0.446639

Using: Electrostatic(O2)

Label: Fit1

This provides information about the fit of Log(Keq) to the charge on oxygen, in particular, the value of R^2. This will tend to unity as the quality of the fit improves.

7. Inside the **Regression Properties** dialog, try fitting to different (single) properties in the **Using** list. (The entries toggle “on” and “off” with repeated *clicking*.) Maximize the value of R^2. Next, try all combinations of two properties. The combination of **E LUMO** and **Electrostatic (OX)** should give the highest value of R^2. With this combination selected, bring up the **Plots** dialog (**Display** menu) and select **Log(Keq)** from the **X Axis** menu, and **FitVals (Fit1)** from the **Y Axes** list and *click* on **OK**. Next, *click* on the curve (not on the axes) to bring up the **Curve Properties** dialog (which replaces the **Regression Properties** dialog). Select **Linear LSQ** (to replace **Cubic Spline**) from the **Fit** menu. The resulting plot should show good correlation.

8. Close ***carbonyl compounds*** and remove any remaining dialogs from the screen.

---

[*] Numbering depends on the order that atoms were introduced during building, but the reference is to the carbonyl oxygen.

10 mins

Acidities of Carboxylic Acids

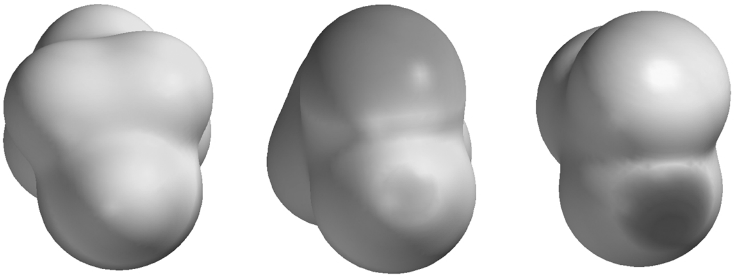
Acid strength is among the most important molecular properties. It is readily available from calculation, either in terms of absolute deprotonation energy,

$$\mathrm{AH} \longrightarrow \mathrm{A^-} + \mathrm{H^+}$$

or, more commonly, as the deprotonation energy relative to that of some standard acid (A°H).

$$\mathrm{AH} + \mathrm{A^{\circ -}} \longrightarrow \mathrm{A^-} + \mathrm{A^{\circ}H}$$

An alternative measure of (relative) acid strength is the value of the electrostatic potential in the vicinity of the acidic hydrogen in the neutral acid. Electrostatic potential maps are known to uncover gross trends in acidity, for example, the acidic hydrogen in a strong acid, such as nitric acid, is more positive than that in a weak acid, such as acetic acid, which in turn is more positive than that in a very weak acid, such as ethanol.



ethanol acetic acid nitric acid

In this tutorial, you will explore the use of electrostatic potential maps to quantify changes in acid strength due to subtle variations in structure. You will use the Spartan Molecular Database of calculated structures, energies and properties may be used to shorten the time required for an investigation.

1. One after the other, build trichloroacetic, dichloroacetic, chloroacetic, formic, benzoic, acetic and pivalic acids. Put all molecules into the same document (use **New Molecule** from the **File** menu following the first molecule). *Click* on ✓ when you are done.

2. All of the molecules that you have built are available in the Spartan Molecular Database. *Click* on ▲ to the left of the name of the presently selected molecule at the bottom of the screen. The **SMD Preview** dialog will appear. This displays the structure of the selected molecule on the left and a list of theoretical models for which calculated results are available on the right. *Check* the yellow square to the left of **3-21G** and *click* on **Replace All** at the bottom of the dialog. Structures obtained from Hartree-Fock 3-21G calculations will replace those you have built. However, you need to calculate a wavefunction for each of the molecules in order to produce electrostatic potential maps.

3. Enter the **Calculations** dialog (**Setup** menu). Request a Hartree-Fock 3-21G energy calculation, and make certain that **Global Calculations** is checked. *Click* on **OK**. Enter the **Surfaces** dialog (**Setup** menu). Make certain that **Global Surfaces** at the bottom of the dialog is checked. *Click* on **Add...** at the bottom of the dialog, select **density** from the **Surface** menu and **potential** from the **Property** menu (**medium** from the **Resolution** menu) in the **Add Surface** dialog that appears and then *click* on **OK**. Leave the **Surfaces** dialog on screen. Submit the job (**Submit** from the **Setup** menu). Name it ***carboxylic acids***.

4. While you are waiting for the calculations to complete, bring up the spreadsheet (**Spreadsheet** from the **Display** menu). Expand it so that you can see all seven molecules, and that three data columns are available. *Click* inside the header cell of a blank column. *Click* on **Add...** at the bottom of the spreadsheet, select **Name** from the list of entries and *click* on **OK**. The name of each molecule will appear. Next, *click* inside the header cell of the next available data column, *type* **pKa** and *press* the **Enter** key (**return** key on Mac). Enter the experimental pK_a's (given on the next page) into the appropriate cells under this column. You need to *press* the **Enter** (**return**) key following each entry.

acid	pK_a	acid	pK_a
trichloroacetic (Cl_3CCO_2H)	0.7	benzoic ($C_6H_5CO_2H$)	4.19
dichloroacetic (Cl_2CHCO_2H)	1.48	acetic (CH_3CO_2H)	4.75
chloroacetic ($ClCH_2CO_2H$)	2.85	pivalic ($(CH_3)_3CCO_2H$)	5.03
formic (HCO_2H)	3.75		

Experimental data from: E.P. Sargeant and B. Dempsey, ***Ionization Constants of Organic Acids in Aqueous Solution***, IUPAC no. 23, Permagon Press, 1979.

5. After all calculations have completed, arrange the seven molecules on screen such that you can clearly see the acidic hydrogen on each. To display all molecules at once, *check* the box on the right hand side of the **Label** column (in the spreadsheet) for each entry. To manipulate them independently of one another, select **Coupled** from the **Model** menu.

6. Bring up the **Surfaces** dialog (**Setup** or **Display** menu) and select **density...** to turn on the electrostatic potential map for each molecule. Bring up the **Properties** dialog (**Display** menu) and *click* on P to the right of **Maximum**. The maximum value of the electrostatic potential (corresponding to the acidic proton) will be pasted to the spreadsheet.

7. Plot experimental pK_a vs. maximum in the electrostatic potential. Bring up the **Plots** dialog (**Display** menu), select **pKa** under the **X Axis** menu and **Property Max (Surface)** from the **Y Axes** list, and *click* on **OK**. The data points are connected by a smooth curve (a so-called cubic spline). To get a least squares fit, select **Properties** from the **Display** menu, *click* on the curve, and select **Linear LSQ** from the **Fit** menu in the **Curve Properties** dialog.

8. Close ***carboxylic acids*** and any remaining dialogs from the screen.

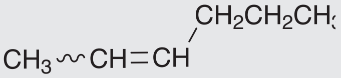
30 mins

Stereochemical Assignments from ^{13}C Spectra *(cannot be completed with the Essential Edition)*

NMR spectroscopy, in particular ^{13}C spectroscopy, is without doubt the method of choice to establish the three-dimensional structure of organic molecules. Only X-ray diffraction provides more definitive results, although the requirement of a crystalline sample severely limits its application. It is now practical to routinely calculate the NMR spectra of organic molecules. In time, the availability of a "virtual NMR spectrometer" will offer organic chemists an entirely new paradigm for structure determination, that is direct comparison of a measured spectrum with calculated spectra for one or more chemically reasonable candidates.

Here, you will obtain ^{13}C chemical shifts for *cis* and *trans* stereoisomers of 2-hexene and *endo* and *exo* stereoisomers of 2-methylnorbornane, and compare these to experimental shifts. The Hartree-Fock 6-31G* model will be employed, but you will get all structures from the Spartan Molecular Database. You will establish the extent to which the calculations are able to reproduce differences in chemical shifts as a function of stereochemistry.

1. Build *cis*-2-hexene. *Click* on ▲ at the bottom of the screen (to the left of the molecule name), *check* the box to the left of the **6-31G*** in the **SMD Preview** dialog that appears and *click* on **Replace**. ***Do not minimize***. Select **New Molecule** from the **File** menu, build *trans*-2-hexene, *check* the box to the left of **6-31G*** in the preview dialog and *click* on **Replace**. ***Do not minimize***. *Click* on ✓.
2. Enter the **Calculations** dialog and specify a Hartree-Fock energy calculation using the 6-31G* basis set. *Check* **NMR** to the right of **Compute**. Submit the job with the name ***2-hexene***.
3. When completed, examine the ^{13}C chemical shifts, either from the **Atom Properties** dialog or as atom labels (**Configure...** under the **Model** menu and *check* **Chem Shift** under **Atom** in the dialog which results). Compare them to measured values with particular attention to the difference in shifts between *cis* and *trans* stereoisomers.



	cis	*trans*	Δ
C_1	11.4	16.5	5.1
C_2	122.8	123.9	1.1
C_3	129.7	130.6	0.9
C_4	28.2	34.1	5.9
C_5	21.4	22.1	0.7
C_6	12.5	12.5	0.0

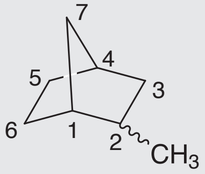
Do the calculations distinguish between the two isomers?

4. Close ***2-hexene***.

5. Build *endo*-2-methylnorbornane. As you did for 2-hexene, replace your structure with the (6-31G*) structure in the Spartan Molecular Database. Select **New Molecule** (**File** menu) and repeat the process for the *exo* isomer. *Click* on V.

6. Inside the **Calculations** dialog, specify a Hartree-Fock 6-31G* energy calculation, and *check* **NMR** (to the right of **Compute**). Submit the job with the name ***2-methylnorbornane***.

7. When completed, compare the ^{13}C chemical shifts with experimental values with particular attention to differences between *endo* and *exo* stereoisomers.



	endo	*exo*	Δ
C_1	11.4	16.5	5.1
C_1	11.4	16.5	5.1
C_1	43.5	42.2	-1.3
C_2	36.8	34.6	-2.2
C_3	40.2	40.7	0.5
C_4	37.3	38.2	0.9
C_5	30.3	30.6	0.3
C_6	29.0	22.4	-6.6
C_7	35.0	38.9	3.9
CH_3	22.3	17.4	-4.9

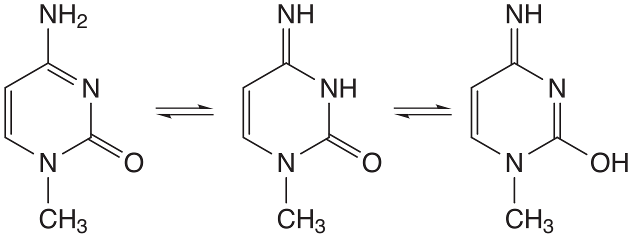
Do the calculations distinguish between the two isomers?

8. Close ***2-methylnorbornane***.

5 mins/30 mins

Tautomers of Nucleotide Bases

Protons bound to heteroatoms in heterocyclic compounds are likely to be very mobile in solution and, where two or more heteroatoms are present in a structure, different isomers (tautomers) may be in equilibrium. As a case in point, consider the nucleotide base cytosine (where a methyl group has replaced the sugar-phosphate backbone).



The existence of a low-energy tautomer could have far-reaching consequences, given that the valence structure of cytosine is key to hydrogen bonding in DNA. In this tutorial, you will examine the possible tautomers of 1-methylcytosine for evidence of low-energy structures.*

1. Build 1-methylcytosine. Start with **Amide** from the **Groups** menu. Select planar trigonal nitrogen for the external amino group. Minimize (to C_s symmetry) and *click* on V.
2. Note that the word **Tautomer** appears at the bottom right of the screen, indicating that tautomers exist. Select **Tautomers** from the **Search** menu (or *click* on the icon at the top of the screen). Step through the tautomers using the ◀ and ▶ keys that appear at the bottom right of the screen. To put the tautomers in a list, *click* on ▾ at the bottom right of the screen and *click* on **OK** in the dialog that results.
3. Enter the **Calculations** dialog with the list of tautomers (close the molecule you built to get the tautomers). Specify calculation

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* Note, however, that were the energy of an alternative tautomer only 10 kJ/mol higher than that for the normal structure, this would translate into a relative abundance of only about 1% at room temperature. Thus, any alternative tautomers would need to be very close in energy to the lowest-energy tautomer to have noticeable effect.

of equilibrium geometry using the 3-21G Hartree-Fock model. Submit the job with the name ***cytosine tautomers***.

4. After the calculations have completed, bring up the spreadsheet and *click* on the line corresponding to the structure for cytosine that you originally built. *Click* on **Add** at the bottom of the spreadsheet, select **rel.E** and **Boltzmann** from the available quantities and **kJ/mol** from the **Energy** menu and *click* on **OK**. Are either of the alternatives close in energy to the normal form of cytosine?

5 and 6 optional *(cannot be completed with the Essential Edition)*

To get a better estimate of relative tautomer energies, perform energy calculations using the RI-MP2/6-31G* model.

5. Make a copy of ***cytosine tautomers***. Name it ***cytosine tautomers RI-MP2***. Enter the **Calculations** dialog (**Setup** menu) with this copy. Specify **Energy** from the top menu to the right of **Calculate** and **RI-MP2** and **6-31G*** from the two bottom menus. Submit the job.

6. When the calculations have completed, bring up the spreadsheet and again examine relative tautomer energies and Boltzmann populations. Are either of the alternative structures competitive?

7. Remove all molecules and remaining dialogs from the screen.

Chapter 6

Organic Reactions

This chapter outlines and illustrates strategies for locating and verifying transition states for organic reactions as well as for exploring changes in product distributions as a function of substituents and reactant stereochemistry.

The treatment of chemical reactions adds an entirely new dimension to the application of quantum chemical models. Whereas unique valence structures may generally be written for most molecules and, based on these structures, reasonable guesses at bond lengths and angles may be made, it is often difficult to designate appropriate valence structures for transition states, let alone specify detailed geometries. This is, for the most part, due to a complete absence of experimental data on the structures of transition states. However, calculated transition-state geometries are now commonplace. ***Spartan*** provides both an extensive library of calculated transition states and a facility for automatically matching an entry in this library with the reaction at hand.* This library is also available as the Spartan Reaction Database (SRD), and may be searched by substructure to yield all available transition states of reactions related to the one of interest.

Spartan also provides a procedure for driving user-defined coordinates. Aside from conformational analysis (see discussion in previous chapter), the major application of this is to force reactions, thereby permitting identification of transition states.

The first four tutorials in this chapter illustrate ***Spartan's*** automatic procedure for guessing transition state geometries based on its library of organic reactions. The last two of these show how a transition state for one reaction may be used to provide a good guess at the transition state of a closely-related reaction. These tutorials also illustrate the use of vibrational analysis (infrared spectroscopy) to verify that a particular structure corresponds to a transition state and to show the motion connecting it to reactants and products. The fifth tutorial illustrates how a reaction may be “driven” through a transition state. This tutorial, along with the fourth tutorial, draw the connection between relative activation energies and kinetic product distributions. The last tutorial in this chapter illustrates how transition states may be extracted from the Spartan Reaction Database.

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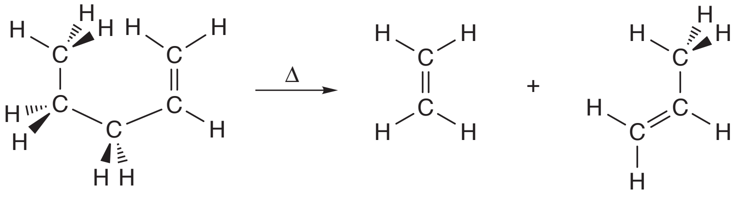
* Where a reaction is unknown to ***Spartan's*** library, a fallback technique which averages reactant and product geometries (similar to the so-called linear synchronous transit method) is invoked.

An example of a transition state calculation for an organometallic reaction is provided in **Chapter 9**.

10 mins/20 mins

Ene Reaction of 1-Pentene



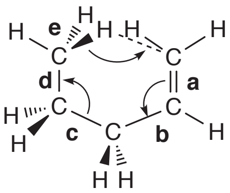
1-pentene ethylene propene

The proposed mechanism of the ene reaction involves simultaneous transfer of a hydrogen atom and CC bond cleavage. Here, you will obtain the transition state for the ene reaction of 1-pentene from 3-21G Hartree Fock calculations, and examine the reaction coordinate for evidence of concerted motion. Optionally, you will perform B3LYP/6-31G* density functional energy calculations to estimate the activation energy for the reaction.

1. Bring up the organic model kit and build 1-pentene in a conformation in which one of the terminal hydrogens on the ethyl group is poised to transfer to the terminal methylene group. Minimize (*click* on) and *click* on .

2. First, save 1-pentene as ***1-pentene density functional*** for optional use later ()*. Also make a copy for immediate use; name it ***ene reaction 1-pentene***.

3. Select **Transition States** from the **Search** menu (or *click* on the icon at the top of the screen). *Click* on bond **a** in the figure on the following page and then *click* on bond **b**. A curved arrow from bond **a** to bond **b** will be drawn.



Next, *click* on bond **c** and then on bond **d**. A second curved arrow from bonds **c** to **d** will be drawn. Finally, *click* on bond **e** and, while holding down the **Shift** key, *click* on the (methyl) hydrogen to be transferred and on the terminal (methylene) carbon to receive this hydrogen. A third curved arrow from bond **e** to the center of a dotted line that has been drawn between the hydrogen and oxygen will appear.

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* This is not necessary for users of the essential edition of ***Spartan***, where density functional models are not available.

If you make a mistake, you can remove an arrow by selecting **Delete** from the **Build** menu (*click* on ⁜) and then *clicking* on the arrow. (You will need to select ↷ to continue.) Alternatively, hold down the **Delete** key as you *click* on an arrow. With all three arrows in place, *click* on ⟳ at the bottom right of the screen. Your structure will be replaced by a guess at the ene transition state. If the resulting structure is unreasonable, then you have probably made an error in the placement of the arrows. In this case, select **Undo** from the **Edit** menu to return to the model with the arrows and modify accordingly.

4. Enter the **Calculations** dialog (**Setup** menu), and specify calculation of transition-state geometry using the 3-21G Hartree-Fock model. Select **Transition State Geometry** from the top menu to the right of **Calculate** and **Hartree-Fock** and **3-21G** from the two bottom menus. Also, *check* **IR** to the right of **Compute**. This will allow you to confirm that you have found a transition state, and that it smoothly connects reactant and product. *Click* on **Submit**.

5. When the job completes, animate the motion of atoms along the reaction coordinate. Select **Spectra** from the **Display** menu and *click* on the **IR** tab. *Click* on the top entry in the list in the **IR** dialog that results. It corresponds to an imaginary frequency, and will be designated with an **i** in front of the number.

> A vibrational frequency is proportional to the square root of a quantity that reflects the curvature of the potential surface divided by a mass. At a transition state (the “top of a hill”), the curvature is negative (it “points down”). Since mass is positive, the quantity inside the square root is negative and the frequency is an imaginary number.

Is the vibrational motion consistent with an ene reaction of interest and not with some other process?

6. Controls at the bottom of the **IR** dialog allow for changing both the amplitude of vibration (**Amp**) and the number of steps that make up the motion (**Steps**). The latter serves as a speed control. Change the amplitude to 0.3. *Type* **0.3** in the box to the right of **Amp** and *press* the **Enter** key (**return** key on Mac). Next, *click* on **Make List** at the bottom of the dialog. This will give rise to a group of structures that follow the reaction coordinate down from the transition state both toward reactant and product. Remove the original transition state from the screen. *Click* on ***ene reaction 1-pentene*** (the vibrating molecule) and close it, along with the **IR** dialog.

7. Enter the **Calculations** dialog and specify calculation of energy using the 3-21G Hartree-Fock model (the same level of calculation used to obtain the transition state and calculate the frequencies). Make certain that **Global Calculations** is checked. Next, enter the **Surfaces** dialog and specify evaluation of two surfaces: a bond density surface and a bond density surface onto which the electrostatic potential has been mapped. *Click* on **Add . . .**, select **density (bond)** for **Surface** and **none** for **Property** and *click* on **Apply**. Select **density (bond)** for **surface** and **potential** for **Property** and *click* on **OK**. Make certain that **Global Surfaces** is checked.

8. Submit for calculation. Name it ***ene reaction 1-pentene sequence***. Once the job has completed, enter the **Surfaces** dialog and, one after the other, select the surfaces that you have calculated. For each, step through the sequence of structures (◀ and ▶) keys at the bottom of the screen) or animate the reaction (▶). Note, in particular, the changes in bonding revealed by the bond density surface. Also pay attention to the value of the potential on the migrating atom. This reflects its charge. Is it best described as a proton (blue), hydrogen atom (green) or hydride anion (red)?

9. Close ***ene reaction 1-pentene sequence*** as well as any remaining dialogs.

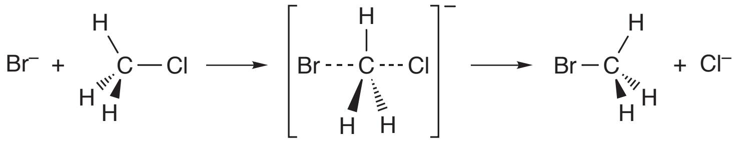
10 to 14 optional ***(cannot be completed with the Essential Edition)***

Methods that account for electron correlation are generally needed to furnish accurate estimates of absolute activation energies. Perform B3LYP/6-31G* density functional energy calculations on both 1-pentene and on the ene reaction transition state (using 3-21G geometries).

10. Open ***ene reaction 1-pentene*** (📂) and make a copy (💾). Name it ***ene reaction 1-pentene density functional***.
11. Enter the **Calculations** dialog, and specify calculation of energy using the B3LYP/6-31G* density functional model. Remove the checkmark from **IR**. Submit the job.
12. Open ***ene reaction 1-pentene density functional*** (📂). Specify calculation of energy using the B3LYP/6-31G* density functional model. Also select **3-21G** from the **Start from** menu. This designates that a 3-21G equilibrium structure is to be used (that is, the same as employed for the transition state geometry). Submit the job.
13. Obtain the activation energy (difference in total energies between 1-pentene and the ene reaction transition state).
14. Remove any molecules and dialogs from the screen.

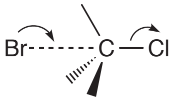
2 mins/5mins

S_N2 Reaction of Bromide and Methyl Chloride



1. The S_N2 reaction passes through a transition state in which carbon is in a trigonal bipyramid geometry and the entering and leaving groups are colinear. To build it, first construct methyl chloride. Then *click* on the **Insert** button at the bottom right of the screen or hold down the **Insert** key (**alt** key on Mac), select bromine from the palette of icons in the model kit and *click* anywhere on screen. Two detached fragments, methyl chloride and hydrogen bromide, appear on screen. *Click* on ⁜ and then *click* on the free valence on bromine. *Click* on ✚. Alternatively, hold down the **Delete** key and *click* on the free valence on bromine. You are left with methyl chloride and bromine atom (bromide). Manipulate the two such that bromide is poised to attack methyl chloride from the backside (as in the transition state above). (Recall that translations and rotations normally refer to both fragments, but can be made to refer to a single fragment by first *clicking* on the fragment and then holding down on the **Ctrl** key while carrying out the manipulations.) ***Do not minimize***. *Click* on ✓.

2. *Click* on ↷. *Click* on bromide and, while holding down the **Shift** key, *click* again on bromide and then on carbon. A dotted line will be drawn from bromine to carbon, together with an arrow from bromine to the center of this line. Next, *click* on the CCl bond and then *click* on the chlorine. A second arrow from the carbon-chlorine bond to the chlorine will be drawn.

   Click on ⟳ at the bottom right of the screen. Your structure will be replaced by a guess at the transition state.

3. *Click* on ‹?› and then on the CBr bond. Replace the current CBr distance in the box at the bottom right of the screen by **3.8** (3.8Å) and *press* the **Enter** key (**return** key on Mac). You have now made a complex representing the reactant.

4. Select **Constrain Distance** from the **Geometry** menu (or *click* on the 🔒 icon at the top of the screen). *Click* on the CBr bond, and then *click* on 🔓 at the bottom right of the screen. The icon will change to 🔒 indicating a constraint is to be applied to this distance. Next, bring up the **Properties** dialog and *click* on the constraint marker. The **Constraint Properties** dialog appears. *Click* on **Dynamic**. Leave the value **3.8** (3.8Å) in the box to the right of **Value** alone, but change the number in the box to the right of **to** to **1.9** (1.9Å) and *press* the **Enter** (**return**) key. You have requested 10 (the default number) structures with CBr bond lengths from 3.8Å (the starting point) to 1.9Å (the ending point). The transition state should have a CBr distance in between these values. Dismiss the **Constraint Properties** dialog.

5. Enter the **Calculations** dialog, and select **Energy Profile**, **Semi-Empirical** and **AM1** from the appropriate menus to the right of **Calculate**. You need to change **Total Charge** to **Anion**.

6. Submit the job. Name it ***bromide+methyl chloride***. When completed, it will give rise to a sequence of calculations placed in ***bromide+methyl chloride.M001***. Open this file[*], and align the molecules. *Click* on ≋, select **Structure** from the **Align by** menu at the bottom right of the screen and, one after the other, *click* on the three hydrogens. Finally *press* the **Align by** button at the bottom right of the screen. *Click* on V.

7. Bring up the **Spreadsheet** and *click* on **Add....** Select **E** from among the quantities listed at the top of the dialog, **kJ/mol** from the **Energy** menu, and *click* on **OK**. Next, enter the CBr distances and bromine charges in the spreadsheet. *Click* on ‹?›, select the CBr distance and *click* on P at the bottom right of the screen. *Click* on V. Bring up the **Properties** dialog. *Click* on bromine

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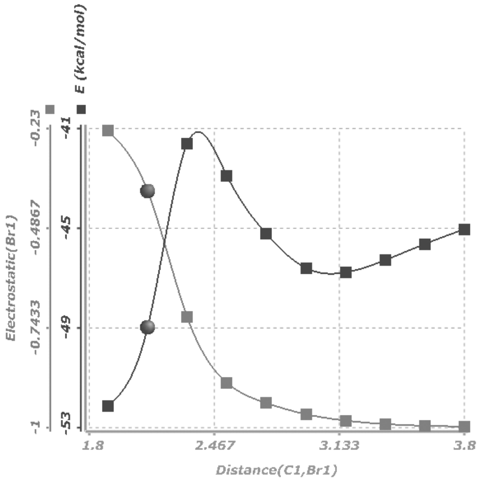
[*] The Macintosh version will automatically open the resulting file (**NAW**, **NAL**).

and *click* on P to the left of **Electrostatic** under **Charges** in the **Properties** dialog. Finally, bring up the **Plots** dialog, and select **Distance (C1,Br1)** from the **X Axis** menu, and both **E (kJ/mol)** and **Electrostatic (Br1)** from the **Y Axes** list. *Click* on **OK**.

One plot gives the energy as the reaction proceeds and the other gives charge on bromine. Are the two related? Explain.



S_N2 reactions involving charged species normally need to be carried out in highly-polar media, for example, water. ***Spartan*** accounts for the solvent by way of the SM5.4 model of Cramer and Truhlar (see **Appendix A**) in which the solvent is represented by a reaction field.

8. Add aqueous phase data to the spreadsheet. *Click* on an empty column header, *click* on **Add...**, select **Eaq** from the list of available quantities (**kJ/mol** from the **Energy** menu), and *click* on **OK**. Bring up the **Plots** dialog and select **Distance (C1,Br1)** from the **X Axis** and **Eaq(kJ/mol)** from the **Y Axes** list. *Click* on **OK**.

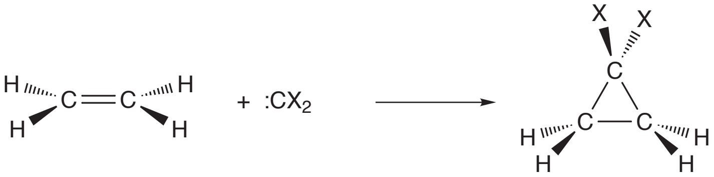
9 to 12 optional

9. With ***bromide+methyl chloride.M001*** selected, enter the **Calculations** dialog. Specify **Energy** (**Semi-Empirical** and **AM1** should be selected) and *click* on **OK**.

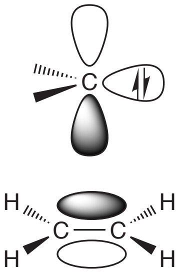
10. Enter the **Surfaces** dialog. *Click* on **Add...**. Select **density (bond)** from the **Surface** menu and **none** from the **Property** menu and *click* on **Apply**. Select **density (bond)** from the **Surface** menu, but this time **potential** from the **Property** menu. *Click* on **OK**.
11. Submit the job. When completed, *select* **density...** inside the **Surfaces** dialog. *Click* on ▶ at the bottom left of the screen to animate the display. Note, that bonds are smoothly broken and formed during the course of reaction. *Click* on ⏸ at the bottom of the screen when you are done.
12. Reenter the **Surfaces** dialog. Turn "off" display of the bond density (select **density...**), and turn "on" display of the electrostatic potential mapped onto the bond density (*select* **density potential...**). *Click* on ▶. Relate the migration of negative charge during reaction as indicated by colors in the electrostatic potential map to the plot you constructed earlier in step 7. Recall, that colors near red indicate maximum negative potential.
13. Remove all molecules and any remaining dialogs from the screen.

5 mins/15 mins

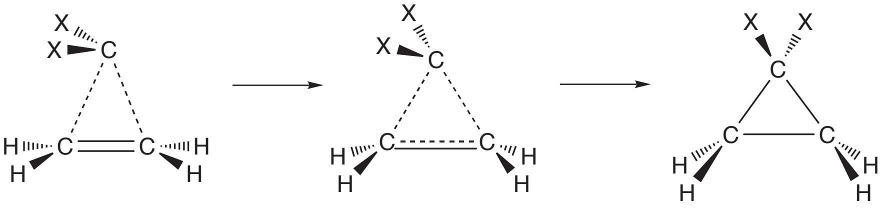
Carbene Additions to Alkenes



Singlet carbenes add to alkenes to yield cyclopropanes. Since a singlet carbene possesses both a high-energy filled molecular orbital in the plane of the molecule, and a low-energy, out-of-plane unfilled molecular orbital, this reaction presents an interesting dilemma. Clearly it would be more advantageous for the low-lying vacant orbital on the carbene, and not the high-lying filled orbital, to interact with the olefin π system during its approach.



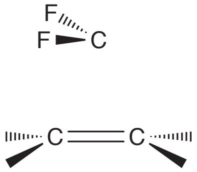
However, this leads to a product with an incorrect geometry. The carbene must "twist" by 90° during the course of reaction.



In this tutorial, you will use the Hartree-Fock 3-21G model to find the transition state and to analyze the motion of the fragments.

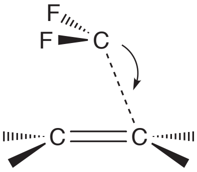
1. Bring up the organic model kit and build ethylene.
2. Select >C- from the model kit. *Click* on the **Insert** button at the bottom right of the screen or hold down the **Insert** key (**alt** key on Mac) and then *click* anywhere on screen. Next, select -F from the model kit and *click* on two of the free valences on

the sp^3 carbon. Next, *click* on ⁘ and, one after the other, *click* on the remaining two free valences on the sp^3 carbon. Finally, *click* on +. You are left with two fragments, ethylene and difluorocarbene. Orient the two as to be poised for reaction.*

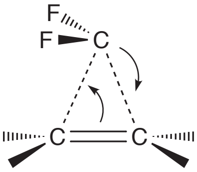


Translations and rotations normally refer to the complete set of fragments, but if you *click* on a fragment (not on a free valence) to select it, and then hold down the **Ctrl** key they will refer to an individual fragment.

3. *Click* on ↷. *Click* on the carbon on the CF_2 fragment and then, while holding down the **Shift** key, *click* first on the CF_2 carbon and then on one of the carbons on the ethylene fragment. A dotted line between the two carbons that are to be bonded will be drawn and an arrow will be drawn from the methylene carbon to the center of this line.



Next, *click* on the CC double bond and then, while holding down the **Shift** key, *click* on the other ethylene carbon and then on the CF_2 carbon. A second dotted line and second arrow will be added to the structure.



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* Proper orientation of the two fragments is not crucial in this case, but is primarily to allow you to associate the arrows with the intended reaction. Proper orientation is, however, essential where different stereochemical outcomes are possible.

Click on ⟳ at the bottom right of the screen. Your structure will be replaced by a guess at the transition state.

4. Enter the **Calculations** dialog, and specify calculation of a transition-state geometry using the 3-21G Hartree-Fock model. *Check* **IR** to the right of **Compute**, and *click* on **Submit**. Name the job ***difluorocarbene+ethylene***.

5. When the job is complete, examine the geometry of the transition state. In light of the previous discussion, would you describe your structure as corresponding to an early or late transition state? Animate the vibration corresponding to the reaction coordinate. Bring up the **IR** dialog (**Spectra** under the **Display** menu and *click* on the **IR** tab). *Click* on the imaginary frequency at the top of the list of frequencies. Does the animation show that the carbene reorients as it approaches the double bond? Turn “off” the animation by again *clicking* on the imaginary frequency.

6. Select **Properties** (**Display** menu) and, in turn, *click* on each of the four hydrogens in the transition state. Change the value in the **Mass Number** menu in the **Atom Properties** dialog from **1** to **2 Deuterium**. Resubmit the job. (No additional quantum chemical calculations are involved, but the vibrational analysis needs to be repeated to account for change in atomic masses.) When complete, examine the new set of vibrational frequencies. Note that they are uniformly smaller than those for the undeuterated system, and that the largest changes are for vibrational motions where hydrogens are involved.

7 to 10 optional

7. Make a copy of ***difluorocarbene+ethylene*** name it ***difluorocarbene+cyclohexene***.

8. Bring up the organic model kit with the copy (*click* on ✚). Select **Freeze Center** from the **Geometry** menu (or *click* on the ‡ icon at the top of the screen). One after the other, *click* on all atoms and free valences in the transition state except two of the free valences

on one side of the ethylene fragment.* Each of the selected atoms will be given a magenta colored marker, indicating that it is to be frozen (not moved during optimization).** Using sp^3 carbon >C- from the model kit and then , connect the two free valences that you have not frozen by a chain of four methylene groups to make a cyclohexene ring. *Click* on ↓E. Note that the only four methylene groups move and not the underlying transition state. You have produced an excellent guess at the transition state for difluorocarbene addition to cyclohexene based on your previous transition state for the simpler process.***

9. Enter the **Calculations** dialog. It should already specify calculation of transition-state geometry using the 3-21G Hartree-Fock model. Remove the checkmark on **IR** (to the right of **Compute**). *Click* on **Submit**.

10. When completed, compare the geometries of the two transition states (corresponding to addition of difluorocarbene to ethylene and cyclohexene, respectively). To do this, you need to put the two transition states into the same group. Select **Append Molecule(s)...** from the **File** menu and *double click* on ***difluorocarbene+ethylene*** in the browser that results. Then bring up the spreadsheet (**Spreadsheet** from the **Display** menu) and *check* each of the boxes to the right of the molecule names. *Click* on , select **structure** from the **Align by** menu at the bottom right of the screen and, one after another, *click* on the three carbons which make up the cyclopropane ring. Finally, *click* on **Align by** at the bottom right of the screen, and then *click* on V . Are the two transition states very similar as expected?

11. Remove all molecules and dialogs from the screen.

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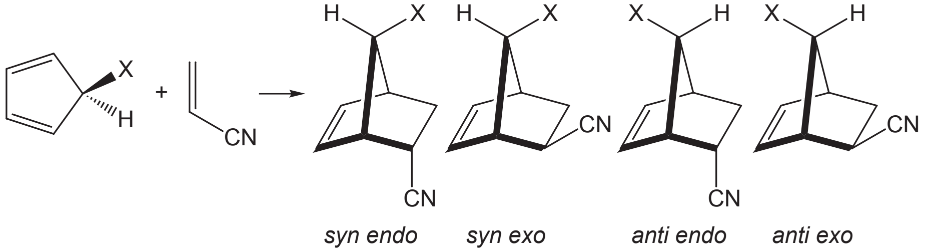
* You could do this more quickly by first *clicking* on , then drawing a selection box around all atoms to be frozen, and then *clicking* inside this box.

** You can remove the frozen atom markers from the model by bringing up the **Molecule Properties** dialog (**Display** menu), *clicking* on ▾ at the bottom right of the dialog and then removing the checkmark from **Frozens** in the **Molecule Utilities** dialog that results.

*** It is not necessary to replace the two deuteriums by hydrogens. You will not request an IR spectrum and calculated geometry does not depend on atomic mass.

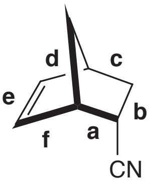
5 mins/10 mins

Stereospecific Diels-Alder Reactions

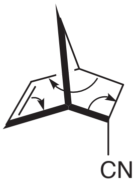


Diels-Alder cycloaddition of 5-substituted cyclopentadienes with acrylonitrile can lead to four stereoproducts, in which the substituent, X, at the 5 position is *syn* or *anti* to the dienophile, and the nitrile is *endo* or *exo*. *Anti* products are preferred when X is alkyl (consistent with steric dictates), while *syn* products are favored when X is halogen or alkoxy. In general, *endo* adducts are kinetically favored over *exo* adducts (see following tutorial). In this tutorial, you will use AM1 calculations to obtain both *syn* and *anti* transition states for *endo* addition of both 5-methylcyclopentadiene and 5-fluorocyclopentadiene and acrylonitrile, and then use Hartree-Fock 3-21G calculations to estimate relative activation energies. As the four transition states are likely to be very similar that for the parent cycloaddition (cyclopentadiene and acrylonitrile), you will first obtain a transition state for this reaction, and then to use it as a starting point for locating transition states for the substituted systems.

1. Construct the following substituted norbornene (the product of *endo* addition of cyclopentadiene and acrylonitrile).



2. *Click* on ↷. *Click* on bond **a** (see figure above) and then on bond **b**. A curved arrow will be drawn from **a** to **b**. Next, *click* on bond **c** and then on bond **d**; a second curved arrow from **c** to **d** be drawn. Finally, *click* on bond **e** and then on bond **f**, leading to a third curved arrow. The model on screen should now appear as follows.



Click on ⟳ at the bottom right to produce a guess at the transition state.

3. Inside the **Calculations** dialog, specify calculation of transition state geometry using the semi-empirical AM1 model. *Check* **IR** under **Compute** to specify calculation of vibrational frequencies. This will allow you to verify that you have indeed located a reasonable transition state.

4. Submit the job. Name it ***cyclopentadiene+acrylonitrile***. When completed, examine the resulting structure and calculated frequencies. Make certain that there is one and only one imaginary frequency. Animate the motion associated with the imaginary frequency (**Spectra** under the **Display** menu, *click* on the **IR** tab and *check* the box to the left of the imaginary frequency in the dialog that results) to verify that it corresponds to the expected motion along the reaction coordinate.

5. Place the transition-state structure onto the clipboard. Position the cursor slightly above and slightly to the left of the model, then, with both buttons depressed, *drag* the mouse to a position slightly below and slightly to the right of the model, and finally release both buttons. Dotted lines will enclose the model. Select **Copy** from the **Edit** menu. Close ***cyclopentadiene+ acrylonitrile*** (📂).

6. Bring up the organic model kit (📄). *Click* on **Clipboard** (at the bottom) and then *click* anywhere on screen. The transition-state structure will appear. Add a fluorine to the methylene group of the cyclopentadiene fragment of the transition state either *syn* or *anti*. ***Do not minimize***. Your starting structure should provide an excellent guess at the transition state for the substituted system.

7. Select **New Molecule** from the **File** menu. The screen will clear. *Click* on **Clipboard** and then *click* anywhere on screen. Add fluorine to the other methylene group position.

   Repeat the process two more times (starting with **New Molecule**), to add methyl both *syn* and *anti* on the methylene group. When you are done (four substituted transition states in total), *click* on V.

8. Enter the **Calculations** dialog and specify calculation of transition state geometry using the semi-empirical AM1 model. *Check* **IR** to the right of **Compute**. Make certain that **Global Calculations** is checked. Submit the job (name it ***Diels-Alder stereochemistry***. When it has completed, verify that all four structures correspond to transition states (using **Spectra** from the **Display** menu).

9. Make a copy of ***Diels-Alder stereochemistry*** (💾). Name it ***Diels-Alder stereochemistry Hartree-Fock***. Enter the **Calculations** dialog with this copy and specify a 3-21G Hartree-Fock energy calculation. Make certain that you remove the checkmark on **IR** and that **Global Calculations** is checked before you exit the dialog.

10. Submit the job. When it completes, bring up the spreadsheet (**Display** menu) and enter the total energies. *Click* on the header cell of a blank column and then on **Add...** at the bottom of the spreadsheet. Select **E** from the menu of available quantities and **au** (atomic units) from the **Energy** menu. *Click* on **OK**. Are your results consistent with the observed *syn/anti* selectivity in these reactions?*

11. Remove all molecules and any remaining dialogs from the screen.

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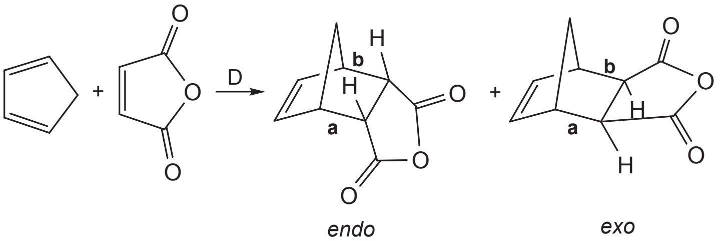
* You can use the spreadsheet to calculate relative energies. Select (*click* on) the label for one of the fluorine substituted transition states in the spreadsheet, then *click* on **Add...** and select **rel. E** from the menu of available quantities and select appropriate energy units. *Click* on **OK**. Repeat for the methyl substituted transition states.

5 mins/15 mins

Thermodynamic vs. Kinetic Control

Chemical reactions may yield different products depending on the conditions under which they are carried out. High temperatures and long reaction times favor the most stable (thermodynamic) products, whereas low temperatures and short reaction times favor the most easily formed (kinetic) products. For example, the kinetic product in Diels-Alder cycloaddition of cyclopentadiene and maleic anhydride is the *endo* adduct, whereas it seems likely that the less-crowded *exo* adduct is the thermodynamic product.



Here you will first obtain pathways for reactions leading to both *endo* and *exo* adducts using the PM3 semi-empirical model and then follow these by 3-21G Hartree-Fock energy calculations to get a better estimate of the difference in activation energies.

1. Build the *endo* Diels-Alder adduct of cyclopentadiene and maleic anhydride and minimize (E).

2. Select **Constrain Distance** from the **Geometry** menu (or *click* on 🔒), and *click* on bond **a** in the figure above. *Click* on the icon 🔓 at the bottom right of the screen (it will then turn to 🔒). *Click* on ✓.

3. Select **Properties** from the **Display** menu, and *click* on the constraint marker for bond **a**. The **Constraint Properties** dialog appears, with the value of the constraint for bond distance **a** (1.54Å) given in a box to the right of **Value**. Change this to 1.5Å by *typing* **1.5** inside the box and then *pressing* the **Enter** key (**return** key on Mac). *Check* **Dynamic** inside the dialog. This leads to an extended form of the **Constraint Properties** dialog, that allows the single constraint value to be replaced by

a sequence of constraint values. *Type* **2.7** (2.7Å) into the box to the right of **to** and *press* the **Enter** (**return**) key. Set **Steps** to **13**. *Type* **13** and *press* the **Enter** (**return**) key. You have specified that bond **a** will be constrained first to 1.5Å, then to 1.633Å, then to 1.767Å, etc. and finally to 2.7Å.

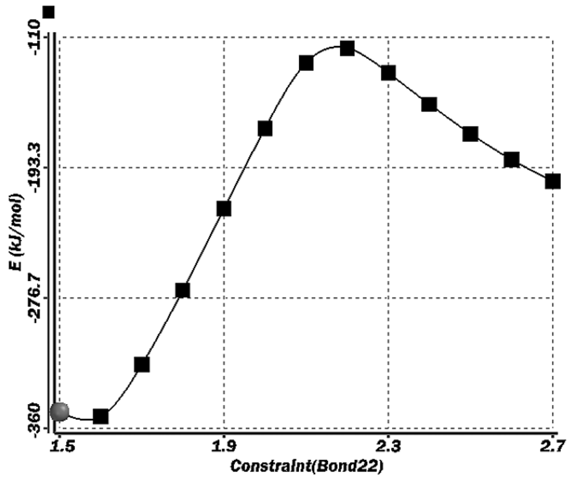
You need to repeat the process starting with step 2 for bond **b**. When you are done, both bonds **a** and **b** will be constrained from 1.5Å to 2.7Å in 13 equal steps. Close the **Constraint Properties** dialog.

4. Bring up the **Calculations** dialog and select **Energy Profile** from the top menu to the right of **Calculate**, and **Semi-Empirical** and **PM3** from the two bottom menus. *Click* on **Submit** at the bottom of the dialog. Name it ***cyclopentadiene+ maleic anhydride endo***.
5. When completed the job will give rise to a new file ***cyclopentadiene+maleic anhydride endo.M001*** containing the 10 steps that make up the energy profile. Open this file.[*]
6. Bring up the **Spreadsheet**, and *click* on **Add...** at the bottom. Select **E** from among the entries, **kJ/mol** from the **Energy** menu, and *click* on **OK**. Next, *click* on 🔒 and *click* on one of the two CC bonds varied in the energy profile. *Click* on P at the bottom right of the screen. *Click* on V. Finally, bring up the **Plots** dialog, and select **Constraint (BondX)**[**] from among the items in the **X Axis** menu and **E (kcal/mol)** from the **Y Axes** list. *Click* on **OK**.

---

[*] The Macintosh version will automatically open the resulting file. To avoid confusion, it is a good idea to close the original file ***cyclopentadiene+maleic anhydride endo***.

[**] Bonds are numbered in the order they were formed upon initial construction of the molecule.



Identify both the reactant and transition state from the plot and estimate the activation energy for the cycloaddition reaction.

7. Repeat steps 1 to 6 for the *exo* adduct. Compare the activation energy for *exo* addition to that for *endo* addition (above). What is the kinetic product?
8. Remove all molecules and dialogs from the screen.

9 to 11 optional

9. Open ***cyclopentadiene+maleic anhydride endo.M001*** (📂) and make a copy (💾). Name it ***cyclopentadiene +maleic anhydride endo Hartree-Fock***. Enter the **Calculations** dialog and specify a Hartree-Fock 3-21G energy calculation. Submit. When completed, perform the same spreadsheet and plot operations you did for the PM3 calculations.
10. Repeat the above procedure for the *exo* adduct and compare the two activation energies. What is the kinetic product?
11. Remove all molecules and dialogs from the screen.

5 mins

Activation Energies of Diels Alder Reactions

In an earlier tutorial ***Dienophiles in Diels-Alder Reactions*** (**Chapter 5**), you examined the extent to which LUMO energies for a series of related dienophiles correlated with relative rates of Diels-Alder cycloadditions involving cyclopentadiene. In this tutorial, you will compare calculated activation energies for this same set of reactions with the experimental rates. You will use the previous set of calculations on the dienophiles and obtain transition states from the Spartan Reaction Database (SRD). The only quantum chemical calculation that is required is for cyclopentadiene.

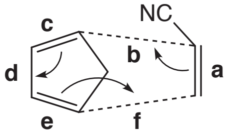
1. Build cyclopentadiene and minimize (E). Before you proceed with the next step, copy cyclopentadiene onto the clipboard. Position the cursor above and to the left of cyclopentadiene, hold down both mouse buttons, *drag* the mouse below and to the right of cyclopentadiene and finally release the buttons. A selection box will be drawn. Select **Copy** from the **Edit** menu to put cyclopentadiene onto the clipboard.

2. Enter the **Calculations** dialog (**Setup** menu) and specify an equilibrium geometry calculation using the Hartree-Fock 3-21G model. Submit the job with the name ***cyclopentadiene***. Move it off to the side of the screen for use later on.

3. Enter the builder (🗎). *Click* on **Clipboard**. The structure of cyclopentadiene will appear at the top of the model kit. Click anywhere on screen and cyclopentadiene will appear.

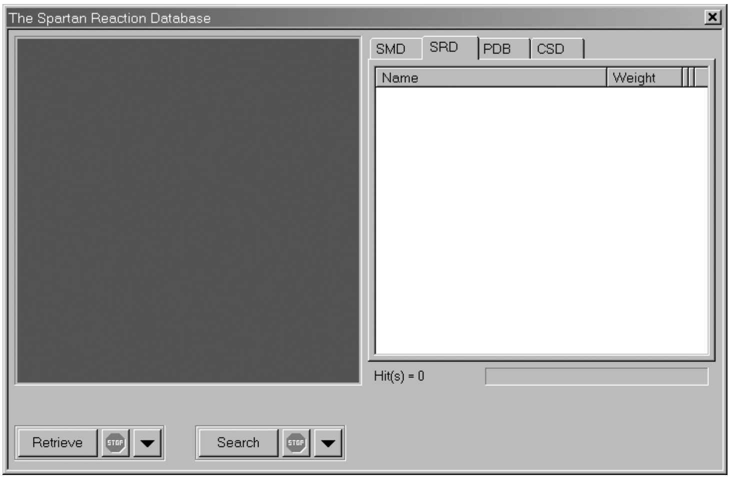
4. Select **Ethylene** from the **Groups** menu, *press* the **Insert** button (at the bottom right of the model kit) or hold down the **Insert** key (**alt** key on Mac) and *click* on screen. Both cyclopentadiene and ethylene will appear on screen, but they will not be connected. Select **Cyano** from the **Groups** menu and *click* on one of the free valences on ethylene. Both cyclopentadiene and acrylonitrile will appear on screen.

5. Orient the two molecules such that they are poised for a Diels-Alder reaction leading to an *endo* product.

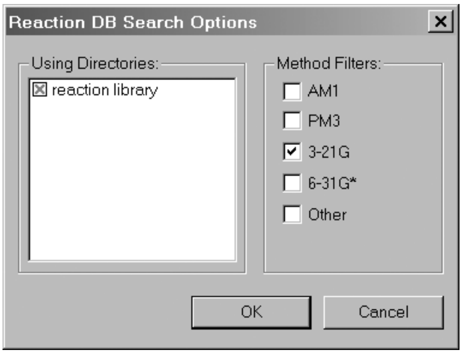


Select **Transition States** from the **Search** menu (*click* on ↷). *Click* on the bond marked **a** in the above figure and, while holding down the **Shift** key, *click* on the two carbons that when connected will lead to the bond marked **b**. A dotted line will be drawn between these carbons and an arrow drawn from the center of bond **a** to the center of bond **b**. Next, *click* on bond **c** and then on bond **d**. A second arrow will be drawn. Finally, *click* on bond **e** and, while holding down the **Shift** key, *click* on the two carbons that when connected will lead to the bond marked **f**. A second dotted line and a third arrow will be drawn.

6. Select **Databases** from the **Search** menu (*click* on ▯) and *click* on the **SRD** tab at the top of the dialog that results. This leads to the **Spartan Reaction Database (SRD)** dialog.



Click on all three free valences on acrylonitrile. They will be replaced by orange cones, meaning that anything (including hydrogen) may be attached to these positions. Before you begin the search, *click* on ▾ to the right the **Search** button at the bottom of the dialog. This brings up the **SRD Search Options** dialog.

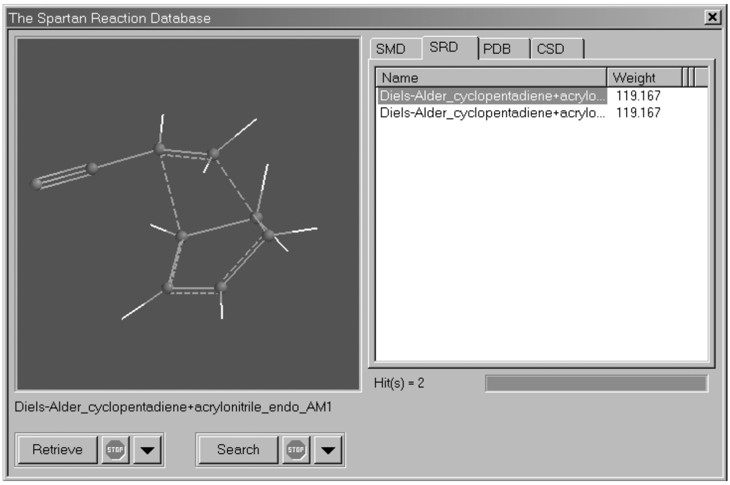

Reaction DB Search Options

Using Directories:
☒ reaction library

Method Filters:
☐ AM1
☐ PM3
☑ 3-21G
☐ 6-31G*
☐ Other

Check **3-21G** under **Method Filters**, and make certain that **Structure** is selected under **Search by**. *Click* on *OK*. *Click* on the **Search** button to search the Spartan Reaction Database for Diels-Alder transition states between cyclopentadiene and substituted acrylonitriles.

7. When the search completes, a listing of hits appears at the right of the dialog.


The Spartan Reaction Database

Name	Weight
Diels-Alder_cyclopentadiene+acrylo...	119.167
Diels-Alder_cyclopentadiene+acrylo...	119.167

Hit(s) = 2

Diels-Alder_cyclopentadiene+acrylonitrile_endo_AM1

This should contain all six Diels-Alder transition states for *endo* additions of cyclopentadiene and acrylonitrile, *trans*-1,2-dicyanoethylene, *cis*-1,2-dicyanoethylene, 1,1-dicyanoethylene, tricyanoethylene and tetracyanoethylene. All need to be retrieved into a single document. *Click* on ▼ to the right of the **Retrieve** button at the bottom of the dialog to bring up the **Retrieve Options** dialog. *Click* on **New Document** inside this dialog and *click* on **OK**. *Click* on the transition state corresponding to *endo* addition of cyclopentadiene and acrylonitrile in the list of available transition states. Its structure will be shown in the window at the left of the **Spartan Reaction Database** dialog and may be manipulated in the usual way. *Click* on the Retrieve button to transfer this structure into ***Spartan's*** file system.

8. Again *click* on ▾ to the right of the **Retrieve** button at the bottom of the **Spartan Reaction Database** dialog. Change **New Document** to **Current Document** in the **Retrieve Options** dialog that results. This ensure that the remaining transition states will go into the same document as the transition state for reaction of cyclopentadiene and acrylonitrile.

9. One after the other and in proper order, select (*click* on) end transition states for reactions of cyclopentadiene and *trans*-1,2-dicyanoethylene, *cis*-1,2-dicyanoethylene, 1,1-dicyanoethylene, tricyanoethylene and tetracyanoethylene (five transition states), and after each selection *click* on the **Retrieve** button. You are left with a single document containing all six Diels-Alder transition states.

10. Bring up a spreadsheet (**Spreadsheet** under the **Display** menu) and size it to contain all six transition states. *Click* on **Add** at the bottom of the dialog, select **Name** and **E** from the list of the available quantities and **au** from the **Energy** menu and *click* on **OK**. Transition state names and energies will populate the spreadsheet. Change the title of the column of energies to **Ets** (from **E (au)**). Also provide titles for three empty columns: **Ecyclopentadiene**, **Edienophile** and **log(rate)**. Save the document (💾) with the name ***Diels-Alder transition states***.

11. Open ***Diels-Alder dienophiles*** that you created in an earlier tutorial.* Bring up a spreadsheet for this document. This should contain the experimental relative rate data. If it does not already contain calculated energies, *click* on **Add**, select **E** from the list of

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* If you have not completed this tutorial, a copy of the document ***Diels-Alder dienophiles*** may be found in the ***organic reactions*** sub-directory (***tutorials*** directory).

quantities and **au** from the **Energy** menu and *click* on **OK**. Verify that the ordering of dienophiles in this document is the same as the ordering of transition states in ***Diels-Alder transition states***.

Click on the top entry in the column under the **log(rate)** in the spreadsheet for Diels-Alder dienophiles and then, while holding down the **Shift** key, *click* on the bottom entry. Select **Copy** from the **Edit** menu. Move to the spreadsheet for ***Diels-Alder transition states***, *click* inside the top cell under **log(rate)** and select **Paste** from the **Edit** menu. The experimental rate data will be added to the spreadsheet for ***Diels-Alder transition states***, Repeat for energy values in ***Diels-Alder dienophiles*** (**E (au)**), copying them to **Edienophile** in ***Diels-Alder transition states*** spreadsheet. Close ***Diels-Alder dienophiles*** (📂).

12. Locate ***cyclopentadiene*** on screen and bring up a spreadsheet. *Click* on **Add**, select **E** from the list of quantities and **au** from the **Energy** menu and *click* on OK. *Click* inside the cell containing the energy and select **Copy** from the **Edit** menu. Move to the spreadsheet for ***Diels-Alder transition states*** and paste this value into all six cells below **Ecyclopentadiene** (**Paste** from the **Edit** menu). Close ***cyclopentadiene*** (📂).

13. Calculate activation energies (in kJ/mol). Inside the header cell of a an empty column (in the spreadsheet for ***Diels-Alder transition states***) *type* ***Eact=(Ecyclopentadiene+Edienophile-Ets)*@hart2kJ*** (The last quantity provides conversion from atomic units to kJ/mol; see **Table 16-4** in **Chapter 16**).

14. Plot calculated activation energies vs. experimental relative reaction rates. Select **Plots** from the **Display** menu. Select **log(rate)** from the list of items in the **X Axis** menu and **Eact** from the **Y Axis** list. *Click* on **OK**. The curve displayed smoothly connects the data points, but is of little value for establishing the quality of the correlation. A better representation is provided by a simple least-squares fit. Select **Properties** from the **Display** menu and click anywhere on the curve. Select **Linear LSQ** from the **Curve Properties** dialog that appears. This leads to

a conventional least squares plot relating calculated activation energies and experimental relative rates.

15. Close all molecules and any open dialogs.

Chapter 7

Medicinal Chemistry

This chapter illustrates applications of ***Spartan*** *to problems of relevance to medicinal chemists. The first involves an investigation of the relationship between polar surface area (defined both by atom counts and by electrostatic potential maps) and the rate of transport between blood and brain. The second uses a published pharmacophore to decide whether the antihistamine terfenadine should be considered a potential potassium channel blocker. The third seeks to find molecules with similar analgesic activity as morphine, based first on similar structure and then on similar chemical functionality.*

Many molecular properties may now be calculated using quantum chemical methods, some more accurately than they can be measured. Still, some quantities of key interest to medicinal chemists are not yet subject to calculation. A good example is the rate at which a molecule passes through a membrane. Here, overall molecular polarity plays an obvious role. Too polar and the lipid will not take up molecule; not sufficiently polar and it will be unable to dissolve in the “aqueous” environment on either side of the membrane. One descriptor commonly used to account for polarity is the so-called polar surface area, defined as the area of space-filling model due to nitrogen and oxygen together with any bonded hydrogens. The first tutorial in this chapter examines the correlation between polar surface area and blood-brain transport and then proposes an alternative based on the electrostatic potential.

Many (if not most) drugs act by binding to a protein or nucleotide, either promoting a particular process (agonists) or inhibiting one (antagonists). New drugs can be found by identifying molecules that are structurally and/or functionally similar to compounds that are known or presumed to bind. The second tutorial attempts to establish whether the antihistamine, terfenadine is likely to show serious side effects because of fitting into a protein. Here, the similarity analysis is not carried out between molecules but between a molecule and an environment. The third and final tutorial makes use of similarity analysis to suggest compounds that look like morphine and hence might exhibit similar action.

Anticipating Blood-Brain Transport

An important characteristic of a drug is its ability to be transported throughout the body. This includes intestinal absorption and, in the case of CNS drugs, passage across the blood/brain barrier. In this tutorial, you will first examine the extent to which the polar surface area, defined in the usual way as the area of space-filling model due to nitrogen and oxygen atoms together with any attached hydrogens, correlates with log (C_{brain}/C_{blood})[*]. No calculations are involved.

1. Open ***blood brain transport*** from the ***medicinal chemistry*** sub-directory (***tutorials*** directory). This comprises a list of CNS drugs/drug candidates for which experimental data relating to the ratio of concentrations in the brain and in the blood (C_{brain}/C_{blood}) are available. These span a range of nearly 5 log units.

2. Bring up a spreadsheet (**Spreadsheet** under the **Display** menu) and size it to show all compounds, several extra rows and three columns, in addition to the column of experimental data **log(brain/blood)** that is already displayed.

3. *Click* on the **Add** button at the bottom of the spreadsheet. Select **PSA** (polar surface area) from the quantities listed in the dialog that appears and *click* on **OK**. Polar surface area values will fill one column in the spreadsheet. Again, *click* on the **Add** button, and select (*click* on) the **Linear Regression** tab at the top of the dialog that appears (most likely the **Add Columns** dialog). This leads to the **Add Linear Regression** dialog.

   Select **log(brain/blood)** from the **Fit** menu and *click* on **PSA** from the quantities in the box below **Using**. *Click* on **OK**. Bring up the **Regression Properties** dialog by first selecting **Properties** from the **Display** menu and then *clicking* on the cell labelled **Fit1** under **Label** in the spreadsheet. RMSD and R^2 values are reported. The smaller RMSD and the closer to unity R^2, the better the fit. Leave the **Regression Properties** dialog on screen.

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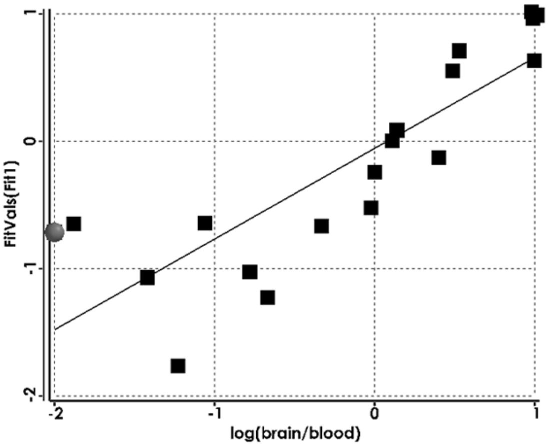
[*] J. Kelder *et al*, Pharmaceutical Res., **16**, 1514 (1999). The 19 named compounds considered in this paper have been included.

4. Make a plot of log(brain/blood) vs. the regression fit. Select **Plots** from the **Display** menu to bring up the **Plots** dialog. Select **log (brain/blood)** from the **X Axis** menu, **Fit Vals (Fit 1)** from the **Y Axis** list and *click* on **OK**. Initial presentation uses a smooth curve (cubic spline) to connect the data points. *Click* on the curve (not on the axes) to bring up the **Curve Properties** dialog. Select **Linear LSQ** from the **Fit** menu to give a least squares line.

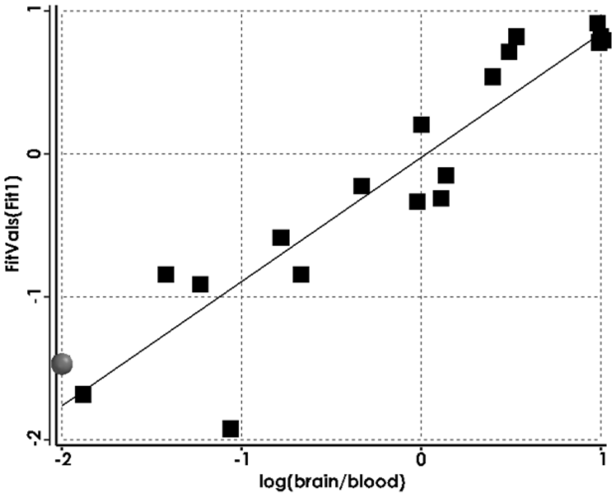


Next, you will consider an alternative definition of polar surface area, based on electrostatic potential maps.

5. Select **Surfaces** from the **Display** menu and select **density...** in the dialog that results. An electrostatic potential map for the selected CNS drug appears (maps for the remaining drugs may be seen by stepping through the list). The overall size and shape is that of the electron density and corresponds roughly to a conventional space-filling model. The colors indicate the value of the electrostatic potential. Colors toward red designate areas of negative potential (where a positive charge is most likely to be attracted), while colors toward blue designate areas of positive potential (where a positive charge is least likely to be attracted). To see the molecular skeleton underneath the electrostatic potential map, change to a transparent or mesh display. *Click* on the map to select it and select **Transparent** or **Mesh** from the **Style** menu that appears at the bottom right of the screen.

6. Select **Properties** from the **Display** menu. *Click* on the map. *Click* on the P button to the left of **P-Area** inside the **Surfaces Properties** dialog that results. Polar areas, defined as the area for which the absolute value of the electrostatic potential is > 100 kJ/mol[*], will be added to the spreadsheet.

7. *Click* on the **Add** button at the bottom of the spreadsheet and *click* on the **Linear Regression** tab at the top of the dialog that results. Select **log(brain/blood)** from the **Fit** menu and *click* on **Polar Area** from the quantities in the box below **Using**. *Click* on **OK**. Bring up the **Regression Properties** dialog by *clicking* on the cell labelled **Fit2** under **Label** in the spreadsheet. Note that the R^2 value is better (closer to unity) for this fit than for the previous fit (to PSA defined in the usual manner). Make a plot of log (brain/blood) vs. the new regression fit. Select **Plots** from the **Display** menu, choose **log (brain/blood)** from the **X-Axis** menu and **FitVals (Fit 2)** (instead of **Fit Vals (Fit 1)** from the **Y Axis** list and *click* on **OK**. Switch to a least square fit by *clicking* on the curve that results and selecting **Linear LSQ** from the **Fit** menu in the **Curve Properties** dialog.



8. Close ***blood brain transport*** when you are finished.

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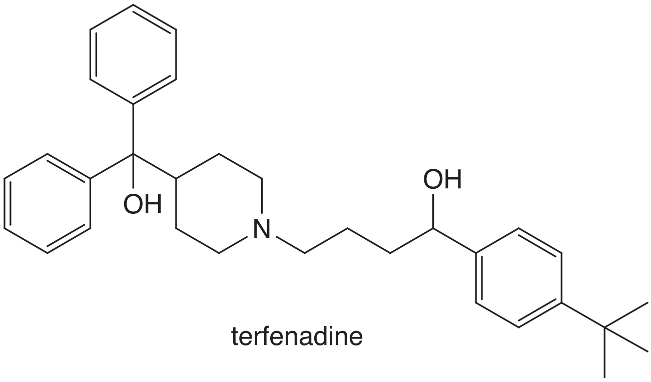
[*] This value may be changed in the **Settings Preferences** dialog (**Preferences** under the **Options** menu; **Chapter 18**).

30 mins

Terfenadine. A Potassium Channel Blocker?
(cannot be completed with the Essential Edition)

Cardiovascular toxicity due to blocking of potassium ion channels is commonly screened early in the drug development process. One way this is done is to compare drug candidates to a pharmacophore deduced from 3D QSAR studies. This tutorial uses a published pharmacophore* to see whether the antihistamine, terfenadine should be considered a potential channel blocker.



terfenadine

1. Bring up the organic model kit (🗎), *click* on the **Rings** button, select **Cyclohexane** from the menu and *click* anywhere on screen. *Click* on trigonal planar nitrogen (N-) and *double click* on one of the carbons (not a free valence) in cyclohexane to make piperidine.

   Build a four carbon chain off nitrogen using tetrahedral carbon (C-) to make N-butylpiperidine. Add a hydroxyl group (O-) and a phenyl ring (**Benzene** from the **Rings** menu) to the end of this chain. Add a *para tert*-butyl group to the phenyl ring using sp^3 carbon (C-).

   Add sp^3 carbon (C-) to the 4-position on piperidine. Use the *equatorial* free valence. Add a hydroxyl group (O-) and two phenyl rings (**Benzene** from the **Rings** menu) to this carbon. Name the molecule. Select **Properties** from the **Display** menu to bring up the **Molecule Properties** dialog. *Type* ***terfenadine*** in the box to the right of **Label**. *Click* on ✓ to remove the model kit.

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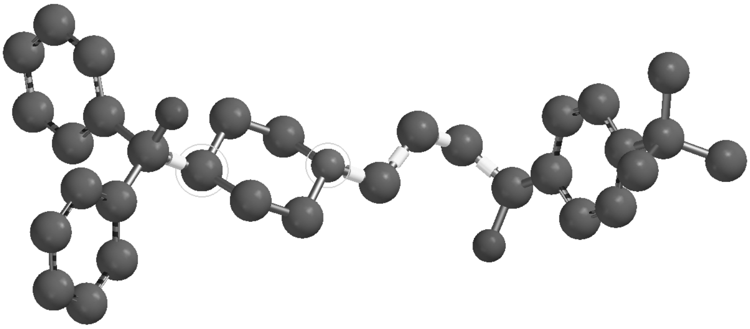
* S. Ekins *et al*, J. Pharmacology and Experimental Therapeutics, **301**, 427 (2002).

> You can find out which enantiomer you have built by selecting **Configure...** from the **Model** menu, *checking* **R/S** under **Atom** and *clicking* on **OK**. An R or S label will appear on the appropriate carbon. If it is necessary to change chirality, first select **Add Fragment** from the **Build** menu (or *click* on the + icon at the top of the screen) and then *double click* on this carbon while holding down the **Ctrl** key.

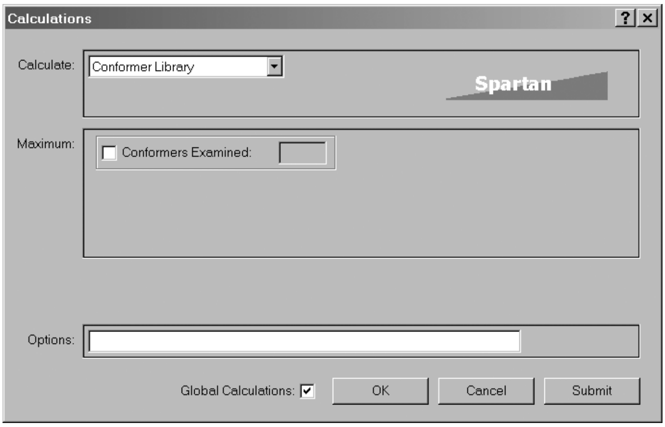
2. Hydrogen positions are not considered in conformer library generation and the torsional degrees of freedom involving the two OH bonds in terfenadine may be removed.* Select **Set Torsions** from the **Geometry** menu (or *click* on the ⟲ icon at the top of the screen). Your model will be augmented with yellow cylinders and circles to designate flexible bonds and rings, respectively. Remove the markers from the bonds connecting the two hydroxyl groups to tetrahedral carbons and the pyramidal nitrogen by *double clicking* on each in turn. These bonds will no longer be included in the conformational search. Five single bonds and two ring atoms are now selected.



3. Bring up the **Calculations** dialog (**Calculations...** from the **Setup** menu). Choose **Conformer Library** from the top left menu to the right of **Calculate**.

---

* This will already have been done if **Conformer Rules** in the **Settings Preferences** dialog (**Preferences** under the **Options** menu; **Chapter 18**) has been set to **Trimmed**.



Calculate: Conformer Library

☐ Conformers Examined:

Global Calculations: ☑

Click on **Submit** at the bottom of the dialog and supply the name ***terfenadine conformer library***. The job will require several minutes to complete. When it does you need to close it before carrying out the similarity analysis.*

4. Open ***potassium channel blocker pharmacophore*** from the ***medicinal chemistry*** sub-directory (***tutorials*** directory). This is a five-point pharmacophore comprising four hydrophobes (blue spheres) and one positive ionizable center (red sphere).

5. Select **Set Similarity Centers** from the **Geometry** menu (or *click* on the ⊙ icon at the top of the screen) and then select **CFD** from the menu at the bottom right of the screen. In turn, *click* on each of the (five) pharmacophore elements. In response, each will be surrounded by a violet circle indicating that it is to be used in the similarity analysis.

6. Select **Calculations...** from the **Setup** menu. Select **Similarity Analysis** from the top left menu to the right of **Calculate** inside the **Calculations** dialog. This leads to a new form of the **Calculations** dialog.

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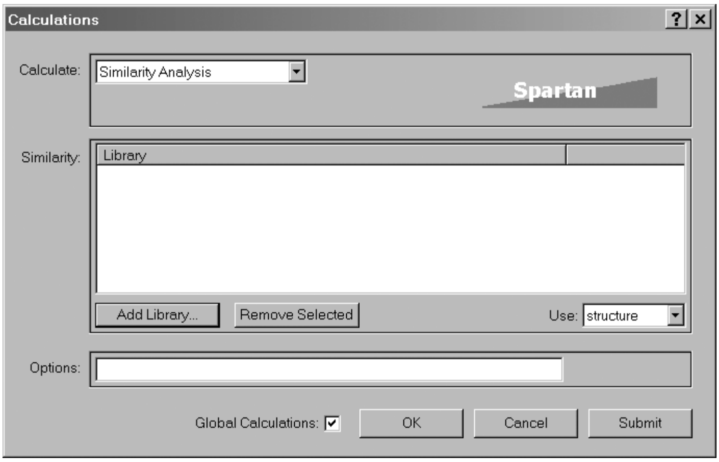
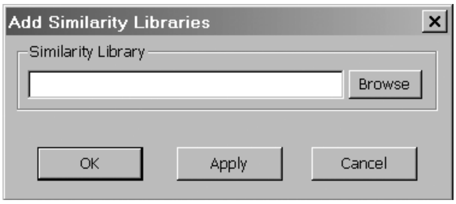
* If you don't want to wait, ***terfenadine conformer library*** may be found under the ***medicinal chemistry*** sub-directory (***tutorials*** directory).

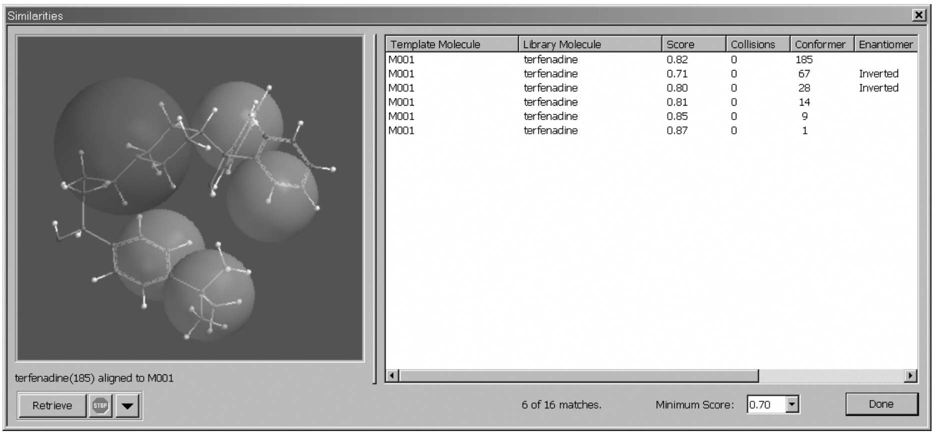

Calculations
Calculate:
Similarity Analysis
Spartan
Similarity:
Library
Add Library...
Remove Selected
Use:
structure
Options:
Global Calculations: ☑
OK
Cancel
Submit

Click on **Add Library** to bring up the **Add Similarity Libraries** dialog.


Add Similarity Libraries
Similarity Library
Browse
OK
Apply
Cancel

Click on the **Browse** button, locate ***terfenadine conformer library*** in the ***medicinal chemistry*** sub-directory (***tutorials*** directory) and *click* on **OK**. This indicates that the library of terfenadine conformers will be searched for a match to the pharmacophore. *Click* on **Submit**.

7. Execution will take a few minutes. When it has completed, select **Similarities...** from the **Display** menu to bring up the **Similarities** dialog.



Template Molecule	Library Molecule	Score	Collisions	Conformer	Enantiomer
M001	terfenadine	0.82	0	185	
M001	terfenadine	0.71	0	67	Inverted
M001	terfenadine	0.80	0	28	Inverted
M001	terfenadine	0.81	0	14	
M001	terfenadine	0.85	0	9	
M001	terfenadine	0.87	0	1	

terfenadine(185) aligned to M001

6 of 16 matches.

Minimum Score: 0.70

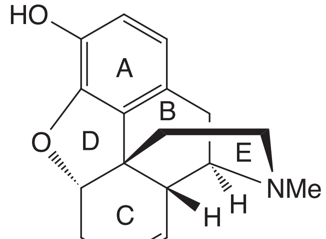
One or more hits will appear in the box at the right of the dialog, together with a similarity score (limiting on 1.0 which means a perfect match). If there is more than one hit, *click* on that with the largest score. A composite graphic of terfenadine and the pharmacophore will appear in a window at the left of the dialog. You can manipulate the two (as a single object) in the usual way (you need to position the cursor inside the window). Note that the positive ionizable center is positioned above the nitrogen, while the four hydrophobes are above the phenyl rings and the *tert*-butyl group.

The scoring algorithm not only accounts for position but also for direction of any nitrogen or oxygen centers that overlap with (non-hydrophobe) pharmacophore elements.

8. You can if you wish retrieve your hit (without the pharmacophore), by *clicking* on the **Retrieve** button at the bottom left of the **Similarities** dialog. This can be used for further analysis.
9. Close all open documents on screen.

5 mins

Morphine. Structure vs. Pharmacophore
(cannot be completed with the Essential Edition)



morphine

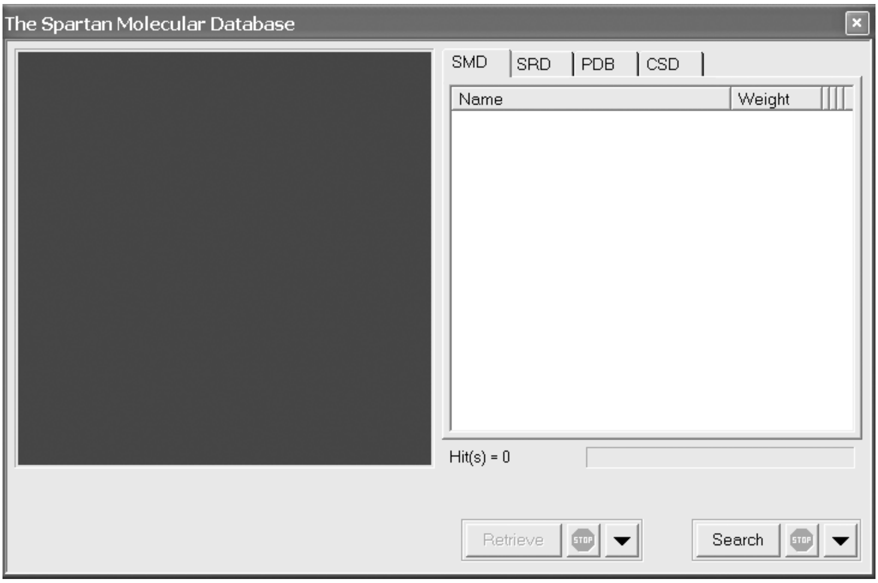
Three elements of morphine appear to be required in order for the molecule to act as an analgesic. These are: i) the nitrogen center (assumed to be protonated in the protein-bound complex), ii) the aromatic ring and iii) the hydroxyl group attached to the aromatic ring. Loss of any of these results in significant loss of activity. This knowledge may either be used as is to identify other likely analgesics based on structure, or indirectly to construct a simple 3-point pharmacophore, that in turn may be employed to find compounds with potentially comparable analgesic activity.

This tutorial comprises three parts. In the first part, you will identify molecules in SMD that incorporate the three required elements. In practice, you will look for molecules that incorporate a nitrogen center substituted by a methyl group and two other (sp^3) carbons and a substituted phenol. You will then select a single hit and generate a conformer library for similarity analysis. (In a comprehensive investigation, you would likely use several hits or all hits, and the restriction here is simply in order to save computer time.)

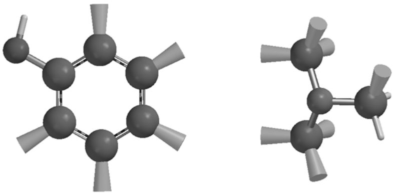
1. Bring up the organic model kit (🗎). Select **Benzene** from the **Rings** menu and *click* anywhere on screen. Select sp^3 oxygen (O-) and *click* on one of the free valences of benzene. You have made phenol. Select sp^3 nitrogen (N), *click* on the **Insert** button at the bottom of the screen or hold down the **Insert** key (**alt** key on Mac) and *click* anywhere on screen. Two molecules (phenol and ammonia) appear on screen. *Click* on sp^3 carbon (C-) and *click* on all three free valences on the nitrogen. Phenol and trimethylamine

now appear on screen. *Click* on V remove the model kit.

2. Select **Databases** from the **Search** menu (▯). *Click* on the **SMD** tab in the dialog that results.

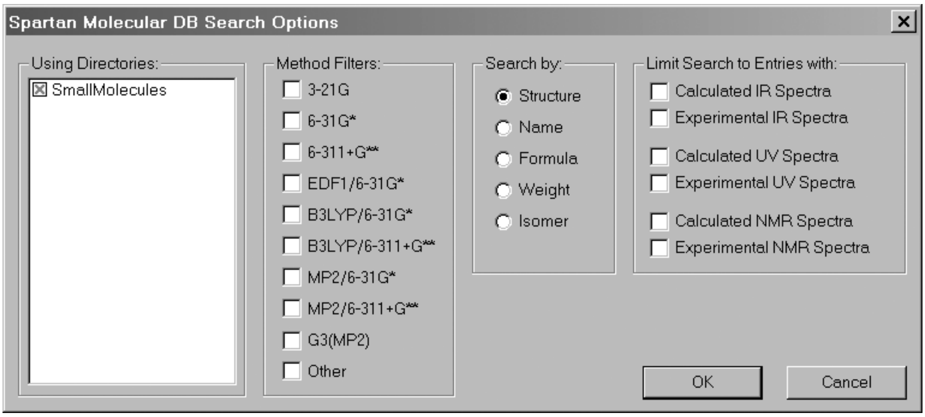

The Spartan Molecular Database
SMD
SRD
PDB
CSD
Name
Weight
Hit(s) = 0
Retrieve
STOP
Search
STOP

Click on all five free valences on the carbons in phenol and on all three free valences on two of the three methyl groups and on one free valence for the remaining methyl group in trimethylamine. Orange cones will appear at all (twelve) selected positions.



Anything can be grown from these positions (including hydrogen) but any hit must contain phenol and a nitrogen bonded to three sp^3 carbon centers.

Click on ▾ to the right of the **Search** button in the **SMD** dialog to bring up the **SMD Search Options** dialog.


Spartan Molecular DB Search Options
☒
Using Directories:
☒ SmallMolecules
Method Filters:
☐ 3-21G
☐ 6-31G*
☐ 6-311+G**
☐ EDF1/6-31G*
☐ B3LYP/6-31G*
☐ B3LYP/6-311+G**
☐ MP2/6-31G*
☐ MP2/6-311+G**
☐ G3(MP2)
☐ Other
Search by:
● Structure
○ Name
○ Formula
○ Weight
○ Isomer
Limit Search to Entries with:
☐ Calculated IR Spectra
☐ Experimental IR Spectra
☐ Calculated UV Spectra
☐ Experimental UV Spectra
☐ Calculated NMR Spectra
☐ Experimental NMR Spectra
OK
Cancel

Check **6-31G*** under **Method Filters** and **Structure** under **Search by** in the **Search Options** dialog. *Click* on **OK**. Finally, *click* on the **Search** button at the bottom of the **SMD** dialog.

3. The search will result in upwards of 100 hits. Find and *click* on ***cephaeline*** from among those hits listed inside in the scroll box at the right of the **SMD** dialog. Its structure will be displayed in the window at the left of the dialog[*]. You can manipulate the model in the usual way by positioning the cursor inside this window. *Click* on ▼ to the right of the **Retrieve** button at the bottom of the **SMD** dialog to bring up the **Retrieve Options** dialog. *Check* **New Document** under **Retrieve Options** and *click* on **OK**. Finally, *click* on the **Retrieve** button. Dismiss the **SMD** dialog by *clicking* on ☒ at the top right-hand corner.

   Close the molecule used for the search (phenol and trimethylamine) without saving (📂). Save the molecule you retrieved under the name ***cephaeline*** (💾).

4. To shorten computer time, remove some of the degrees of conformational freedom from ***cephaeline***. Select **Set Torsions** from the **Geometry** menu (or *click* on ⟲). Your model will be augmented with yellow cylinders and circles to designate flexible bonds and rings, respectively. Remove the markers from the bonds connecting the three methoxy groups to aromatic rings by *double clicking* on each in turn. These bonds will no longer

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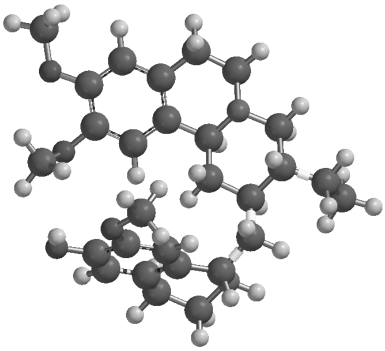
[*] *Click* on **Name** at the top of the list to sort in alphabetical order.

be included in the conformational search. Your model should now appear as follows with only three single bonds selected.

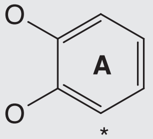


5. Bring up the **Calculations** dialog (**Calculations...** from the **Setup** menu). Select **Conformer Library** from the top left menu to the right of **Calculate**. No further information is required. *Click* on **Submit** at the bottom of the dialog. Continue with the tutorial while you are waiting for the job to complete.

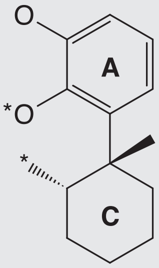
In the second part of the tutorial, you will identify the key structural components in morphine and perform a similarity analysis based on structure on the conformer library for ***cephaeline***.

6. You can either build morphine or (to save time) open it: ***morphine*** from the ***medicinal chemistry*** sub-directory (***tutorials*** directory).

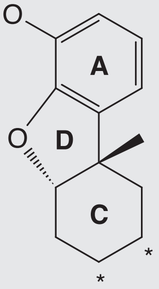
To build morphine, start with **Benzene** from the **Rings** menu. Add two (*ortho*) sp^3 oxygens (ˋo-) to make catechol and orient as below (free valences not drawn).



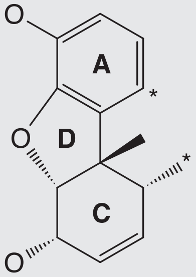
Select **Cyclohexane** from the **Rings** menu and *click* on the free valence on the *'ed carbon in catechol. Orient as below, with the free valence on the cyclohexane carbon used to attach to benzene pointing straight up.



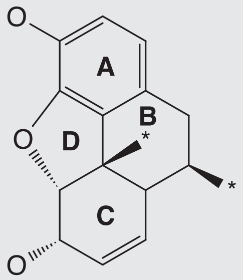
Select **Make Bond** from the **Build** menu (or *click* on). *Click* on the *'ed free valences indicated in the structure above, one on oxygen and one on carbon pointing down (relative to the free valence on the carbon used to attach the two rings). A bond will be drawn to make the **D** ring.



Make Bond is still selected. *Click* on *axial* free valences on the *'ed carbons in the cycohexane ring to introduce a double bond. Also, add a hydroxyl group to this ring (O-) adjacent to the double bond. (Pay attention to stereochemistry.) Select **Minimize** from the **Build** menu (or *click* on E) to refine your structure.

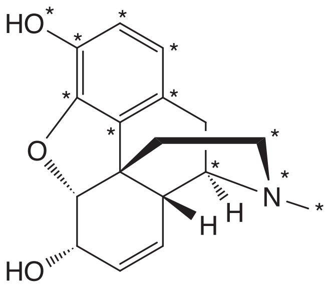


Add sp^3 carbons (C-) to free valences at the *'ed positions in the figure above (pay attention to stereochemistry on the cyclohexene ring). *Click* on and then *click* on free valences on each of the two sp^3 carbons that you have just added. You have made the **B** ring. Check that the stereochemisty is as it should be.



Connect the two *'ed free valences in the figure above with a chain of two sp^3 carbons (>C-) and an sp^3 nitrogen (>N). Add an sp^3 carbon to the nitrogen. You have made morphine (its name should appear at the bottom of the screen). *Click* on E to produce a refined structure and on V to remove the model kit.

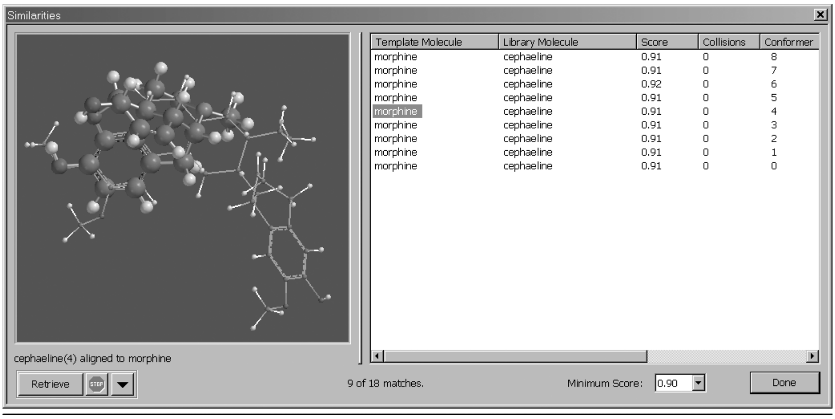
7. Select **Set Similarity Centers** from the **Geometry** menu (or *click* on ⊙) and select **structure** from the menu at the bottom right of the screen. *Click* on the eleven *'ed atoms in the figure below. A red circle will be drawn around each. If you make a mistake and select the wrong atom, *click* on the circle to deselect it.



8. Select **Calculations...** from the **Setup** menu. Select **Similarity Analysis** from the top left menu to the right of **Calculate** inside the **Calculations** dialog. *Click* on **Add Library** to bring up the **Add Similarity Libraries** dialog. *Click* on **Browse** inside this dialog, locate and select ***cephaeline***, and *click* on **OK**. Make certain that **Structure** is selected from the **Use** menu at the lower right of the dialog. You have requested that the library of cephaline conformers be searched for a match to the key

structural elements of morphine. *Click* on **Submit**.[*] Supply the name ***morphine***.

9. The similarity analysis will require a few seconds. When it completes, select **Similarities...** from the **Display** menu.



Template Molecule	Library Molecule	Score	Collisions	Conformer
morphine	cephaeline	0.91	0	8
morphine	cephaeline	0.91	0	7
morphine	cephaeline	0.92	0	6
morphine	cephaeline	0.91	0	5
morphine	cephaeline	0.91	0	4
morphine	cephaeline	0.91	0	3
morphine	cephaeline	0.91	0	2
morphine	cephaeline	0.91	0	1
morphine	cephaeline	0.91	0	0

cephaeline(4) aligned to morphine

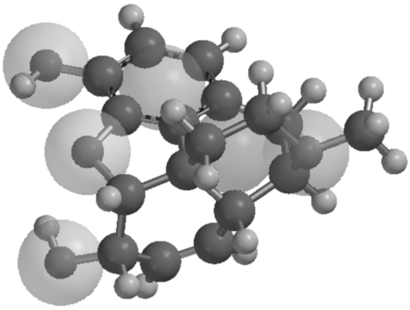
9 of 18 matches.

Minimum Score: 0.90

10. One or more hits should appear in the box at the right of the dialog together with a score. Sort according to score (best on top) by *clicking* on **Score** at the top of the box. Select (*click* on) one of the best matches. A composite graphic consisting of morphine and the matching cephaeline conformer from the library will appear in a window at the left. You can manipulate the two structures (as a single object) in the usual way.

Repeat the similarity analysis using CFD's rather than structure.

11. Select **Set Similarity Centers** from the **Geometry** menu (⊙), but this time select **CFD** from the menu at the bottom right of the screen. CFD's will augment the morphine structure.



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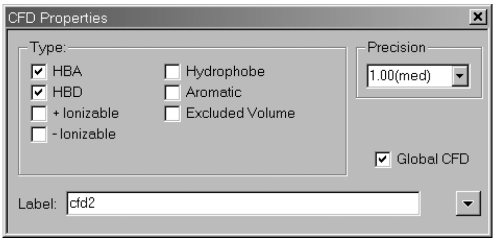
[*] You need to close ***cephaeline*** before carrying out the similarity analysis.

12. Designate three of the CFD’s as similarity centers. Select **Properties** from the **Display** menu and *click* on the CFD over the phenolic oxygen. A violet circle will surround this center indicating that it is to be used in the similarity analysis. (If you make a mistake and select the wrong CFD, *click* on the circle and it will disappear.) *Check* both **HBA** and **HBD** in the **CFD Properties** dialog that appears.



CFD Properties

Type:

☑ HBA

☑ HBD

☐ + Ionizable

☐ - Ionizable

☐ Hydrophobe

☐ Aromatic

☐ Excluded Volume

Precision: 1.00(med)

☑ Global CFD

Label: cfd2

Repeat the process for the CFD at nitrogen, designating it as both a hydrogen-bond acceptor and a positive ionizable center and for the CFD at the middle of the phenol ring, designating it as both a hydrophobe and an aromatic.

13. Enter the **Calculations** dialog. This should already designate **Similarity Analysis** and the appropriate library (***cephaeline***). Change the entry in the **Use** menu to **CFD**. *Click* on **Submit**.

14. When the analysis is complete, bring up the **Similarities** dialog (**Similarities...** under the **Display** menu). One or more hits should appear in the box at the right of the dialog. Select a hit to get a composite graphic (CFD and structure from the library). You can easily see the extent to which the two are matched.

15. Close all documents open on screen.

Chapter 8

Polypeptides to Proteins

This chapter introduces the peptide model kit and shows how a structure from the Protein Data Bank (PDB) may be brought into ***Spartan*** *for further analysis.*

At present, calculations on real biopolymers (proteins and RNA/DNA strands) are limited to molecular mechanics models. However, quantum chemical calculations are now routinely applicable to molecules bound into biopolymers and to the investigation of the electronic and steric factors that are responsible.

This chapter comprises three tutorials. The first illustrates ***Spartan's*** peptide model kit to construct triglycine and decaglycine in idealized helical arrangements. Comparisons are made between zwitterion and non-zwitterion forms in and out of water and electrostatic potential maps are employed to investigate charge separation.

The second tutorial illustrate ***Spartan's*** on-line access to PDB. A small molecule is extracted from a protein structure and the question is posed as to the energy of its (bound) conformer compared to that of the free conformer.

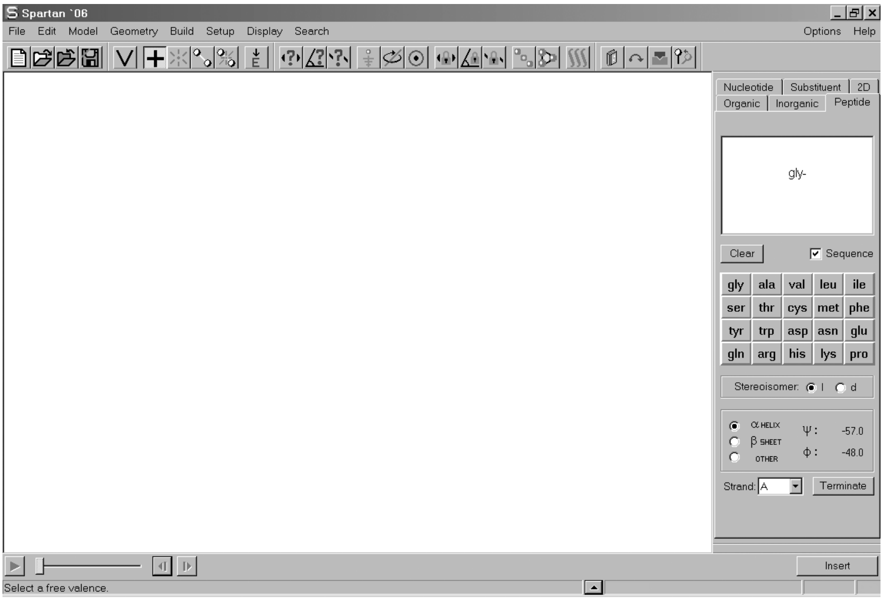
The third tutorial also involves extraction from a PDB file, but this time the quantity of interest is not the molecule itself, but rather its environment. This is turned into a so-called pharmacophore (a very much simplified representation of the environment), and a search for other molecules that would also be consistent with this environment is carried out.

5 mins/10 mins

Polyglycine

Triglycine and decaglycine may be used to illustrate construction of simple amino acid sequences using ***Spartan's*** peptide model kit, as well as to investigate the role of aqueous media in altering the equilibrium between neutral and zwitterionic forms and to show the utility of electrostatic potential maps in conveying information about overall charge distribution.

1. Bring up the peptide model kit by *clicking* on 🗋, and then *clicking* on the **Peptide** tab at the top of the organic model kit.


Spartan '06
File
Edit
Model
Geometry
Build
Setup
Display
Search
Options
Help
Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
Clear
gly
ala
val
leu
ile
ser
thr
cys
met
phe
tyr
trp
asp
asn
glu
gln
arg
his
lys
pro
α HELIX
β SHEET
OTHER
Terminate
Insert

gly-

☑ Sequence

Stereoisomer: ● l ○ d

● α HELIX ○ β SHEET ○ OTHER ψ: -57.0 φ: -48.0

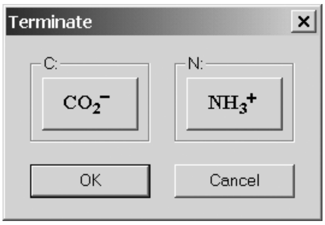
Strand: A

Select a free valence.

2. Make certain that **Sequence** is checked, and then *click* three times on gly (glycine) from the selection of amino acid codes. The sequence **gly-gly-gly** will appear in the box at the top of the model kit.

3. α **Helix** near the bottom of the model kit should be selected. If it is not, *click* on it. The backbone ψ and φ angles which define an α helix will appear at the right. *Click* anywhere on screen. Triglycine will appear, although it will not be properly terminated.

4. First consider the non-zwitterionic structure. *Click* on **Terminate** in the model kit. The **Terminate** dialog will appear allowing you to specify C and N terminating groups.



Select **CO_2H** for the C terminating group (*click* on the icon to cycle between groups), and **NH_2** for the N terminating group. *Click* on **OK**.

> Amino acids replace atomic fragments, functional groups, rings and ligands as the basic building blocks in the peptide model kit, and these other building blocks are missing. Therefore, most modifications of peptides, aside from modifications in sequence of amino acids and in overall conformation, need to be carried out using either the organic or inorganic model kits.

5. Select **Freeze Center** from the **Geometry** menu (or *click* on ‡). *Click* on **Freeze Heavy** at the bottom right of the screen. This indicates that all heavy (non-hydrogen) atoms are not to be moved during molecular mechanics minimization.[*] *Click* on ↓E to produce a refined structure (subject to the restriction that heavy atoms are kept in place).

6. Select **New Molecule** from the **File** menu. *Click* anywhere on screen. *Click* on **Terminate** inside the model kit and this time select **CO_2^-** and **NH_3^+** for C and N terminating groups, respectively. *Click* on **OK**. *Click* on ‡ and then *click* on **Freeze Heavy** at the bottom of the screen. Finally, *click* on ↓E.

7. Dismiss the model kit by *clicking* on V. Both forms of triglycine now occupy the same group. Enter the **Calculations** dialog and specify an energy calculation using the Hartree-Fock 3-21G

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[*] This is necessary to maintain the idealized helix structure.

model. Do not change **Total Charge** (from **Neutral**) for the zwitterionic form of triglycine. Even though its Lewis structure incorporates formal + and - charges, the molecule is neutral. Also make certain that **Global Calculations** is checked. *Click* on **Submit** at the bottom of the dialog. Name the job ***triglycine***.

8. After the calculations complete, bring up the spreadsheet, *click* on the header cell of an empty column, and *click* on **Add...** at the bottom of the spreadsheet. Select both **E** and **Eaq** from the list of available properties at the top of the dialog which appears, and **kJ/mol** from the **Energy** menu, and then *click* on **OK**.

   Which form of triglycine, zwitterion or non-zwitterion, is favored in the gas phase? Which form of triglycine, zwitterion or non-zwitterion, is favored in water? Rationalize any differences in relative energies between the gas and aqueous-phase results.

9. Remove ***triglycine*** and remaining dialogs from the screen.

10 to 14 optional

An electrostatic potential map for the zwitterionic form of a larger polypeptide, decaglycine, clearly shows charge separation, and explain why such a structure is not favored in the gas phase.

10. Bring up the peptide model kit.* *Click* seven times on gly (glycine) from the selection of amino acid codes. A sequence of ten glycines has now been requested. *Click* anywhere on screen. *Click* on **Terminate** in the model kit and select **CO_2^-** and **NH_3^+** for C and N terminating groups, respectively, and then *click* on **OK**. *Click* on ‡ and then *click* on **Freeze Heavy** at the bottom of the screen. *Click* on ↓E, and then *click* on V to dismiss the model kit.

11. Enter the **Calculations** dialog and specify an AM1 energy calculation. *Check* **Converge** (near the bottom right of the dialog). Semi-empirical calculations on molecules of this

---

* The following instructions assume that this section follows the building of triglycine, that is, that the box at the top of the peptide model kit already contains a sequence of three glycines. If you are starting from scratch, first make certain that **Sequence** is checked, then *click* ten times on gly, then *click* on α **Helix** and finally *click* anywhere on screen.

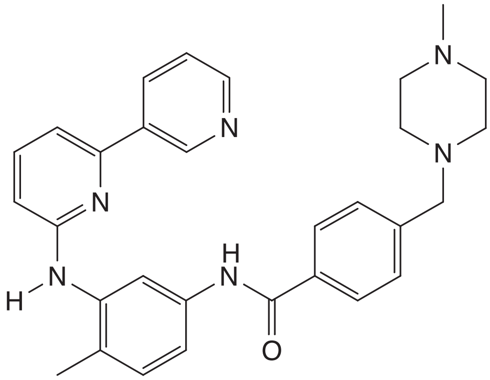
complexity often have trouble converging and this option invokes a number of special convergence techniques.

12. Bring up the **Surfaces** dialog and request calculation of an electrostatic potential map. *Click* on **Add...**, select **density** from the **Surface** menu and **potential** from the **Property** menu, and *click* on **OK**.

13. Submit the job. Name it ***decaglycine zwitterion***. Execution will take several minutes due primarily to calculation of the graphic. When completed, again enter the **Surfaces** dialog. *Click* on the line ***density potential...***. Examine the electrostatic potential map. Recall that colors near red correspond to areas on the surface which are negatively charged (attracted to a point-positive charge), while colors toward blue designate regions of positive charge. Intermediate colors (greens) represent neutral regions. What do you conclude about the environment in which decaglycine wishes to exist?

14. Remove decaglycine and any remaining dialogs from the screen.

Gleevec. Protein Bound vs. Free Conformer
(cannot be completed with the Essential Edition)



gleevec

Gleevec (Glivec, Inatinib) is a protein kinase inhibitor used in anticancer therapy. It specifically targets a protein kinase coded for in the rogue gene "bcr-abl". Several crystal structures for gleevec docked in protein kinases have appeared in the literature and are available in the PDB. In this tutorial, you will examine one of them[*] to establish whether or not the conformation of gleevec in the protein is identical (or similar) that for the free (gas-phase) molecule, and if not, what energy penalty needs to be paid. The next tutorial will return to this same structure and extract a pharmacophore (gleevec's footprint).

1. Retreive the protein structure from the PDB website.

> If you are not online, you may skip this step as the structure is available as ***1opj*** in the ***polypeptides to proteins*** sub-directory (***tutorials*** directory). Open this document.

Select **Databases** from the **Search** menu and *click* on the **PDB** tab to bring up the **PDB** dialog.

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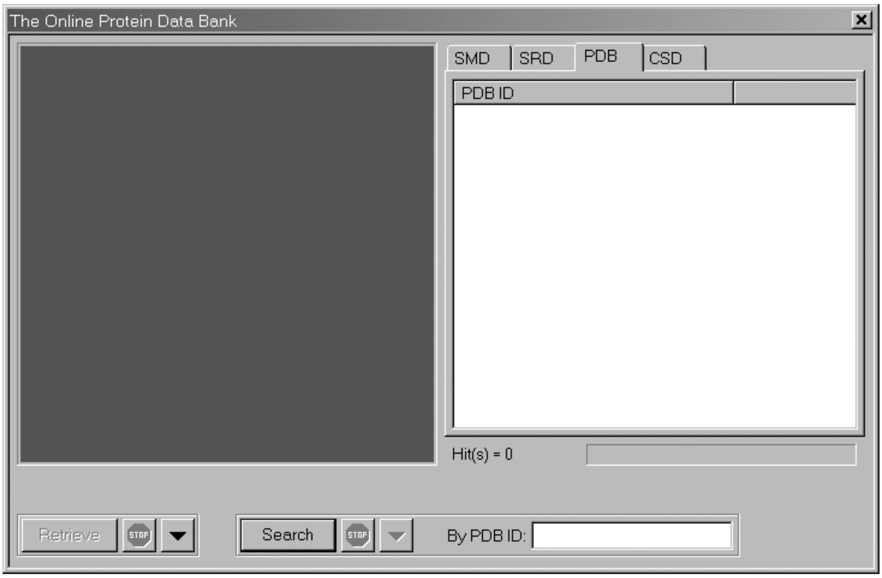
[*] B. Nager *et al*, Cell, **112**, 859 (2003): PDB identification 1opj.

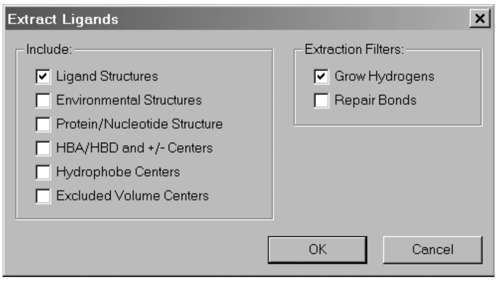


Type **1opj** into the box to the right of **By PDB ID** at the bottom of the dialog and *click* on the **Search** button. In a few seconds, the PDB entry 1opj will appear on the large box at the right of the dialog. Select (*click* on) it and then *click* on the **Retrieve** button. Close the dialog by *clicking* on ☒ at the top right-hand corner.

> The monochrome ribbon display may be modified, by selecting **Configure...** from the **Model** menu and *clicking* on the **Ribbons** tab. Coloring **By Secondary Structure** will display helices in red and β sheets in blue, while coloring **By Residue** will give each amino acid its own unique color.

The protein will be represented by a ribbon model and any incorporated molecules by a set of translucent spheres, much like a space-filling model. Gleevec is the larger of the two incorporated molecules and is designated by its PDB HET code STI.

2. Select **Ligands** from the **Search** menu (or *click* on the ▼ icon at the top of the screen). Select (*click* on) gleevec inside the protein structure and *click* on the **Extract Ligands** button at the bottom right of the screen. This leads to the **Extract Ligands** dialog.


Extract Ligands

Include:

☑ Ligand Structures
☐ Environmental Structures
☐ Protein/Nucleotide Structure
☐ HBA/HBD and +/- Centers
☐ Hydrophobe Centers
☐ Excluded Volume Centers

Extraction Filters:

☑ Grow Hydrogens
☐ Repair Bonds

Check **Ligand Structures** under **Include** and both **Repair Bonds** and **Grow Hydrogens** under **Extraction Filters** inside the dialog and *click* on **OK**.

3. A ball-and-spoke model for gleevec will appear on screen. (You don’t need the protein any more so select and close it.) Put a copy of gleevec on the clipboard. Position the cursor above and to the left of the structure on screen, then hold down both the left and right buttons and *drag* the mouse below and to the right of the structure and finally release both buttons. A selection box will be drawn. Select **Copy** from the **Edit** menu.

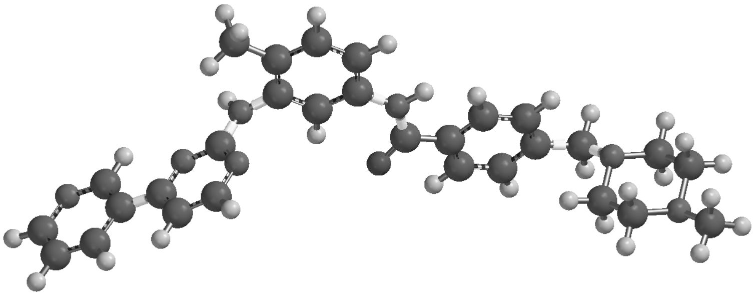
4. Select **New Molecule** (not **New**) from the **File** menu. Select **Clipboard** from the model kit and *click* anywhere on screen. *Click* on V to remove the model kit. You now have two copies of gleevec in a single document. You can step between them using the step buttons at the bottom left of the screen.

5. Select the first copy and then select **Calculations...** from the **Setup** menu. **Equilibrium Geometry** from the top left menu to the right of **Calculate** and **Molecular Mechanics** and **MMFF** from the two bottom menus. The conformation will remain unchanged, but bond lengths and angles will be optimized.

> This is necessary in order to establish the energy difference between protein-bound and free conformations of gleevec. The resolution of protein X-ray crystallography is not adequate to establish bond lengths and angles to chemical accuracy.

Remove the checkmark from **Global Calculations** at the bottom of the dialog to signify that your choice (geometry optimization) only applies to this copy of gleevec. *Click* on **OK**.

6. Select the second copy of gleevec. Remove some degrees of conformational freedom in order to shorten the computer time for the conformational search. *Click* on . Your model will be augmented with yellow cylinders and circles to designate flexible bonds and rings, respectively. Remove the marker from the bond connecting the phenyl ring to the carbonyl end of the amide group, by *double clicking* on it. Also, remove the (two) circles on the piperazine ring by *double clicking* on each in turn. The conformation of the piperazine ring will not change during the search. The model should now appear as below.



7. Re-enter the **Calculations** dialog. Select **Equilibrium Conformer** from the top left menu to the right of **Calculate** and (as before) **Molecular Mechanics** and **MMFF** from the two bottom menus. *Click* on **Submit**, and provide the name ***gleevec protein bound vs. free conformer***.

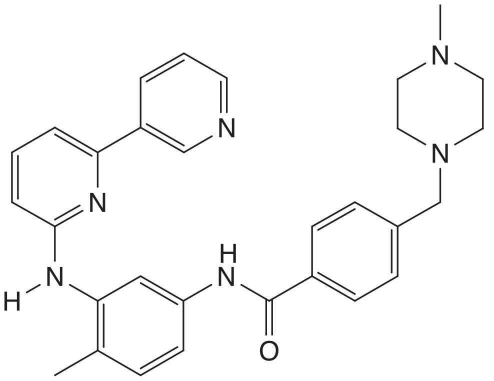
8. When the calculations have completed, bring up the spreadsheet (**Spreadsheet** under the **Display** menu), *click* inside the cell under **Label** for the second molecule and *click* inside the header cell for a blank data column. *Click* on **Add** at the bottom of the dialog and select **Rel. E** from the scroll box in the dialog that appears and **kJ/mol** from the **Energy** menu. The relative energy of the protein bound conformer is provided in the spreadsheet.

Your result shows that the conformation of the protein-bound molecule is significantly higher in energy than that conformer adopted by isolated gleevec. It suggests that focus should be on identifying diverse conformers rather than only the lowest-energy conformers.

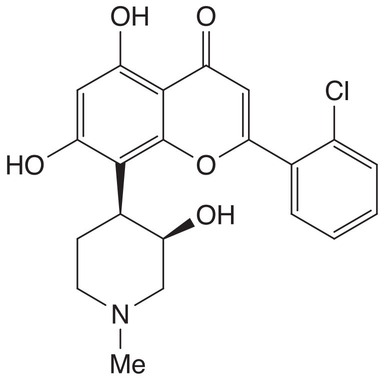
9. Close ***gleevec protein bound vs. free conformer***.

5 mins

Gleevec. Making a Pharmacophore from PDB *(cannot be completed with the Essential Edition)*



gleevec



flavopiridol

In the previous tutorial, you extracted gleevec from a PDB structure of a protein kinase in order to see if the bound conformer was the same as the free conformer. Here, you will start from the same protein structure[*], but instead of abstracting the molecular structure of gleevec, you will abstract its footprint, that is, the locations from which it interacts with its protein host in terms of hydrogen-bond or charge-charge interactions (non-steric contacts). This information, together with knowledge of either the steric requirements of the guest or the space occupied by the protein (excluded volumes), constitutes a pharmacophore, that is, a template for scrutiny of other possible guests. In this tutorial, you will use a subset of the non-steric contacts together with excluded volume elements to see to what extent this pharmacophore fits another protein kinase inhibitor, flavopiridol.

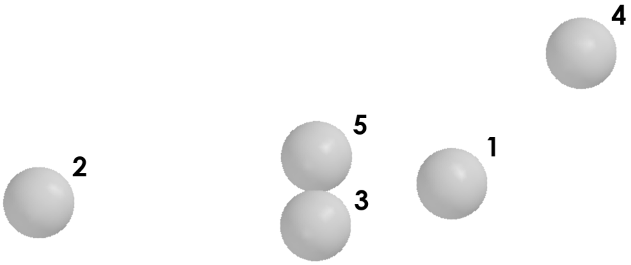
1. Open ***1opj*** from the ***polypeptides to proteins*** sub-directory (***tutorials*** directory). Select **Ligands** from the **Search** menu (or *click* on), *click* on the model for gleevec inside the protein structure (displayed as a set of transparent spheres and look much like a space-filling model) to select it, and *click* on the **Exact Ligands** button. Inside the **Extract Ligands** dialog, *check* both ***HBA/HBD and +/- Centers*** and **Excluded Volume Centers** and *click* on **OK**.

---

[*] B. Nager *et. al.*, Cell, **112**, 859 (2003): PDB identification 1opj.

2. You are finished with ***1opj*** and can close it (📂). Also, simplify the display of the extracted information by removing the excluded volume elements from view. Select **Configure...** from the **Model** menu and *click* on the **CFDs** tab. *Uncheck* **Excluded Volumes** and *click* on **OK**.

3. The model that now appears comprises five gold spheres representing non-steric contacts between gleevec and its protein host. Turn on labels. Select **Configure...** from the **Model** menu, *click* on the **Labels** tab, *check* **CFD Labels** and *click* on **OK**.



These have been assigned based on the observation that each is within a predefined distance of (one or more) complementary groups on amino acids in the protein host. Because hydrogen positions are not known (in the experimental X-ray structure) it may be impossible to say whether a particular site on the guest is acting as a (hydrogen-bond) donor or acceptor. In fact, it may not even be possible to say whether a particular site is protonated or deprotonated (although pH may dictate this). This being the case, all non-steric contacts have initially been given four CFD definitions: hydrogen-bond acceptor (**HBA**), hydrogen-bond donor (**HBD**), positive ionizable (+) and negative ionizable (–). Examination of the structure of gleevec suggests more focused assignments: **1** (**HBA**, +), **2** (**HBA**, **HBD**), **3** (**HBD**), **7** (**HBA**) and **8** (**HBA**). (See above figure for numbering.)

4. You will use only three elements of this pharmacophore (together with all the excluded volume elements) to assess whether or not flavopiridol is likely to fit into the same host environment as gleevec. Select **Properties** from the **Display** menu. Then select **Set Similarity Centers** from the **Geometry**

menu (or *click* on ⊙). *Click* on the pharmacophore element designated as **1** (see figure above). A violet circle will surround the element designating that it is to be used in the similarity analysis. If you make a mistake and select the wrong element, *click* on the circle and the designation will be removed. Inside the **CFD Properties** dialog, remove checkmarks from **HBD** and **– Ionizable** (you are left with **HBA** and **+ Ionizable**). Repeat the process for the pharmacophore element **3**, designating it as **HBD** only and **8**, designating it as **HBA** only. When you are done, only three of the five pharmacophore elements should be marked. *Click* on ✓.

5. Select **Calculations...** from the **Setup** menu and then **Similarity Analysis** from the top left menu to the right of **Calculate**. *Click* on **Add Library...** and then on **Browse** in the **Add Similarity Libraries** dialog that appears. Locate and select ***flavopiridol*** in the ***polypeptides to proteins*** sub-directory (***tutorials*** directory) and *click* on **OK**. *Click* on **Submit**. Name the document ***flavopiridol fit to gleevec pharmacophore***.

6. When the similarity analysis has completed (a minute or two), bring up the **Similarities** dialog (**Similarities...** from the **Display** menu). First, sort the hits according to similarity score (*click* on **Score** at the top of the dialog). One after the other, *click* on the top scoring entries in the box to the right of the dialog and examine the fits in the window at the left.

   Specification of only non-steric contacts based on existing ligand-host structures may not always provide a suitable pharmacophore. For one, many ligands bind to their host at only one or two points (insufficient to construct a pharmacophore) and some do not exhibit any non-steric contacts. One way to incorporate steric contacts is to designate those regions in space immediately surrounding the ligand that are occupied by the host, so-called excluded volumes. While the score reported by ***Spartan*** does not directly take account of incursions into the excluded volumes, the number of collisions with the guest are tabulated in the dialog. The fewer the collisions, the more likely will the host be able to adjust to the guest.

5. Close any open documents on screen.

Chapter 9

Inorganic and Organometallic Molecules

*This chapter shows how to construct inorganic and organometallic molecules using **Spartan's** inorganic model kit. It also identifies quantum chemical models that appear to be suitable for calculations on molecules incorporating transition metals.*

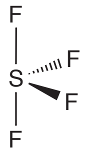
The majority of organic molecules are made up of a relatively few elements and obey conventional valence rules. They may be easily built using the organic model kit. However, many molecules incorporate other elements, or do not conform to normal valence rules, or involve ligands. Most important among them are inorganic and organometallic compounds involving transition metals. These need to be constructed using the inorganic model kit.

Transition-metal inorganic and organometallic compounds may also require different quantum chemical methods from those that have proven to be satisfactory for organic molecules. In particular, Hartree-Fock and MP2 models are known to produce poor results where transition metals are involved. The PM3 semi-empirical model, that has been parameterized for most transition metals, generally provides a good account of equilibrium geometries, as do density functional models. The latter are also believed to provide a satisfactory account of the thermochemistry of reactions involving transition-metal systems, although there are very little experimental data with which to compare.

The tutorials in this chapter illustrate construction of inorganic and organometallic molecules, as well as the selection of suitable quantum chemical models.

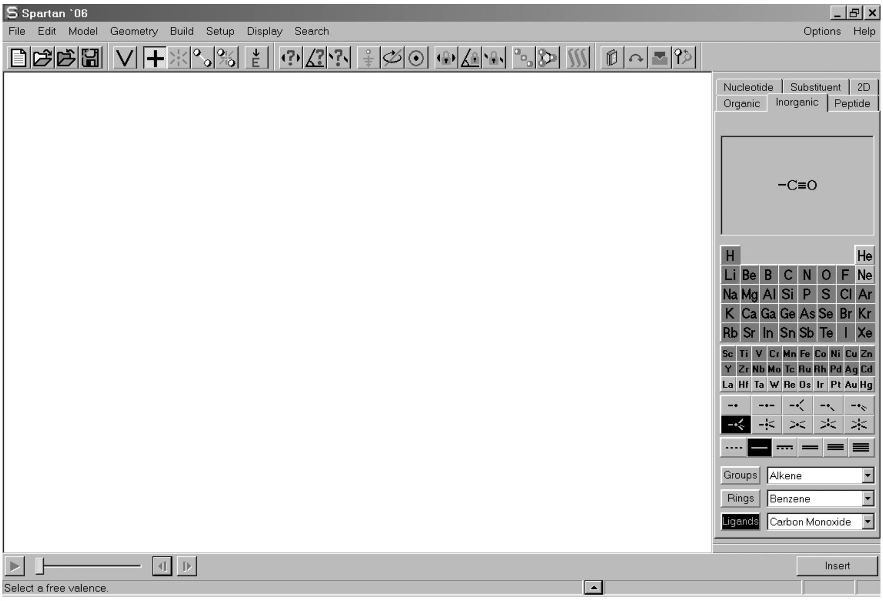
1 min

Sulfur Tetrafluoride



Sulfur tetrafluoride cannot be constructed using ***Spartan's*** organic model kit. This is because sulfur is not in its normal bent dicoordinate geometry, but rather in a trigonal bipyramid geometry with one of the *equatorial* positions vacant. However, the molecule can easily be made using the inorganic model kit.

1. Bring up the inorganic model kit by *clicking* on 🗋 and then *clicking* on the **Inorganic** tab at the top of the (organic) model kit.


Spartan '06
File
Edit
Model
Geometry
Build
Setup
Display
Search
Options
Help
Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
-C≡O
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Ga Ge As Se Br Kr
Rb Sr In Sn Sb Te I Xe
Sc Ti V Cr Mn Fe Co Ni Cu Zn
Y Zr Nb Mo Tc Ru Rh Pd Ag Cd
La Hf Ta W Re Os Ir Pt Au Hg
Groups
Alkene
Rings
Benzene
Ligands
Carbon Monoxide
Insert

Select a free valence.

The inorganic model kit comprises a *Periodic Table*[*] followed by a selection of atomic hybrids, then bond types, and finally

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[*] Macintosh and Linux versions do not display a partial *Periodic Table* but rather require the user to *click* on an atom button (below the display at the top of the model kit) to bring up a full *Periodic Table*. See **Chapter 14** for a discussion. Not all methods are available for all elements listed. Elements for which a specific method (selected in the **Calculations** dialog) are available will be highlighted in the *Periodic Table* if **Element Overlay** in the **Settings Preferences** dialog (**Preferences...** under the **Options** menu; see **Chapter 18**) is turned "on". Note also that elements beyond those listed in the *Periodic Table* may be specified. For a discussion, see **Atom Properties** under the **Display** menu (**Chapter 16**).

Rings, **Groups** and **Ligands** menus (the first two of which are the same as found in the organic model kit).

2. Select (*click* on) **S** in the *Periodic Table* and the five coordinate trigonal bipyramid structure -⁖ from the list of atomic hybrids. *Click* on screen. A trigonal bipyramid sulfur will appear.
3. Select **F** in the *Periodic Table* and the one-coordinate entry -• from the list of atomic hybrids. One after the other, *click* on both *axial* free valences of sulfur, and two of the three *equatorial* free valences.
4. It is necessary to delete the remaining free valence (on an *equatorial* position); otherwise it will become a hydrogen. *Click* on ⁜ and then *click* on the remaining *equatorial* free valence.
5. *Click* on ↓E. *Click* on ✓ to remove the model kit.
6. Select **Calculations...** from the **Setup** menu. Specify calculation of equilibrium geometry[*] using the Hartree-Fock 3-21G model.[**]
7. Submit the job. Name it ***sulfur tetrafluoride***.When completed, select **Properties (Display** menu) and *click* on an atom, for example, sulfur. Three different atomic charges will appear in the (**Atom Properties**) dialog (corresponding to different methods for establishing atomic charge). Of these, the procedure based on fitting the electrostatic potential is generally considered to be the best. Are the electrostatic charges consistent with covalent or ionic bonding?
8. Remove ***sulfur tetrafluoride*** and any remaining dialogs from the screen.

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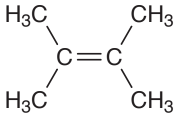
[*] It should be noted that were an incorrect geometry specified at the outset, optimization would lead to the correct structure, as long as the starting geometry possessed no symmetry (C_1 point group). Thus, square planar SF_4 in D_{4h} symmetry would remain square planar, while an almost square planar structure (distorted only slightly from D_{4h} symmetry to C_1 symmetry) would collapse to the proper structure.

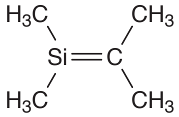
[**] The 3-21G$^{(*)}$ basis set, that incorporates a set of unoccupied d-type functions, is used in place of 3-21G for the sulfur atom.

5 mins

Reactivity of Silicon-Carbon Double Bonds



2,3-dimethyl-2-butene



tetramethylsilaethylene

With the exception of so-called phosphorous ylides, compounds incorporating a double bond between carbon and a second-row element are quite rare. Most curious perhaps is the absence of stable compounds incorporating a carbon-silicon double bond. This can be rationalized by using local ionization potential and LUMO maps to compare the reactivities of olefins and silaolefins.

1. Build 2,3-dimethyl-2-butene, minimize (↓E) and copy onto the clipboard. Select **New Molecule** (not **New**) from the **File** menu, *click* on **Clipboard** inside the organic model kit and *click* anywhere on screen. *Click* on the **Inorganic** tab (at the top of the organic model kit) to bring up the inorganic model kit. *Click* on **Si** in the *Periodic Table* and *double click* on one of the sp^2 carbons to substitute a silicon atom for a carbon atom and to make tetramethylsilaethylene. *Click* on ↓E and then on V. You are left with 2,3-dimethyl-2-butene and tetramethylsilaethylene in the same document.

2. Use the structures in SMD to save computer time. *Click* on ▲ to the left of the molecule name (either 2,3-dimethyl-2-butene or tetramethylsilaethylene) at the bottom of the screen, select **3-21G** from the entries in the **SMD Preview** dialog and *click* on **Replace All**.

3. Select **Calculations** from the **Setup** menu. Specify calculation of energy using the Hartree-Fock 3-21G model. *Click* on **OK**.

4. Select **Surfaces** from the **Setup** menu. First request a local ionization potential map. *Click* on **Add**, select **density** from the **Surface** menu and **ionization** from the **Property** menu and *click* on **OK**. Then request a LUMO map. *Click* on **Add** a second time

and again select **density** from the **Surface** menu. Select **LUMO** from the **Property** menu and *click* on **OK**.

5. Submit the job. Name it ***tetramethylsilaethylene***. When completed, bring up the spreadsheet (**Spreadsheet** under the **Display** menu) and *check* the box to the right of the label for both entries. This allows simultaneous display of both molecules. Select **Coupled** (**Model** menu) to uncouple the motions of the molecules. Position the two molecules side by side on screen.

6. Inside the **Surfaces** dialog, select ***density ionization...***. Compare local ionization potential maps for the olefin and silaolefin, recognizing that the more red the color, the lower the ionization potential and the more susceptible toward electrophilic attack. Which molecule do you conclude is likely to be more reactive? Turn "off" local ionization potential maps by again selecting ***density ionization...***. Select ***density |LUMO|...*** to turn on LUMO maps. Here, the more blue the color, the greater the concentration of the LUMO and the more susceptible toward nucleophilic attack. Which molecule do you conclude is likely to be more reactive? Close ***tetramethylsilaethylene*** when you are finished.

7 - 10 Optional *(Requires Access to the Cambridge Structural Database, NAM)*

Identify molecules in the Cambridge Structural Database (CSD) that incorporate a carbon-silicon double bond.

7. Build parent silaethylene, $H_2Si=CH_2$, by starting from ethylene and substituting a silicon for one of the carbons.

8. Bring up the **Cambridge Structural Database** (**CSD**) dialog by first selecting **Databases** from the **Search** menu and then *clicking* on the **CSD** tab. *Click* on all four free valences in silaethylene. They will be marked by orange cones. *Click* on the **Search** button at the bottom of the dialog. In a few seconds, hits will begin to appear in the box at the right of the dialog. Examine each in turn (in the window at the left of the dialog) by *clicking* on its CSD

reference code (**REFCODE**). Identify a structure that appears to be representative for closer scrutiny. Before you retrieve it, *click* on ▼ to the right of the **Retrieve** button at the bottom of the dialog. *Check* all four boxes under **Post Retrieval Filters** in the **Retrieve Options** dialog that results and *click* on **OK**. *Click* on the selected **REFCODE** and then *click* on the **Retrieve** button. Dismiss the **CSD** dialog.

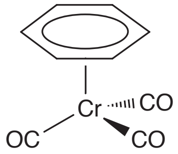
9. *Click* on ↓E. Except for hydrogens, all atoms in the structure you have retrieved will be fixed and energy minimization will only change hydrogen positions. This is to compensate for the fact that hydrogens are generally not well located in X-ray crystal structure determinations.

   Change the display to a space-filling model. Pay particular attention to the incorporated silicon-carbon double bond. Is it accessible in all of the compounds or is it encumbered by the surrounding groups? What, if anything, do your observations suggest about why this particular compound can be (has been) made?

10. Close silaethylene (without saving) and any open dialogs.

2 mins/30 mins

Benzene Chromium Tricarbonyl

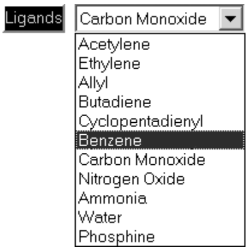


benzene chromium tricarbonyl

Comparison of electrostatic potential maps for this system and that of free benzene will allow you to classify Cr(CO)$_3$ as an electron donor or an electron acceptor substituent.

1. *Click* on 🗎 and bring up the inorganic model kit. Select **Cr** from the *Periodic Table* and the four-coordinate tetrahedral structure -< from the list of atomic hybrids. *Click* anywhere on screen.

2. *Click* on **Ligands** in the model kit, select **Benzene** from the menu of available ligands.


Ligands
Carbon Monoxide
Acetylene
Ethylene
Allyl
Butadiene
Cyclopentadienyl
Benzene
Carbon Monoxide
Nitrogen Oxide
Ammonia
Water
Phosphine

Click on one of the free valences on the four-coordinate chromium center.

3. Select **Carbon Monoxide** from the **Ligands** menu, and *click* on the remaining (three) free valences on chromium. *Click* on E to produce a refined structure.

4. Select **New Molecule** from the **File** menu. The screen will blank. Build benzene and *click* on E. *Click* on V.

5. Select **Calculations...** (**Setup** menu). Specify calculation of equilibrium geometry with the semi-empirical PM3 model. Make certain that **Global Calculations** (at the bottom of the dialog) is checked. You want the calculations to apply to both benzene chromium tricarbonyl and benzene. *Click* on **OK**.

6. Select **Surfaces** (**Setup** or **Display** menu). *Click* on **Add...**. Specify **density** from the **Surface** menu, and **potential** from the **Property** menu, and *click* on **OK**. Make certain that **Global Surfaces** is checked.

7. Submit the job (two separate calculations). Name it ***benzene chromium tricarbonyl***. When completed bring up the spreadsheet (**Spreadsheet** from the **Display** menu), and *check* the box to the right of the label for both entries. This allows the two molecules to be displayed simultaneously on screen. If **Coupled** (**Model** menu) is *checked*, remove the checkmark by selecting it. The two molecules may now be moved independently. Orient each molecule so that you can clearly see the benzene face (exposed face in the case of the organometallic).

8. Inside the **Surfaces** dialog, select ***density potential...***. Compare electrostatic potential maps for both free and complexed benzene, with attention to the exposed face on benzene.* Is the effect of the $Cr(CO)_3$ group to donate or to withdraw electrons from the ring? Would you expect the aromatic ring in benzene chromium tricarbonyl to be more or less susceptible to electrophilic attack than free benzene? More or less susceptible to nucleophilic attack?

9 optional *(cannot be completed with the Essential Edition)*

9. Repeat the two calculations using density functional theory. Make a copy of ***benzene chromium tricarbonyl*** (💾); name it ***benzene chromium tricarbonyl density functional***. Inside the **Calculations** dialog, specify an energy calculation using the BP/6-31G* model. Submit. When completed, examine the electrostatic potential maps. Are they qualitatively similar to those from the PM3 calculations?

10. Remove all molecules and any remaining dialogs from the screen.

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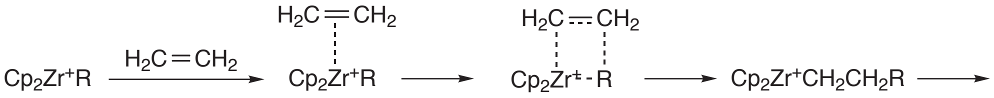
* Electrostatic potential maps (as well as other maps) for molecules in a group will be put onto the same (color) scale. This allows comparisons to be made among different members.

5 mins/90 mins

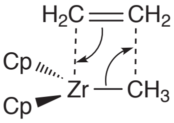
Ziegler-Natta Polymerization of Ethylene

Ziegler-Natta polymerization involves a metallocene. This first complexes an olefin, which then inserts into the metal-alkyl bond.



In this tutorial, you will use PM3 calculations to obtain a transition state for insertion of ethylene into $Cp_2ZrCH_3^+$ and, (optionally), estimate the activation energy using density functional calculations.

1. Bring up the inorganic model kit. Select **Zr** and -<, and *click* on screen. Select **Cyclopentadienyl** from the **Ligands** menu and *click* on two of the free valences on zirconium.
2. Move to the organic model kit. Select sp^3 carbon >C- and *click* on the remaining free valence on zirconium. Select **Alkene** from the **Groups** menu, *click* on the **Insert** button at the bottom of the model kit or hold down the **Insert** key (**alt** key on Mac) and *click* anywhere on screen.
3. Orient the two fragments (Cp_2ZrCH_3 and ethylene) as shown below:

   (To move the two fragments independently, hold down the **Ctrl** key.)
4. Select **Transition States** from the **Search** menu (↷). *Click* on the ZrC (methyl) bond, hold down the **Shift** key and, one after another, *click* on the methyl carbon and on one of the ethylene carbons. Next, *click* on the ethylene double bond, hold down the **Shift** key and, one after another, *click* on the other ethylene carbon and on zirconium. *Click* on ⟳ at the bottom right of the screen. In a few seconds, a guess at the transition state appears.

5. Bring up the **Calculations** dialog. Specify a transition state geometry calculation using the PM3 semi-empirical model. Change **Total Charge** to **Cation** and *check* **IR** to the right of **Compute**. *Click* on **Submit** and name the job ***Cp2ZrMe cation + ethylene***.

6. When the job has completed, bring up the **IR** dialog (**Spectra** from the **Properties** menu and *click* on the **IR** tab) and *click* on the imaginary frequency. Would you describe the process as concerted or occurring in discrete steps?

7 to 9 optional *(cannot be completed with the Essential Edition)*

7. Perform single-point BP/6-31G* density functional calculations to obtain an estimate for the energy barrier for ethylene insertion. Make a copy of ***Cp2ZrMe cation+ ethylene*** (💾); name it ***Cp2ZrMe cation+ethylene density functional***. Enter the **Calculations** dialog with this copy, and specify calculation of an energy using the BP/6-31G* density functional model. *Check* **Pseudopotential** at the far lower right of **Calculate** to specify use of a pseudopotential for Zr associated with the 6-31G* basis set. Remove the checkmark on **IR** (to the right of **Compute**). **Total Charge** should still be set to **Cation**. *Click* on **Submit**.

8. Build both ethylene and $Cp_2ZrCH_3^+$ (name them ***ethylene density functional*** and ***Cp2ZrMe cation***, respectively). For $Cp_2ZrCH_3^+$, start with three-coordinate trigonal Zr, and then add two cyclopentadienyl ligands and a four-coordinate tetrahedral carbon. For each, enter the **Calculations** dialog, and specify calculation of energy using the BP/6-31G* density functional model. Select **PM3** from the **Start from** menu to designate use of a PM3 geometry. For ***Cp2ZrMe cation density functional*** (only) *check* **Pseudopotential**, and set **Total Charge** to **Cation**.

9. Submit both jobs. When they (and the transition-state calculation) have completed, calculate an activation energy for the insertion reaction.

10. Remove all molecules and any remaining dialogs from the screen.

Section III

Features and Functions

This section describes the functions available under the menus incorporated into ***Spartan'06***, and is intended to serve as a general reference to the program. Available molecular mechanics and quantum chemical methods are enumerated as are similarity analysis capabilities, but no commentary is provided as to their performance or computational requirements. Similarly, available graphical displays are enumerated but no description of their use is provided. These issues are treated in detail in ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***.

Chapter 10

The File Menu

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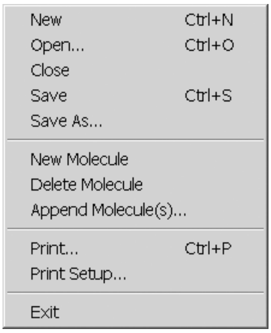
*Operations under the **File** menu access model kits to build, edit and substitute molecules and the file system to read and write both native and external files and print text and on-screen graphics.*


New Ctrl+N
Open... Ctrl+O
Close
Save Ctrl+S
Save As...
New Molecule
Delete Molecule
Append Molecule(s)...
Print... Ctrl+P
Print Setup...
Exit

New (🗋)

Brings up a model kit and clears the screen. Model kits are discussed in **Chapter 14**.

Open... (📂)

Opens a file that contains all information associated with a particular molecule or pharmacophore (or list of molecules and/or pharmacophores). In addition to native (.spartan) files (documents), supported are files containing 2D "drawings": CambridgeSoft (ChemDraw) CDX (.cdx), and MDL SDF (.sdf)*, SKC (.skc), and TGF (.tgf), files containing 3D structures: MacroModel (.mac),

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* SDF files may contain information in addition to geometry, for example, the name of the molecule or its CAS number. If available, each quantity appears in a line following <**xyz**> where **xyz** is a character string denoting the quantity, for example, **CAS**.

<CAS>
22090-26-2

This additional information may be accessed in the spreadsheet by typing the character string into a header cell, for example, typing **CAS** will result in the CAS number.

SYBYL Mol (.mol), SYBYL Mol2 (.mol2), and PDB (.pdb), and files containing 1D “structures”: SMILES (.smi).

> We use the word “file” to refer to any information contained in the “file system” (the disk on your computer) and the word “document” to refer to files that are native to ***Spartan***. Thus, an MDL SDF ***file*** may be read into ***Spartan*** and then written as a ***document***. Documents may contain information on a single molecule or single pharmacophore or on a collection of molecules and/or pharmacophores. This collection is loosely referred to as a “list” or as a “spreadsheet” (in the context that it is presented in a spreadsheet).

Cartesian coordinates from any of these files may be replaced by coordinates generated based on atomic connectivity using the **Replace Coords.** button in the **Molecule Utilities** dialog (**Properties** under the **Display** menu; **Chapter 16**). Non-native files are all normally hidden from view, but may be seen by selecting **All Files** from the **Files of type** menu at the bottom of the dialog.

Close (📂)

Closes the document containing the selected molecule, as well as the spreadsheet, graphics, plots, spectra and document specific dialogs. If the document has not previously been saved, a name is requested. If a previously-saved document has been altered, verification that the changes are to be saved is requested.

Save
Save As... (💾)

Saves the document containing the selected molecule ***exactly as it appears on screen***. Opening the document will bring it on screen exactly as it was last saved. If the document has not previously been named, **Save** behaves as **Save As...**. Documents may be either be saved in native format or in one of the formats listed under **Open**. In addition, bitmap (.bmp), JPEG (.jpg) and PNG (.png) graphics file formats are supported as is the SpartanEntry (.spentry) format for creating custom databases (see **Appendix G**). Selection is made under the **Save as type** menu in the **Save As** dialog.

New Molecule

Brings up a model kit and clears the screen. This differs from **New**, in that the resulting molecule is appended to the end of the list associated with the molecule that is presently selected.*

Delete Molecule

Deletes the selected molecule(s) from a document. Deletion of the last molecule leads to empty document.

Append Molecule(s)...

Appends one or more documents onto the end of the document that contains the selected molecule.** **Append Molecule(s)...** leads to a file browser from which one or more documents need to be selected.***

Print...

Prints whatever is presently displayed on screen (according to the specifications made in the **Print Setup** dialog; see next page). To print text output, bring up and select an output window (**Output** under the **Display** menu) and select **Print Output...** (that has replaced **Print...**) from the **File** menu. To print the contents of the spreadsheet, bring up a spreadsheet (**Spreadsheet** under the **Display** menu) and select **Print Spreadsheet...** (that has replaced **Print...**) from the **File** menu.

---

* Examples are provided in the tutorials *Dienophiles in Diels-Alder Cycloadditions and Hydration of Carbonyl Compounds* in **Chapter 5**, *Stereospecific Diels-Alder Reactions* in **Chapter 6**, *Polyglycine* in **Chapter 7** and *Benzene Chromium Tricarbonyl* in **Chapter 9**.

** An example is provided in the tutorial *Carbene Additions to Alkenes* in **Chapter 6**.

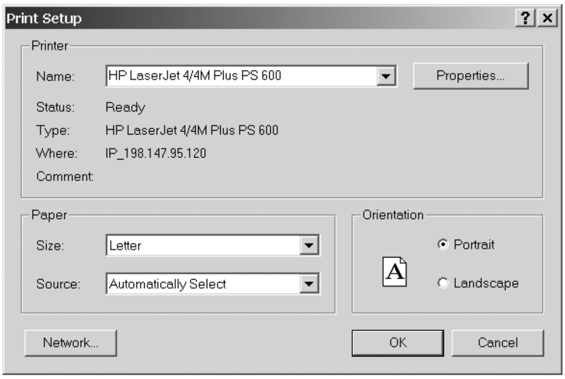
*** Alternatively, molecules may be appended onto an existing document either by copy/paste operations using the clipboard or by *dragging* from an external window. Both require that the spreadsheet associated with the destination document be open on screen.

To copy a molecule open on screen onto the clipboard, first select (*click* on) it, and then select **Copy** from the **Edit** menu. Alternatively, *click* on its label in its spreadsheet (in the leftmost column), and then select **Copy** from the **Edit** menu. The latter permits several molecules to be selected (and copied) at once using the **Shift** and **Ctrl** keys in the usual manner. Once on the clipboard, the molecule or molecules may be moved to the destination list by *clicking* on an empty row header in the spreadsheet (for the destination document), and then selecting **Paste** from the **Edit** menu.

To copy a document from an external window, *drag* it onto the open spreadsheet (associated with the destination document) inside of ***Spartan***. Several documents can be *dragged* at once using the **Shift** and **Ctrl** keys in the usual manner.

Print Setup...

Results in a dialog specific to the available printer.



Printer

Name: HP LaserJet 4/4M Plus PS 600

Status: Ready

Type: HP LaserJet 4/4M Plus PS 600

Where: IP_198.147.95.120

Comment:

Paper

Size: Letter

Source: Automatically Select

Orientation

● Portrait

○ Landscape

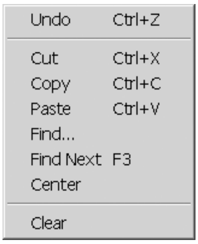
Exit

Exits ***Spartan***, that is, clears the screen and closes all open documents. A prompt for a name is provided for each document that has not previously been saved.

Chapter 11

The Edit Menu

Operations under the ***Edit*** *menu provide for undoing commands, copying items to and from the clipboard, finding text and graphics, centering molecules on screen and clearing the selected molecule.*



Undo

Undoes the last operation from the **Build** and **Edit** menus, from the **Molecule Utilities** dialog and retrieval from the Spartan Molecular Database.

Cut, Copy, Paste

Cut moves the selected item to the clipboard and removes it from the document. **Copy** copies the item to the clipboard. The item is unaffected. **Paste** transfers the contents of the clipboard to the selected location. The contents of the clipboard are unaffected.

There are four important uses of the clipboard within ***Spartan***.

(i) Transferring on-screen graphics into other applications such as Microsoft Word® and PowerPoint®.

(ii) Temporary storage of a molecular structure for use in molecule building.

(iii) Transferring data between ***Spartan*** spreadsheets and between a ***Spartan*** spreadsheet and other applications such as Microsoft Excel®.

(iv) Making multi-molecule documents and/or transferring molecules between documents.

Cut operations for (i) and (ii) require drawing a selection box. First position the cursor slightly above and slightly to the left of the item to be transferred. Then, while holding down both buttons, *drag* the mouse to a location slightly below and slightly to the right of the item to be transferred. Finally, release both buttons. **Copy** operations for (i) and (ii) also refer to the contents of a selection box ***if one has been drawn***, but to the selected molecule if a box has not been drawn. **Copy** operations from a ***Spartan*** spreadsheet refer to all information associated with a molecule if selection is made on the **Label** (in the leftmost column), but only to the selected (text) information if selection is made on any other column[*]. Further discussions relating to use of the clipboard spreadsheet in molecule building is provided in **Chapter 14** and for operations involving multi-molecule documents in **Chapter 15**.

Find..., Find Next

Find locates a text string defined in the **Find** dialog if an output window or a spreadsheet is selected, or a structure sequence defined on the clipboard if an on-screen model is selected. **Find Next** locates the next occurrence of a text string or a structure sequence.

Center

Centers on screen all molecules in the document for which the selected molecule is a member.

Clear

Clears (deletes) the structure and other information for the selected molecule, and brings up a model kit. No information is actually removed from the file system until the document is saved.

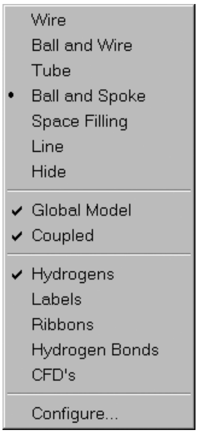
---

[*] Note that this is different from the behavior of previous versions of ***Spartan*** where all selections resulted in all information being transferred to the clipboard.

Chapter 12

The Model Menu

Structure models available under the ***Model*** *menu include wire, ball-and-wire, tube, ball-and-spoke, space-filling (CPK) and line models, with or without hydrogens, with or without hydrogen bonds indicated, with or without chemical function descriptors (CFD's) shown and with or without atom labels, as well as ribbon displays for polypeptides and polynucleotides, with or without labels and with or without hydrogen bonds indicated. The menu also provides for configuring atom labels to display element name, R/S chirality, mass number or charge, and for specifying color coding and display style for ribbon labels, as well as turning "on" and "off" a variety of other labels. Finally, it allows model style to be applied globally (to all molecules in a document) and models to be manipulated in concert.*


Wire
Ball and Wire
Tube
• Ball and Spoke
Space Filling
Line
Hide
✓ Global Model
✓ Coupled
✓ Hydrogens
Labels
Ribbons
Hydrogen Bonds
CFD's
Configure...

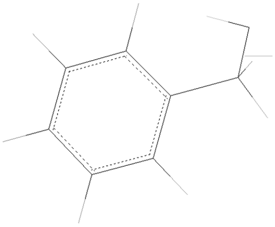
Only one model style **Wire**, **Ball and Wire**, **Tube**, **Ball and Spoke**, **Space Filling** or **Hide**) may be selected. The selected model is designated by a • in front of its entry in the menu. **Global Model**, **Coupled**, **Hydrogens**, **Labels**, **Ribbons**, **Hydrogen Bonds** and **CFD's** operate as toggle switches. A ✓ in front of the entry in the menu indicates that it is turned "on".

All structure models, and graphics may be displayed either in orthogonal or perspective projections. The latter may be valuable in helping to visualize large molecules. Selection is done in the **Settings Preferences** dialog (**Preferences...** under the **Options** menu; **Chapter 18**). Both structure models and graphics may be presented in 3D stereo using either red/cyan glasses or specialized LCD displays (**NAL**, **NAM**). This is also controlled from the **Settings Preferences** dialog. Stereographic displays require perspective projections.

Wire

This represents the molecule as a wire model where the vertices represent the atoms.

Wire Model



The bonds are drawn in two colors, one for each of the atoms making up the bond.* Default atom colors are given in **Table 12-1**.

Atom colors apply globally (to all atoms of given type), and may be changed using the **Set Colors** dialog (**Colors** under the **Options** menu; **Chapter 18**). Colors of individually selected atoms may be set using the **Atom Style** dialog (**Properties** under the **Display** menu; **Chapter 16**). All models use the same color scheme for atoms, and provide for the same mechanism of changing colors globally or individually.

---

* Default colors for several elements have changed from previous "***Spartan*** standards". These previous colors may be restored using the **Colors** dialog (**Colors** under the **Options** menu; **Chapter 18**).

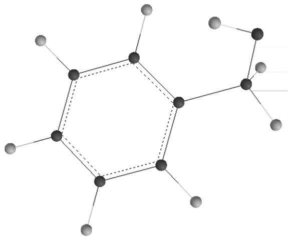
Table 12-1: Default Atom Colors

main group		**main group (con’t)**	
Hydrogen	white	Bromine	dark red
Lithium	tan	Rubidium	red
Beryllium	green	Strontium	red
Boron	tan	Indium	tan
Carbon	gray	Tin	gray
Nitrogen	blue-gray	Antimony	tan
Oxygen	red	Tellurium	tan
Fluorine	pale yellow	Iodine	violet
Sodium	yellow		
Magnesium	blue	**transition metals**	
Aluminum	purple	Scandium-Zinc	green
Silicon	gray	Yttrium-Cadnium	green
Phosphorus	orange	Lanthanum-Mercury	green
Sulfur	yellow		
Chlorine	green	**noble gases**	
Potassium	red	Helium	orange
Calcium	red	Neon	orange
Gallium	orange	Argon	orange
Germanium	gray	Krypton	orange
Arsenic	dark orange	Xenon	yellow
Selenium	red orange		

Ball and Wire

This represents atoms by small balls and bonds by wires.

Ball-and-Wire Model

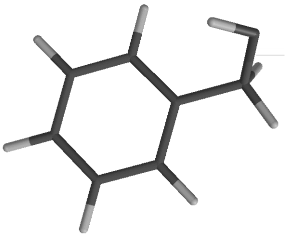


The balls are color coded according to atom type, and the wires representing bonds are drawn in two colors (as in wire models).

Tube

This is similar to the wire model, except that tubes instead of wires are used to represent bonds.

Tube Model

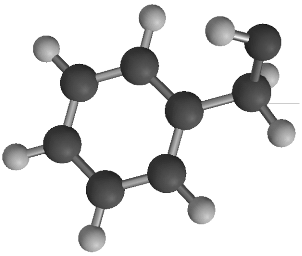


Tubes may either be solid cylinders or be split to represent multiple bonds depending on whether **Split Tubes** in the **Settings Preferences** dialog (**Preferences...** under the **Options** menu; **Chapter 18**) is “off” or “on”. As with wire models, bonds are drawn in two colors.

Ball and Spoke

This represents atoms by balls (the size and color of which depend on atom type), and bonds by spokes.

Ball-and-Spoke Model

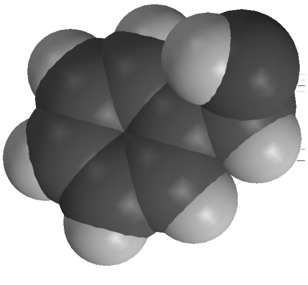


Spokes may either be cylinders or be split to represent multiple bonds depending on whether **Split Tubes** in the **Settings Preferences** dialog (**Preferences...** under the **Options** menu; **Chapter 18**) is "off" or "on". Bond (spoke) color is gray by default but it may be changed using the **Set Colors** dialog (**Colors** under the **Options** menu; **Chapter 18**). Colors of individually selected bonds may be set using the **Bond Style** dialog (**Properties** under the **Display** menu; **Chapter 16**).

Space Filling

This represents the molecule as a composite of spheres, the radii of which have been chosen to approximate van der Waals contact distances. Also known as CPK models, space-filling models are intended to portray overall molecular size and shape.

Space-Filling Model



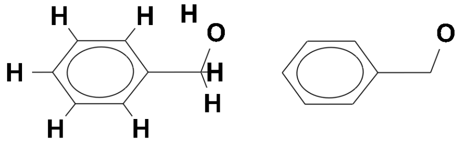
Volume, surface area and polar surface area (PSA)[*] displayed in the **Molecule Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**) correspond to a space-filling model.

---

[*] Polar surface area is defined as the area due to nitrogen and oxygen and any hydrogens attached to nitrogen and oxygen. The user may employ other combinations of atoms to define a partial surface area and partial volume. See **Spreadsheets** under the **Display** menu (**Chapter 16**).

Line

The **Line** model has been provided primarily to allow ***Spartan*** to display native structures from 2D drawing programs such as ChemDraw and IsisDraw. It designates carbons as the termini or the intersection of lines and non-carbons by their elemental symbols without any use of color.



These models are perhaps best shown minus hydrogens (see **Hydrogens** later in this chapter), and include stereochemical cues (▬ and ┈) if these have been provided in the 2D drawing or if they are specified from the **Bond Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**).

Hide

This removes the structure model from the screen where its display may lead to unnecessary crowding, for example, in proteins where ribbon displays are more appropriate. A structure model may be restored by selecting it from the **Model** menu.

> Different parts of a molecule may be rendered in terms of different model styles and colors. This allows focus on specific interesting regions. Regions may be individual atoms and/or bonds or any collection of atoms and/or bonds connected or not. They are selected either by *clicking* on an individual atom or bond or, with the aid of the **Ctrl** (select multiple) or **Command** key (Macintosh), **Shift** (select over a range), and **Alt/Alt Option** (select all bonded) keys, by *clicking* on a set of atoms and/or bonds, or by defining a selection box. Discussion has already been provided in **Chapter 2**. Style and color of selected model components is by way of the "**Selected**" **Style** dialog under **Properties** in the **Display** menu (**Chapter 16**).

Global Model

If *checked*, this signifies that all molecules in a document will share attributes. These include presentation of hydrogens, atom and other labels, hydrogen bonds, CFD's and ribbon displays. Global model style is controlled from the **Molecule Preferences** dialog (**Preferences...** under the **Options** menu; **Chapter 18**) **Global Model** acts in a toggle manner, switching between global and local display.

Coupled

If *checked*, this signifies that all molecules in a document selected for simultaneous display will be moved together. **Coupled** is turned "on" following molecule alignment (see **Align** under the **Geometry** menu; **Chapter 13**). **Coupled** acts in a toggle manner, that is, repeated selection couples and decouples the molecules.

Hydrogens

If *checked*, this signifies that hydrogens are to be included in the model. Note that structures from the Cambridge Structural Database or the Protein Data Bank may lack hydrogens. These need to be grown before they can be displayed and before CFD's can be assigned. This may be done either upon retrieval (see **Databases** and **Ligands** under the **Search** menu; **Chapter 17**) or using **Grow Hydrogens** in the **Molecule Utilities** dialog (**Properties** under the **Display** menu; **Chapter 16**). **Hydrogens** acts in a toggle manner, that is, repeated selection turns "on" and "off" the display of hydrogens.

Labels

If *checked*, this signifies that labels associated with atoms, ribbons and bonds as well as with other attributes specified in **Configure...** (see discussion following) are to be displayed in the model. **Labels** acts in a toggle manner, that is, repeated selection turns "on" and "off" display of labels. **Labels** is automatically turned "on" following selection of **Apply** or **OK** in the **Configure** dialog.

Ribbons

If *checked*, this signifies that ribbons are to be displayed along with the selected model. (If only ribbons are desired, for example, in proteins, select **Hide** for the model.) **Ribbons** acts in a toggle manner, that is, repeated selection turns "on" and "off" display of ribbons.

Hydrogen Bonds

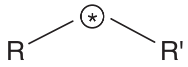
If *checked*, this signifies that hydrogen bonds are to be drawn as part of the model. Hydrogen bonds are defined as non-bonded contacts between a nitrogen or oxygen and a hydrogen attached to nitrogen or oxygen separated by a distance ranging from 1.6 to 2.1Å and making an X–H--Y (X,Y = N, O) angle of >120°. **Hydrogen Bonds** acts in a toggle manner, that is, repeated selection turns "on" and "off" display of hydrogen bonds.

CFD's

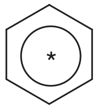
If *checked*, this signifies that **C**hemical **F**unction **D**escriptors (CFD's) are to be displayed along with the structure model. CFD's are attributes given to a molecule in order to characterize or anticipate its chemical behavior or to identify commonality among molecules with different structures. This is also the purpose of terms in common chemical language such as *lone pair*, indicating among other things the possibility that it might act as a hydrogen bond acceptor, and *sterically crowded*, suggesting that getting close may be difficult. ***Spartan*** uses seven different kinds of CFD, the first six of which may be though of as attributes of a molecule.

	CFD	**chemical language**
1.	hydrophobe	sterically-crowded region
2.	aromatic	aromatic π system
3.	hydrogen-bond donor	acidic hydrogen
4.	hydrogen-bond acceptor	lone pair
5.	positive ionizable site	basic site
6.	negative ionizable site	acidic site

Default CFD assignments follow from atomic connectivity and rules covering common organic functional groups. They may be modified on a case-by-case basis using the **CFD Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**). CFD's (represented by *'s in the figures below) may either be atom centered, or they may be centered in between atoms. For example, a hydrogen-bond acceptor CFD is placed on an ether oxygen, while an aromatic CFD is placed at the center of a benzene ring.

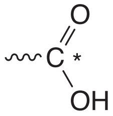


hydrogen-bond acceptor

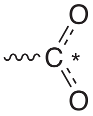


aromatic

More complicated are CFD's corresponding to a number of common functional groups. For example, a single CFD is provided for the carboxylic acid group, sited in-plane and equidistant from the carbon and two oxygens.



neutral pH: hydrogen-bond donor
hydrogen-bond acceptor



acidic pH: negative ionizable site

At neutral (or basic) pH this CFD should be designated both as a hydrogen-bond donor and a hydrogen-bond acceptor. At acidic pH this should be designated as a negative ionizable site.

Note that default assignments for hydrogen-bond donors and acceptors depend not only on atomic type (N, O, . . .) and (in the case of hydrogen-bond donors) on the availability of hydrogens, but also on known (or presumed) chemical behavior. For example, an amide nitrogen is not considered to be a hydrogen-bond acceptor and no (hydrogen bond acceptor) CFD is provided. It is assigned to be a hydrogen-bond donor (if hydrogens are available) and the amide oxygen is assigned as a hydrogen-bond acceptor.

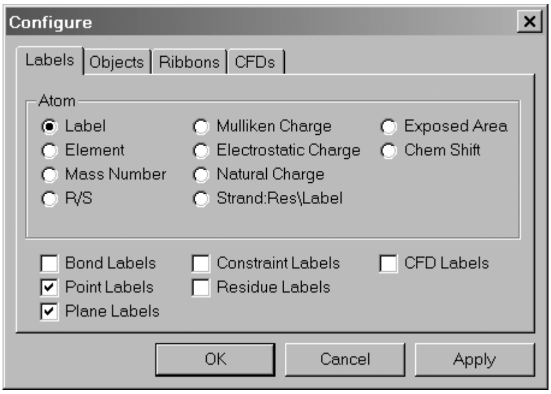
Hydrogen-bond acceptor and donor CFD's may be related to the electrostatic potential obtained from quantum chemical calculations. For example, a negative potential associated with an oxygen center suggests that it might serve as a hydrogen-bond acceptor, while a positive potential associated with a hydrogen attached to such a center suggests its role as a hydrogen-bond donor. These are, of course, the same conclusions that a chemist would draw simply by looking at the molecule. Where the calculations have an edge is in being able to say which acceptor or donor sites are likely to be strong and which are likely to be weak.

Calculations also offer significant advantage when there are no heteroatoms and hydrogen bonding is not possible. Here, regions of significant negative potential offer a hostile environment, that is, they are hydrophobes. The π systems of benzene and other aromatics provide the most common examples. The same conditions that make the ring susceptible to electrophilic aromatic substitution mean that it repels other electron-rich regions (and attracts electron-poor regions).

A seventh CFD type, excluded volume, derives from knowledge of a molecule incorporated into a host. Excluded volumes may be obtained from PDB files using the **Ligands** dialog (**Ligands** under the **Search** menu; **Chapter 17**).

Configure...

This selects the types of labels attached to atoms, ribbons and CFD's. Upon initial entry, the **Labels** tab is selected and the **Configure Labels** dialog appears.

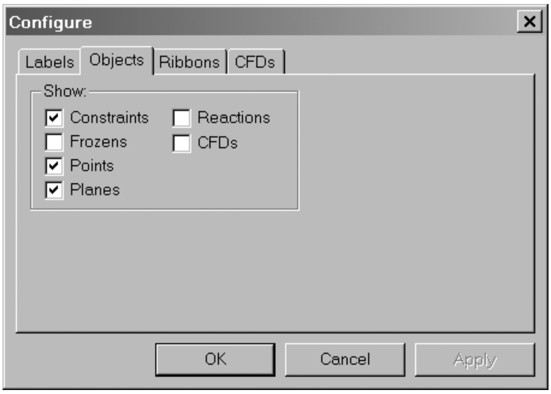


● Label
○ Element
○ Mass Number
○ R/S
○ Mulliken Charge
○ Electrostatic Charge
○ Natural Charge
○ Strand:Res\Label
○ Exposed Area
○ Chem Shift

☐ Bond Labels
☑ Point Labels
☑ Plane Labels
☐ Constraint Labels
☐ Residue Labels
☐ CFD Labels

Atom labels may be selected from among the following: **Labels**, a unique element/number combination that may be changed from the **Atom Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**), **Element**, **Mass Number**, **R/S** (chirality), **Mulliken Charge**, **Electrostatic Charge**, **Natural Charge**, **Strand: Res\Label** (polypeptides and polynucleotides), **Exposed Area** (of an atom in a space-filling model) or **Chem Shift**. In addition, **Bond Labels**, **Point Labels**, **Plane Labels**, **Constraint Labels**, **Residue Labels** and/or **CFD Labels** may be provided.

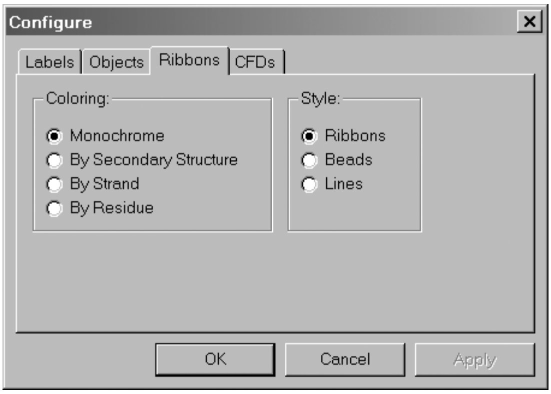
Clicking on the **Objects** tab at the top of the dialog leads to the **Configure Objects** dialog.



Show:
☑ Constraints
☐ Frozens
☑ Points
☑ Planes
☐ Reactions
☐ CFDs

This contains a series of boxes that, if checked, attach to the model **Constraint** and **Frozen** markers, **Points** and **Planes**, **Reaction** arrows and **CFD's**. If not checked, these are shown only in the respective models, for example, **Frozen** markers are shown only if **Freeze Center** is selected.

Clicking on the **Ribbons** tab at the top of the dialog leads to the **Configure Ribbons** dialog.


Configure
Labels
Objects
Ribbons
CFDs
OK
Cancel
Apply

Coloring:

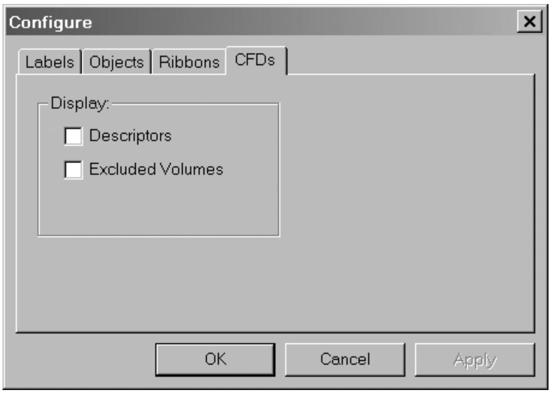
● Monochrome
○ By Secondary Structure
○ By Strand
○ By Residue

Style:

● Ribbons
○ Beads
○ Lines

Ribbon coloring may be selected from among the following: **Monochrome**, **By Secondary Structure**, **By Strand** or **By Residue**. Ribbon style may be selected from among the following: **Ribbons**, **Beads** or **Lines**.

Clicking on the **CFDs** tab leads to the **Configure CFDs** dialog.


Configure
Labels
Objects
Ribbons
CFDs
OK
Cancel
Apply

Display:

☐ Descriptors
☐ Excluded Volumes

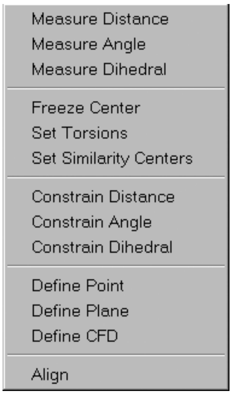
This allows for turning "on" CFD descriptors (identifying the type of CFD) identifiers and CFD's corresponding to excluded volumes.

The **Configure** dialog is removed from the screen with all selections maintained by *clicking* on **OK**. *Clicking* on **Cancel** or on ☒ removes the dialog but selections are lost. *Clicking* on **Apply** maintains the selections but leaves the **Configure** dialog on screen. Note, that **Labels** (from the **Model** menu) will be turned "on" following either *clicking* on **OK** or on **Apply**.

Chapter 13

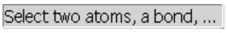
The Geometry Menu

Functions available under the ***Geometry*** *menu allow querying bond lengths, angles and dihedral angles, defining points, planes and CFD locations, setting geometrical constraints, freezing atomic centers, altering default bond and ring assignments, and introducing NOE's in conformational searching, selecting atoms or CFD's for similarity analysis and aligning molecules in a list.*


Measure Distance
Measure Angle
Measure Dihedral
Freeze Center
Set Torsions
Set Similarity Centers
Constrain Distance
Constrain Angle
Constrain Dihedral
Define Point
Define Plane
Define CFD
Align

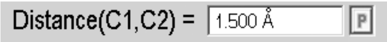
Measure Distance (?)
Measure Angle (?)
Measure Dihedral (?)

Measure Distance displays the distance (in Ångstroms) between two atoms, whether or not they are bonded. Selection results in a message at the bottom left of the screen.



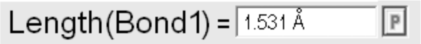
Select two atoms, a bond, ...

Clicking on two atoms displays the distance.



Distance(C1,C2) = 1.500 Å

Alternatively, *clicking* on a bond displays its length.



Length(Bond1) = 1.531 Å

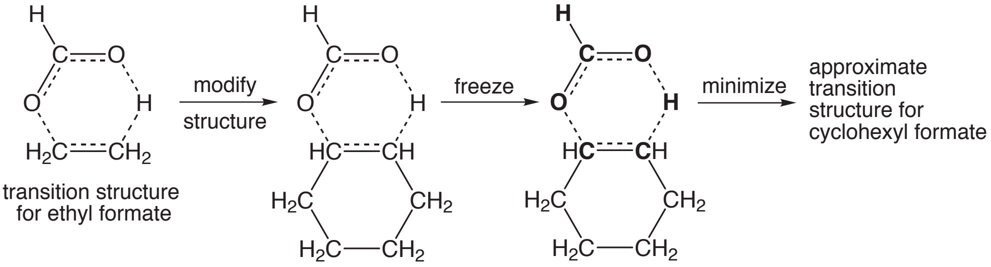
Measure Distance may also be used to alter the distance between atoms (as long as both are not incorporated into the same ring), by altering the contents of the box to the right of **Distance (A,B) =** or **Length (A)=**, and then *pressing* the **Enter** key (**return** key on Mac). The distance (length) may be entered into the spreadsheet by *clicking* on P to the right of its display (see **Spreadsheet** under the **Display** menu; **Chapter 16**).

Angle and dihedral angle queries are handled in a similar manner. Angles require that three atoms or two bonds be identified while dihedral angles require that four atoms or three bonds be identified.

Freeze Center (‡)

This allows one or more atoms to be held in place during minimization (in build mode) or (optionally) during equilibrium or transition-state geometry optimization, conformational searching, or energy profile generation. The latter needs to be explicitly indicated in the **Calculations** dialog (see **Chapter 15**).

Atom freezing may be useful in a number of situations, among them guessing a transition-state geometry for a reaction that is closely related to one for which a transition state is available. For example, a guess at the transition state for pyrolysis of cyclohexyl formate might be obtained by modifying the transition state for pyrolysis of ethyl formate, freezing all but the modified sections (designated in bold in the figure below) and then minimizing.*


H
C
O
O
H
H2C
CH2
transition structure for ethyl formate
modify structure
HC
CH
H2C
CH2
H2C
CH2
freeze
minimize
approximate transition structure for cyclohexyl formate

Selection of **Freeze Center** leads to a message at the bottom left of the screen.

Select atom to freeze.

---

* An example of this is presented in the tutorial *Carbene Additions to Alkenes* in **Chapter 6**.

Clicking on an atom or free valence*, freezes it; *clicking* again thaws it. Buttons at the bottom right of the screen allow for freezing all atoms (**Freeze All**), freezing all heavy (non-hydrogen) atoms (**Freeze Heavy**) and for thawing all atoms (**Thaw All**).

> Another important use of frozen atoms is in conjunction with data resulting from a search of the Cambridge Structural Database (**NAM**) or the ligands database (see **Databases** under the **Search** menu; **Chapter 17**). Hydrogen positions are more often than not poorly located in small molecule X-ray structures, and X–H bond lengths are commonly as much as 0.1 to 0.2Å shorter than they should be. Structures incorporating such bond lengths are clearly inappropriate for energy and property calculations and may also be problematic as starting geometries in quantum chemical calculations. Protein crystal structures always lack hydrogens, and hydrogen positions of bound ligands extracted from PDB files are arbitrary. A solution to both problems is to freeze all heavy (non-hydrogen) atoms (**Freeze Heavy**) and then to carry out molecular mechanics minimization using either **Minimize** from the **Build** menu (see discussion in **Chapter 14**) or from the **Calculations** dialog under the **Setup** menu (see discussion in **Chapter 15**).

Frozen atoms are indicated by magenta colored markers (‡). Whether or not these are included with the model (outside of freeze center mode) for an individual molecule is controlled from the **Molecule Utilities** dialog available under the **Display** menu (see **Chapter 16**). Global settings are controlled from the **Molecule Preferences** dialog under **Preferences...** in the **Options** menu (see **Chapter 18**).

Set Torsions (↻)

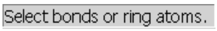
Spartan automatically identifies bonds and rings for conformational searching and specifies default step sizes.*

> Two different rule sets have been provided. **Normal** is intended for use in determining the lowest-energy conformation or in establishing a distribution of low-energy conformers, whereas **Trimmed** is intended for use in building conformer libraries. Selection of rule set is made in the **Settings Preferences** dialog (**Preferences...** under the **Options** menu; **Chapter 18**).

---

* The bond distance in this case is that appropriate for hydrogen being added to the free valence.

Set Torsions allows these defaults to be altered. Selection results in flexible bonds each being marked by a gold cylinder, and flexible rings each being marked by a gold circle around one or more atoms, and a message appears at the bottom left of the screen.


Select bonds or ring atoms.

Clicking on a bond or an atom contained in a ring selects it for rotation. In the case of a ring, rotation means that the atom is to be puckered up and down (restricted rotation). The default rotation is provided in a box to the right of **Fold** at the bottom right of the screen. This is typically 2 or 3 for a single bond (step size of 180° and 120°, respectively) and 3 for a flexible ring. A value of either 0 or 1 indicates that the bond (ring) is not to be rotated (rotation by 360°). Other integer values may be entered into the box, followed by *pressing* the **Enter** key (**return** key on Mac). The original (default) settings may be retrieved by *clicking* on **Defaults** at the bottom right of the screen.

> Six-membered rings are treated as special cases with only chair conformers examined. This is indicated by two circles on opposite atoms. Other conformers can be generated by selecting additional ring atoms.

Double clicking on a marked bond or ring atom removes the marker and eliminates the conformational degree of freedom.

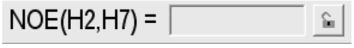
◀ and ▶ buttons at the bottom right of the screen are available to step through the possible single-bond conformers[*]. Geometries have not been optimized and some conformers may be severely crowded. Also, ring conformers are not provided. Any conformer can be selected in lieu of the initial structure. The full set of single-bond conformers may be generated by *clicking* on ▼ (to the right of the step buttons), and then *clicking* **OK** in the dialog that results.[**] Note, that some of the conformers may be severely crowded as their geometries have not been optimized and that duplicate conformers have not been removed.

---

[*] The total number of single-bond conformers is given to the right of **Conformers** at the bottom of the screen.

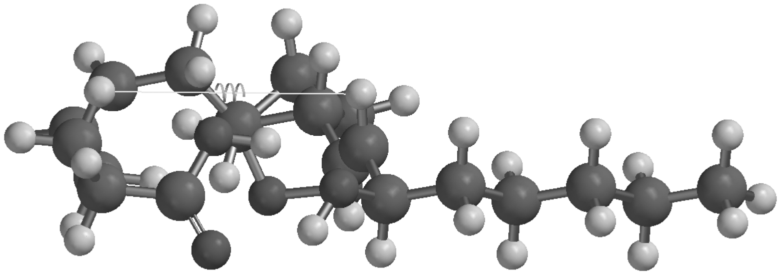
[**] A limit of 1000 conformers is enforced.

Set Torsions is also used to specify non-bonded distances that need to be kept below a threshold value. These follow from NOE (Nuclear Overhauser Effect) measurements and may be referred to as NOE conditions or simply NOEs. NOEs are specified by *clicking* on two (non-bonded) atoms while holding down the **Shift** key. In response, a message appears at the bottom of the screen.



NOE(H2,H7) =

Clicking on 🔓 changes it to 🔒 and enters the default value for the NOE threshold into the box. This value can be changed. A line is drawn between atoms that are to be kept within the threshold value.



Once set, NOEs are used in conformational searching (conformer distribution only) without further user intervention. Note, that they act as a post processor filter to eliminate conformers that do not satisfy the constraints and have no effect on the speed of the search.

Set Similarity Centers (⊙)

This specifies the set of atomic centers, or **C**hemical **F**unction **D**escriptors (**CFD’s**) or pharmacophore elements that are to be used in similarity analysis. Choice of whether the similarity analysis is to be based on structure or CFD’s (pharmacophore elements) is made from a menu that appears at the bottom right of the screen following selection of **Set Similarity Centers**. This menu is also available in the **Similarity Analysis** task in the **Calculations** dialog (**Calculations...** under the **Setup** menu; **Chapter 15**).

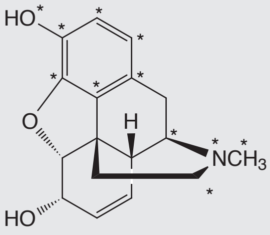
Similarity Analysis Based on Structure

Selection of **structure** from the **Similarity by** menu at the bottom right of the screen results in a message at the bottom left of the screen.

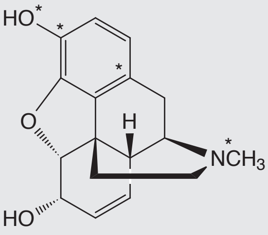
Select atoms.

Clicking on an atom designates it as an alignment center and it marks it with a violet circle. *Clicking* on the circle removes the designation (and the circle). Hydrogens may not be selected.

The computer time required for similarity analysis based on structure depends on the number of molecules in the query, the number of molecules in the library and the choice of similarity centers. Single atoms should never be selected as similarity centers unless they are unique. Rather contiguous groups of atoms that are likely to be unique should be chosen. For example, analysis carried out on morphine based on selection of its phenol and trialkylamine components (left) will be much faster than that based on selection of the phenol oxygen, two carbons on benzene and the nitrogen (right).



good



bad

This is because there will be many few occurences of phenol and trialkylamine substructures in the library entries than there will be aromatic carbons and nitrogen atoms and fewer permutations that need to be examined.

Similarity Analysis Based on CFD's

Similarity analysis may also be based on CFD's. These indicate whether a particular center is likely to act as a hydrogen-bond donor or acceptor, is likely to take on positive or negative charge or is a hydrophobe. This is accomplished by selecting **CFD** from the **Similarity by** menu at the bottom right of the screen. In response, the selected molecule is augmented with CFD’s, and a message appears at the bottom left of the screen.

Select CFD's.

Clicking on a CFD designates it as a similarity center and marks it with a violet circle. *Clicking* on the circle removes the designation (and the circle).

> The computer time required for similarity analysis based on CFD’s depends on the number of molecules and/or pharmacophores in the query, the number of molecules and/or pharmacophores in the library and the nature of the selected CFD’s in the query. For each query/library pair, where the query is represented by i CFD’s of type A, j CFD’s of type B, k CFD’s of type C, etc., the number of different alignment combinations that need to be considered is given by:
>
> $$i!j!k! \ldots$$
>
> (! is the factorial symbol.) This rapidly becomes unmanageable. for example, if there are 6 CFD’s of type A, 3 of type B and 2 of type C, the number of combinations is 6!3!2! or 8640. Considerable savings can be achieved by limiting the number of CFD’s of a given type in the overall representation.

Similarity Analysis Based on a Pharmacophore

Finally, it is possible to base similarity on a pharmacophore. This is set up in exactly the same way as similarity based on CFD’s insofar as a pharmacophore element is a CFD (see previous section).

Selection of similarity centers either needs to be repeated for the remaining molecules in the list or the selections may be designated as global, that is, applying to all molecules in the list. The latter is applicable where the molecules in the list are conformers or are closely related at least insofar as the alignment centers are concerned. Global designation is accomplished by *checking* the **Global Similarity Settings** at the bottom of the screen.

Constrain Distance (🔒)
Constrain Angle (🔒)
Constrain Dihedral (🔒)

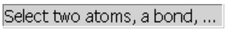
These introduce of one or more geometrical constraints during structure minimization (in build mode), and (optionally) during equilibrium or transition-state geometry optimization, conformational searching or energy profile generation using methods under the **Calculations** dialog (**Chapter 15**). Constraints may be useful in a number of situations:

(i) constructing conformational energy profiles where one or more dihedral angles need to be fixed while other geometrical variables are optimized,

(ii) optimizing molecular structures where the values of certain key parameters are known, for example, optimizing the geometry of a molecule with an intramolecular hydrogen bond or a disulfide linkage, and

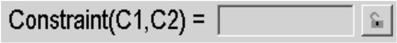
(iii) building molecules with unusual geometries, for example, molecules with very long bonds, as might be required in the construction of transition states and intermolecular complexes.

Selecting **Constrain Distance** results in a message at the bottom left of the screen.



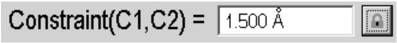
Select two atoms, a bond, ...

Clicking on two atoms, or a bond results in a message at the bottom right of the screen.



Constraint(C1,C2) =

Clicking on 🔓 changes it to 🔒 and shows the current distance.



Constraint(C1,C2) = 1.500 Å

This (constraint) distance can now be changed by altering the contents of the box and then *pressing* the **Enter** key (**return** key on Mac). Alternatively, the existing distance may be used as the constraint distance. If the selected distance had previously been constrained, the icon 🔒 would have been initially displayed. In this case, *clicking* on 🔒 turns "off" the constraint and returns the icon to the 🔓. Finally, the value of the constraint, that may be different from the value of the current distance, may be entered into the spreadsheet by *clicking* on P to its right.

This sequence of operations (bond identification followed by turning "on" and "off" the constraint) may be repeated as many times as necessary. Any bonds or non-bonded distances on which constraints are to be imposed are indicated by magenta colored markers. Any constraints introduced are automatically enforced only upon energy minimization in add fragment mode (↓E), but are optional using methods under the **Calculations** dialog (**Chapter 15**).

Angle and dihedral angle constraints are handled in a similar manner. Note that points and planes may not be used to define constraints.

Constraints may also be modified as well as posted to the spreadsheet from the **Constraint Properties** dialog (available under **Properties** in the **Display** menu; see **Chapter 16**). In addition, a sequence of constraints may also be modified as well as posted to the spreadsheet from the **Constraint Properties** dialog (available under **Properties** in the **Display** menu; see **Chapter 16**). In addition, a sequence of constraints may be defined (from some initial value to some final value in a given number of steps). This allows generation of an energy profile along a predefined set of coordinates[*] (see **Calculations** in **Chapter 15**).

Whether or not constraint markers are included as part of the model (outside of constrain distance, constrain angle or constrain dihedral mode) for an individual molecule is controlled from the **Molecule Utilities** dialog available under the **Display** menu (see **Chapter 16**). Global settings are controlled from the **Molecule Preferences** dialog (**Preferences...** under the **Options** menu; see **Chapter 18**).

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[*] Examples of this are provided in the tutorial *Internal Rotation in Dimethylperoxide* in **Chapter 5**, and the tutorial *Thermodynamic vs. Kinetic Control* in **Chapter 6**.

Define Point, Define Ligand Point ( )

This defines a point as the geometric (unweighted) center of selected atoms (or points) previously defined. Selection results in display of a message at the bottom left of the screen.

Select atoms. Repeat to terminate.

Clicking on atoms (or points) in any order, and *clicking* a second time on any one of the atoms (or points) defines a point (depicted as a small sphere). As many points as desired can be defined and these are treated in the same way as an atom in defining distances, angles, etc. Points move with the molecule as its geometry is altered.

Selecting **Define Point** (or *clicking* on ( )) while holding down on the **Shift** key, followed by *clicking* on the appropriate atoms, leads to a ligand point. This shares all the characteristics of a normal point, but may also be used to bond to atomic fragments, functional groups, etc. See **Make Bond** under the **Build** menu (**Chapter 14**) for a discussion.

> **Delete** from the **Build** menu ( ) or the **Delete** key may be used to remove a point or ligand point.

Whether or not points are shown as part of the model for an individual molecule is controlled from the **Molecule Utilities** dialog available under the **Display** menu (see **Chapter 16**). Global settings are controlled from the **Molecule Preferences** dialog (**Preferences...** under the **Options** menu; see **Chapter 18**).

Define Plane ( )

This defines and displays a reference plane. Selection results in display of a message at the bottom left of the screen.

Select three atoms.

Clicking on three atoms or points defines a plane. As many planes as desired may be defined, and these may be used in defining distances, angles, etc. Planes move with the molecule as its geometry changes.

Delete from the **Build** menu ( ) or the **Delete** key may be used to remove a point.

Whether or not planes are included as part of the model for an individual molecule is controlled from the **Molecule Utilities** dialog available under the **Display** menu (see **Chapter 16**). Global settings are controlled from the **Molecule Preferences** (**Preferences...** under the **Options** menu; see **Chapter 18**).

Define CFD ( )

This defines the position of a new CFD (CFD size and type are defined using the **CFD Properties** dialog described in **Chapter 16**). Selection results in display of a message at the bottom left of the screen.

Select atoms. Repeat to terminate.

Clicking on atoms (or points) in any order, and *clicking* a second time on any one of the atoms (or points) defines the position of a CFD (depicted as a transparent sphere labelled "Null"). As many CFD's as desired can be defined. These move with the molecule as its geometry is altered.

Align ( )

This aligns the selected molecule to all other molecules in the same document based either on structure or on CFD's. If the selected molecule is a pharmacophore, aligns the pharmacophore to all molecules in the same document (based on CFD's). Choice of whether alignment is based on structure or CFD's is made from the **Align by** menu that appears at the bottom right of the screen.

The terms "alignment" and "similarity analysis" are often used interchangeably, but they have subtly different meanings inside of ***Spartan***. Alignment refers to the operation in which the molecules in a document are reoriented to best coincide with the selected molecule (pharmacophore). Where a molecule is selected, alignment may either be based on a set of atoms or on a set of CFD's. Where a pharmacophore is selected, alignment is based on a set of CFD's. A single reorientation is provided for each molecule in the document that can be aligned to the selected molecule (pharmacophore).

Similarity analysis refers to the operation in which all molecules in a user-specifed library comprising one or more documents are compared one-on-one to all molecules and/or pharmacophores in the selected document (in the interface). As with alignment, either structural elements or CFD's may be employed. The result is a score for each successful alignment (success being defined by the user) and a manipulatable model of the two molecules (or molecule and pharmacophore). It is likely that most comparisons will not be successful, and also that some comparisons may lead to more than one score (corresponding to different orientations of the two components).

In short, the role of alignment is to orient molecules and/or pharmacophores in order to highlight their common features, while the role of similarity analysis is to rank pairs of molecules or molecule/pharmacophore pairs according to the extent of their common features.

Alignment Based on Structure

Selection of **Structure** from the **Align by** menu results in a message at the bottom left of the screen.

Select atoms.

Clicking on an atom designates it as an alignment center, and marks it with a red circle. *Clicking* on the circle removes the designation (and the circle). Following selection of alignment centers, *clicking* on the **Align by** button at the bottom right of the screen aligns the molecules.

Following alignment, two or more molecules may be displayed at once using spreadsheet functions (see **Spreadsheet** under the **Display** menu; **Chapter 16**). Their motions (coordinates) will be coupled following alignment, but may be uncoupled allowing the aligned molecules to move independently (see **Coupled** under the **Model** menu; **Chapter 12**). Note that alignment center selections are kept and molecules can be realigned by again selecting **Align** from the **Geometry** menu (or *clicking* on) followed by *clicking* on the **Align by** button.

Alignment Based on CFD’s

It is also possible to base molecule alignment on CFD’s. These indicate whether a particular center is likely to act as a hydrogen-bond donor or acceptor, is likely to take on positive or negative charge or is a hydrophobe. This is accomplished by choosing **CFD** from the **Align by** menu at the bottom right of the screen followed by *clicking* on the **Align by** button. In response, the selected molecule is augmented with CFD’s, and a message appears at the bottom left of the screen.

Select CFD's.

Clicking on a CFD designates it as an alignment center and marks it with a red circle. *Clicking* on the circle removes the designation (and the circle).

The **CFD Properties** dialog (**Properties** in the **Display** menu; **Chapter 16**) allows definitions of the individual CFD’s to be altered.

Following selection of CFD’s, *clicking* on the **Align by** button at the bottom right of the screen aligns the molecules.

Following alignment, one or more molecules may be displayed at once using spreadsheet functions (see **Spreadsheet** under the **Display** menu; **Chapter 16**). Their motions (coordinates) will be coupled following alignment, but may be uncoupled allowing the aligned molecules to move independently (see **Coupled** under the **Model** menu; **Chapter 12**). Note that alignment center selections are kept and molecules can be realigned by again selecting **Align** from the **Geometry** menu (or *clicking* on) followed by *clicking* on the **Align by** button.

Alignment to a Pharmacophore

Finally, it is possible to align molecules to a pharmacophore contained in the same list. This is set up in exactly the same way as alignment based on CFD’s insofar as a pharmacophore element is a CFD (see previous section).

An alignment scor e, from 0 to 1 (perfect alignment), is available in the spreadsheet. This is accessed by *clicking* on the **Add** button at the bottom of the spreadsheet, and selecting **Alignment Score** from the list of available properties (see **Spreadsheet** under the **Display** menu; **Chapter 16**). A 0 score is assigned to molecules that cannot be aligned to the selected molecule.

Chapter 14

The Build Menu

*The **Build** menu provides model kits and tools for building and editing organic, inorganic and organometallic molecules, as well as polypeptides and polynucleotides, for generating lists of substituted molecules, and a molecular mechanics procedure for structure refinement. This menu also provides seamless access to ChemDraw.*

Model Kits

Spartan provides five different model kits for assembling a variety of molecular systems: an organic model kit for most organic molecules, an inorganic model kit for organic molecules not easily represented in terms of classical valence structures, as well as inorganic and organometallic molecules, model kits for polypeptides and polynucleotides and a model kit for attaching substituents to previously built molecules. The organic and inorganic model kits utilize atomic fragments, functional groups and rings (and ligands in the inorganic model kit), while the peptide model kit uses the set of natural amino acids as building blocks, and the nucleotide model kit the set of nucleotide bases. The substituent model kit is different in that it adds substituents to a previously constructed molecule and/or alters one or more incorporated atoms.

Two dimensional molecular structures (drawings) produced using ChemDraw* can also be brought into ***Spartan*** and converted to three dimensional structures.

Molecule construction in ***Spartan*** proceeds much in the same manner as a chemist would assemble a structure from a model kit, that is, pieces are taken from the kit one at a time and added sequentially to the molecule under construction.

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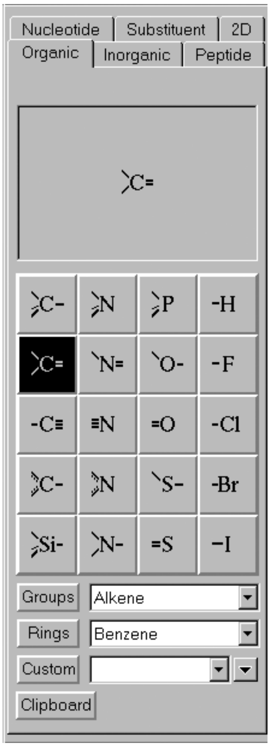
* Seamless access to ChemDraw is provided in the Windows version only. All versions are able to read ChemDraw files. ChemDraw is not included with ***Spartan*** and must be obtained from CambridgeSoft at http://www.cambridgesoft.com.

Organic Model Kit

The organic model kit contains a suite of molecule building/editing tools specifically designed to construct organic molecules.


Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
C=
C-
N
P
-H
C=
N=
O-
-F
-C≡
≡N
=O
-Cl
C-
N
S-
-Br
Si-
N-
=S
-I
Groups
Alkene
Rings
Benzene
Custom
Clipboard

In the center of the model kit are a selection of atomic fragments, which from left to right and then top to bottom, correspond to:

C(sp^3)	N(sp^3)	P(sp^3)	H
C(sp^2)	N(sp^2)	O(sp^3)	F
C(sp)	N(sp)	O(sp^2)	Cl
C(aromatic)	N(aromatic)	S(sp^3)	Br
Si(sp^3)	N(planar)	S(sp^2)	I

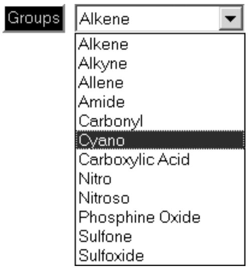
A fragment is chosen by *clicking* on its icon, which is then displayed at the top of the model kit. Once selected, the fragment may be used to initiate building, to add alongside of an existing structure or appended onto an existing structure. To initiate building, *click* anywhere on screen. To add alongside of an existing structure, first *click* on the **Insert** button at the bottom right of the screen or hold down the **Insert** key (**alt** key on Mac), and then *click* anywhere on screen. To bond to an existing structure, *click* on a free valence. (Free valences are colored yellow on the selected molecule.) Bond type in the case of atomic fragments with multiple bond types, for example, sp^2 carbon, depends on the nature of the free valence selected.

> While only H, C, N, O, F, P, S, Cl, Br and I are available from the organic model kit, other elements may be substituted using atom replacement feature available in the inorganic model kit (see **General Molecule Building Functionality** following). Similarly, bond types may be altered in the inorganic model kit. The latter may be necessary in order to correct bonding errors present in structures retrieved from the Cambridge Structural Database or ligands obtained from PDB files. Atom and bond types may also be altered using the **Atom** and **Bond Properties** dialogs, respectively (**Properties** under the **Display** menu; **Chapter 16**).

Menus inside the model kit provide access to a number of pre-built fragments corresponding to functional groups (**Groups**) and rings (**Rings**), and to additional libraries of functional groups and rings (as well as any user-defined structures) stored in the file system (**Custom**). The model kit also accesses the clipboard (**Clipboard**).

Groups

Clicking on **Groups** brings up a menu of groups, and displays an icon of one group at the top of the model kit.

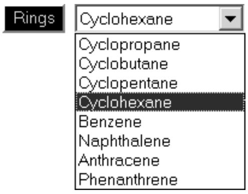


Once selected from the menu, a group may be used to initiate building, to add alongside of an existing structure on screen, or to add to an existing structure.

The amide and carboxylic acid groups have more than one different free valence. The one that is to be used is marked with a gold • (in the icon at the top of the model kit). The marked position circulates among the possible positions with repeated *clicking* on the icon.

Rings

Clicking on **Rings** brings up a menu of rings, and displays an icon of one ring at the top of the model kit.



Once selected from the menu, a ring may be used to initiate building, to add alongside of an existing structure on screen, or to add to an existing structure.

Cyclohexane, napthalene, anthracene and phenanthrene have more than one different free valence. The one that is to be used is marked with a gold • (in the icon). The marked position circulates among the available positions with repeated *clicking* on the icon. Selection of an *axial* or *equatorial* free valence in cyclohexane is indicated by the label **ax** or **eq** appearing alongside the icon. All rings in this menu are hydrocarbons, but heteroatoms may be substituted (see **General Molecule Building Functionality** following).

Custom

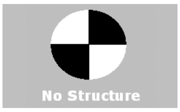
This accesses a document containing one or more molecules that has been previously saved. To access, *click* on the rightmost down arrow key to the right of the **Custom** menu, select (*click* on) an entry from the file browser and *click* on **Open** (or *double click* on the entry). The selected molecule is identified by its name in the menu immediately to the right of **Custom**. Select it and a ball-and-wire model will appear at the top of the model kit. This may be manipulated (rotated, translated, zoomed) using the usual mouse/keyboard commands (you need to position the cursor inside the box). The molecule may be used to initiate building, to add alongside of an existing structure, or to add to an existing structure. In the latter case, the attachment point (on the molecule in the clipboard) needs to be identified by *clicking* on the appropriate free valence. If the document selected from the file system contains more than one molecule, individual molecules may be selected in turn (by selecting different entries from the menu to the right of **Custom**).

> A number of groups not included in the **Groups** menu and a selection of heterocyclic rings are available from the **Custom** menu. These are installed in the directory ***C/ProgramFiles/Wavefunction/Spartan/Library*** (Windows), from the installation directory for ***Spartan*** (Linux), and on the installation CDROM (Macintosh).

Clipboard

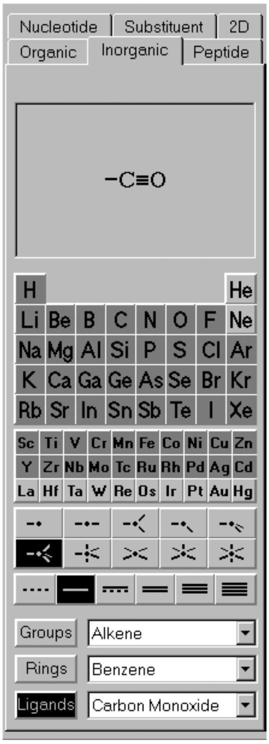
Clicking on **Clipboard** accesses the clipboard. A ball-and-wire model of whatever is on the clipboard is displayed at the top of the model kit. This may be manipulated using the usual mouse/keyboard commands (you need to position the cursor inside the box). Once selected, the molecule may be used to initiate building, to add alongside of an existing structure, or to add to an existing structure. In the latter case, the attachment point needs to be identified by *clicking* on the appropriate free valence in the clipboard.

An empty clipboard will be signaled by:

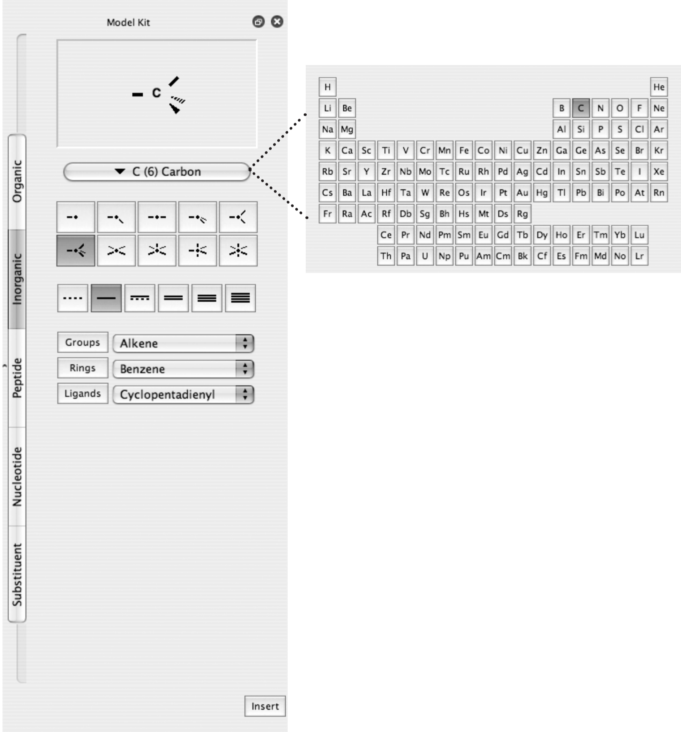


Inorganic Model Kit

Spartan's inorganic model kit allows construction of a much wider class of molecules (including inorganic and organometallic species) than permitted using the organic model kit. Structures that violate conventional bonding rules may also be constructed, as this model kit purposefully provides no checking. The inorganic model kit is reached by *clicking* on the **Inorganic** tab, located at the top of the organic (peptide, nucleotide or substituent) model kit. (Return to the organic, peptide, nucleotide or substituent model kit or to ChemDraw is accomplished by *clicking* on the **Organic**, **Peptide**, **Nucleotide**, **Substituent** or **2D** tab, respectively, in the inorganic model kit).


Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
−C≡O
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Ga Ge As Se Br Kr
Rb Sr In Sn Sb Te I Xe
Sc Ti V Cr Mn Fe Co Ni Cu Zn
Y Zr Nb Mo Tc Ru Rh Pd Ag Cd
La Hf Ta W Re Os Ir Pt Au Hg

Groups: Alkene
Rings: Benzene
Ligands: Carbon Monoxide


Model Kit
Organic
Inorganic
Peptide
Nucleotide
Substituent
C
C (6) Carbon
Insert
H He
Li Be B C N O F Ne
Na Mg Al Si P S Cl Ar
K Ca Sc Ti V Cr Mn Fe Co Ni Cu Zn Ga Ge As Se Br Kr
Rb Sr Y Zr Nb Mo Tc Ru Rh Pd Ag Cd In Sn Sb Te I Xe
Cs Ba La Hf Ta W Re Os Ir Pt Au Hg Tl Pb Bi Po At Rn
Fr Ra Ac Rf Db Sg Bh Hs Mt Ds Rg
Ce Pr Nd Pm Sm Eu Gd Tb Dy Ho Er Tm Yb Lu
Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lr

Groups: Alkene
Rings: Benzene
Ligands: Cyclopentadienyl

Macintosh and Linux: Atoms may be selected by *clicking* on the center atom button, this leads to a full periodic table. **Windows**: In the center of the model kit is a *Periodic Table* covering the first four rows of main-group elements, and all three rows of transition metals.* Main-group elements appear at the top and transition metals at the bottom. If **Element Overlay** (**Settings Preferences** dialog under **Preferences...** in the **Options** menu; see **Chapter 18**) is *checked*, elements which are available for the selected level of calculation (**Calculations** dialog under the **Setup** menu; see **Chapter 15**) will be highlighted (**NAL**, **NAM**). Immediately below is a selection of atomic hybrids. Following this, is a selection of bond types. Further down the model kit below the buttons marked **Groups**, **Rings** and **Ligands** (the first two of which are the same as found in the organic model kit).

Selection of atom type is effected by *clicking* on the appropriate element in the *Periodic Table*. The entry will be highlighted. Selection of an atomic hybrid follows by *clicking* on the appropriate icon which will then be highlighted. This combination (atom type + atomic hybrid) may be used to initiate building, to add alongside of an existing structure or to append onto an existing molecular fragment. To initiate building, *click* anywhere on screen. To add alongside of an existing structure, first *click* on **Insert** at the bottom right of the screen or *press* the **Insert** key (**alt** key on Mac), and then *click* anywhere on screen. To bond to an existing fragment, *click* on the appropriate free valence.

---

* The remaining elements may be specified using the **Atom Properties** dialog under the **Display** menu (see **Chapter 16**) although computational models may not be available.

Two of the hybrids (trigonal bipyramidal and square-based pyramidal) may bond either *axially* or *equatorially*. Selection of the appropriate bonding point, marked by a •, is effected by repeatedly *clicking* on the icon; the bonding point alternates between the two sites.

Atoms are connected with whatever bond type (partial single, single, aromatic, double, triple or quadruple) is selected in the model kit. A bond type may be changed by first selecting a type and then *double clicking* on the bond. Bond types have no impact on quantum chemical calculations, but do affect molecular mechanics calculations (including minimization in the builder; see discussion following).

No valence checking is performed in the inorganic model kit, and the user is free to construct any arrangement of atoms.

Three fragment collections are located inside the inorganic model kit:

Groups

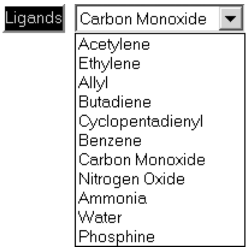
This contains the same groups as in the organic model kit.

Rings

This contains the same rings as in the organic model kit.

Ligands

This provides access to a number of pre-built ligands, useful in the construction of inorganic and organometallic molecules. Its operation is analogous to that for the **Groups** and **Rings** menus. *Clicking* on **Ligands** brings up a menu of available ligands, and results in an icon of one ligand from this menu being displayed at the top of the model kit.



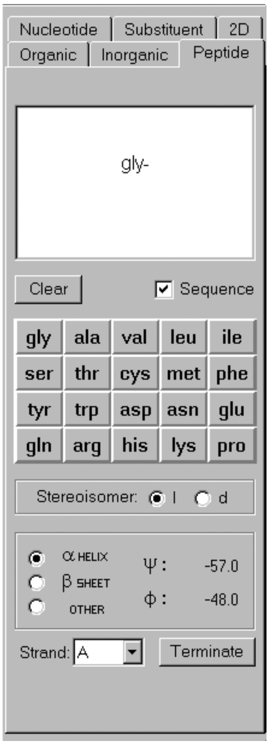
Ligands: Carbon Monoxide

Acetylene
Ethylene
Allyl
Butadiene
Cyclopentadienyl
Benzene
Carbon Monoxide
Nitrogen Oxide
Ammonia
Water
Phosphine

A ligand may be used to initiate building or to add alongside or to an existing structure. Additional ligands are found in a library accessible from **Custom** in the organic model kit. Ligands may also be built using **Define Ligand Point** (**Geometry** menu; **Chapter 13**).

Peptide Model Kit

A model kit for construction of polypeptides is reached by *clicking* on the **Peptide** tab located at the top of the organic, inorganic, nucleotide and substituent model kits. (Return to the organic, inorganic, nucleotide or substituent model kit or to ChemDraw is accomplished by *clicking* on the **Organic**, **Inorganic**, **Nucleotide**, **Substituent** or **2D** tab, respectively, in the peptide model kit.)



gly-

☑ Sequence

Stereoisomer: ● l ○ d

● α HELIX
○ β SHEET
○ OTHER

ψ : -57.0
φ : -48.0

Strand: A

Nucleotide
Substituent
2D
Organic
Inorganic
Peptide
Clear
gly
ala
val
leu
ile
ser
thr
cys
met
phe
tyr
trp
asp
asn
glu
gln
arg
his
lys
pro
Terminate

At the middle of the peptide model kit are icons designating the amino acids (specified by their usual three-letter codes). An amino acid is selected by *clicking* on its three-letter code, following which either an icon of the amino acid is displayed in the box at the top of the model kit, or the three-letter code for the amino acid is appended to the sequence of codes in the box. Amino acids replace atoms, functional groups, rings and ligands as the building blocks in the peptide model kit. Because these other building blocks are missing, modifications of peptides, aside from modifications in sequence and in overall conformation, need to be carried out using the organic or inorganic model kits.

There are two different modes of operation: single amino acid mode and polypeptide mode. The former is used to initiate building with a single amino acid, to add a single amino acid alongside of an existing structure or to add a single amino acid to an existing structure, while the latter is used to construct amino acid sequences (polypeptides). **Sequence** "off" (unchecked) corresponds to single amino acid mode, and "on" (checked) corresponds to polypeptide mode.

Peptide construction (**Sequence** "on") is accomplished in three steps:

Specification of Amino Acid Sequence

This is accomplished by *clicking* in the desired order on the amino acid codes. Building occurs from the N end to the C end of the peptide. In response to each selection, the three-letter code is appended to the sequence of codes in the box at the top of the model kit. The stereochemical configuration of the amino acid is by default the l configuration; this may be changed to the d configuration prior to selection of the amino acid, by *checking* **d** to the right of **stereoisomer** in the model kit. (It may be changed back to l by *checking* **l**). d amino acids are indicated by **.d** following the code in the box.

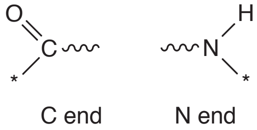
The sequence may be altered by changing the text in the box. Existing amino acid codes may be deleted or changed or new codes can be added. The entire sequence may be specified in this way if desired. Specification of a non-existent code will result in an error message. The sequence can be cleared by *clicking* on **Clear**.

Specification of Macroscopic Structure

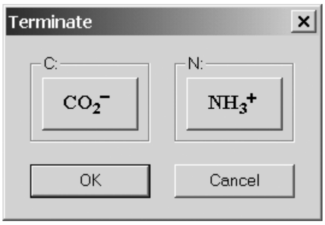
Once sequencing is complete, macroscopic structure (ψ and ϕ angles), is specified by *clicking* on one of α **Helix**, β **Sheet** or **Other**. In the case of the first two, preset angle values are displayed on the right. In the case of specification of **Other**, boxes appear, into which the desired dihedral angles need to be entered.

Termination

The peptide is not yet terminated, and the two ends are still set up for addition of further amino acids.



where the * indicates a free valence. *Clicking* on **Terminate** at the bottom of the model kit leads to the **Terminate** dialog.

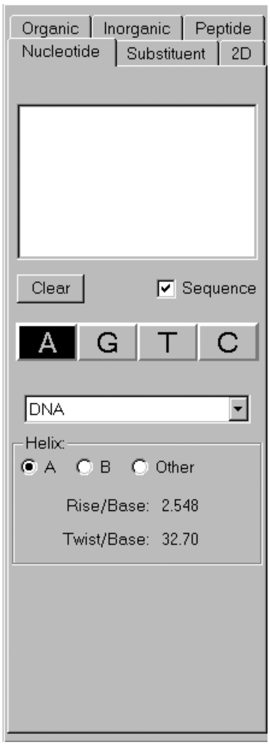


C and N terminating groups may be selected by repeated *clicking* on the C and N icons, respectively. Selection will rotate among the available terminating groups. *Clicking* on **OK** removes the dialog and terminates the polypeptide. *Clicking* on **Cancel** or on ☒ removes the dialog but does not terminate the polypeptide.

The peptide (or single amino acid) may now be used either to initiate building, by *clicking* anywhere on screen or added alongside of an existing structure, by first *clicking* on **Insert** at the bottom right of the screen or *pressing* the **Insert** key (**alt** key on Mac), followed by *clicking* anywhere on screen. If unterminated, it may also be joined onto an existing structure by *clicking* on a free valence. In the latter case, attachment is made from the N end, unless the free valence corresponds to an unterminated peptide fragment, in which case the appropriate end required to make an amide bond is used.

Nucleotide Model Kit

Finally, ***Spartan*** provides a model kit for construction of polynucleotides. It is reached by *clicking* on the **Nucleotide** tab which is located at the top of the organic, inorganic, peptide and substituent model kits. (Return to the organic, inorganic, peptide or substituent model kit or to ChemDraw is accomplished by *clicking* on the **Organic**, **Inorganic**, **Peptide**, **Substituent** or **2D** tab, respectively, in the nucleotide model kit.)



☑ Sequence

DNA

Helix: ● A ○ B ○ Other

Rise/Base: 2.548

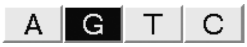
Twist/Base: 32.70

At the middle of the model kit is a menu designating the type of polynucleotide.

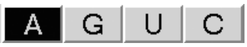
DNA
DNA (single strand)
DNA-RNA

RNA
RNA (double strand)
RNA-DNA

Immediately below this menu are icons, designating the nucleotide bases. Selection of DNA, DNA (single strand) or DNA-RNA from the menu leads to one set of icons.



Selection of RNA, RNA (double strand) or RNA-DNA leads to a second set, the only difference is that uracil (U) has been substituted for thymine (T).



A nucleotide base is selected by *clicking* on its letter, following which either an icon of the base is displayed in the box at the top of the model kit, or the letter for the base is appended to the sequence of letters in the box. Nucleotide bases replace atomic fragments, functional groups, rings and ligands as the building blocks in the nucleotide model kit. Because these other building blocks are missing, modifications of nucleotides, aside from modifications in sequence and helical structure, need to be carried out using either the organic or inorganic model kits.

There are two different modes of operation: single base mode and polynucleotide mode. The former is used to place a single base or base pair on screen, to add a single base or base pair alongside of an existing structure, or to add a single base or base pair to an existing structure, while the latter is used to construct strands of DNA or RNA (or mixed strands). **Sequence** “off” (unchecked) corresponds to single base (base pair) mode and “on” (checked) corresponds to polynucleotide mode.

Polynucleotide construction (**Sequence** “on”) is accomplished in two steps:

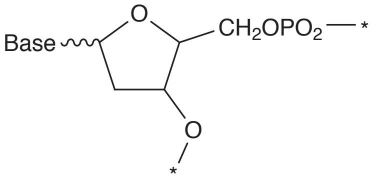
Specification of Base Sequence

This is accomplished by *clicking* in order on the base codes. In response to each selection, the letter code is appended to the sequence of codes in the box at the top of the model kit. The sequence may be altered by editing the contents of the box. Existing base codes may be deleted or changed or new codes added. The entire sequence can be specified in this way if desired. The sequence may be cleared, by *clicking* on **Clear**.

Specification of Helical Structure

Once sequencing is complete, a helical structure may be specified by *clicking* on **A** or **B**. These correspond to A, B and Z helices, respectively. Selecting **Other** allows user modification of the rise (in Å) per base (**Rise/Base**) and twist (in degrees) per base (**Twist/Base**).

Note that the polynucleotide is not yet terminated, and the two ends are still set up for addition of further bases or base pairs.

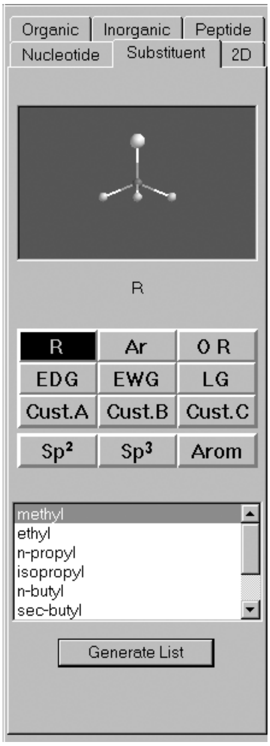


∗ indicates a free valence. Hydrogens occupy all free valences (except the ∗'ed positions at the two ends of the chain).

The polynucleotide (or single base pair) may now be used to either initiate building, by *clicking* anywhere on screen, added alongside of an existing structure, by first *clicking* on **Insert** at the bottom right of the screen or *pressing* the **Insert** key (**alt** key on Mac) followed by *clicking* on screen, or joined onto an existing structure by *clicking* on a free valence. In the latter case, attachment is made from the phosphate end.

Substituent Model Kit

The substituent model kit creates a list of substituted molecules from a single unsubstituted molecule. Additionally, it replaces carbon hybrids by their heteroatom equivalents. The substituent model kit is accessed by *clicking* on the **Substituent** tab located at the top of the organic, inorganic, peptide and nucleotide model kits. (Return to the organic, inorganic, peptide or nucleotide model kit or to ChemDraw is accomplished by *clicking* on the **Organic**, **Inorganic**, **Peptide**, **Nucleotide** or **2D** tab, respectively, in the substituent model kit.)


Organic
Inorganic
Peptide
Nucleotide
Substituent
2D
R
R
Ar
O R
EDG
EWG
LG
Cust.A
Cust.B
Cust.C
Sp²
Sp³
Arom
methyl
ethyl
n-propyl
isopropyl
n-butyl
sec-butyl
Generate List

At the center of the model kit are four rows of buttons. Buttons in the first two rows provide access to predefined substituent libraries: **R** (alkyl groups), **Ar** (aromatic groups), **OR** (alkoxy groups), **EDG** (electron donor groups), **EWG** (electron withdrawing groups) and **LG** (leaving groups). Buttons in the third row allow access to user-defined substituent libraries, while those in the last row permit substitution of heteroatom hybrids for sp^3, sp^2 and aromatic carbons incorporated in a molecule. Immediately below the buttons, a dialog lists the entries in the individual libraries. As entries are selected, they will appear in the window at the top of the dialog. Predefined libraries may not be altered, but existing library entries in custom libraries may be deleted and new entries added.

Creating lists of substituted molecules starting from an unsubstituted molecule occurs in three stages: library preparation, attachment and list generation. Where existing libraries are to be used unaltered, all these stages occur using the substituent model kit. Modifications to substituent libraries need to be performed ***following attachment*** using the **Substituent Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**).

Library Preparation

Six substituent libraries have been provided.

R (alkyl group): methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, *t*-amyl

Ar (aromatic ring): phenyl, p-tolyl, p-nitrophenyl, 1-naphthyl, 2-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl

OR (alkoxy group): methoxy, ethoxy, *n*-propoxy, isopropoxy, *t*-butoxy

EDG (electron donor group): hydroxy, methoxy, ethoxy, phenoxy, amino, dimethylamino, mercapto, methylthio, phenylthio

EWG (electron withdrawing group): cyano, nitro, trifluoromethyl, carboxy, formyl, methoxycarbonyl, ethoxycarbonyl, methyl sulfonyl, methyl sulfoxyl

LG (leaving group): bromo, iodo, tosylate, triflate, mesylate

The contents of a library may be displayed in the scroll box at the bottom of the model kit by *clicking* the appropriate button. A ball-and-wire model of a substituent may be seen at the top of the model kit by *clicking* on its name in the scroll box. The model may be manipulated in the usual way. The attachment point is indicated by a gold ball surrounding a “hydrogen”.

To create a custom substituent library, first *click* on one of the **Custom** buttons inside the model kit. The scroll box is empty.

If a substituent (set of substituents) has previously been copied to the clipboard, it may be pasted into the library by positioning the cursor inside the scroll box, holding down the right button and selecting **Paste** from the menu that appears. Alternatively, a substituent (set of substituents) in any .spartan file may be *dragged* onto the scroll box from the file system. As many substituents (sets of substituents) as desired may be pasted and/or dragged into a library. To remove a substituent from the library, first *click* on its name in the scroll box, then hold down the right mouse button and select **Delete** from the menu that appears. **Ctrl** (**Apple** for Mac) and **Shift** keys may be used in the usual way.

Substituents need to be specified in terms of both their structure and their connection point. The safest way to specify the latter is to replace all free valences ***except the one that will serve as the connection point*** by hydrogens. For example, to designate a 2-pyridyl substituent, you need to add hydrogens (-H from the organic model kit) to four of the five free valences in pyridine, leaving only one free valence in the 2-position available. Alternatively, a connection point can be specified by *clicking* on the appropriate position as the substituent displayed at the top of the model kit.

The three buttons in the last row designate heteroatom equivalents of carbon-based hybrids.

sp^2: carbon (C=), nitrogen (N=)
sp^3: carbon (C-), nitrogen (N), oxygen (O-)
Arom.: carbon (C-), nitrogen (N)

These lists may be used as is or individual entries may be deleted ***following attachment*** using the **Substituent Properties** dialog.

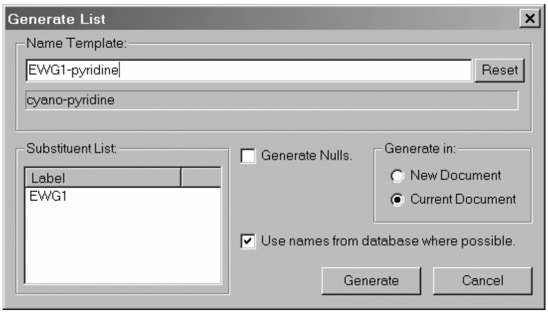
Attachment

Following selection, a substituent library may be used to initiate building, to add alongside of an existing structure or to attach to an existing structure. The model is augmented by an icon containing the library name from the button, for example **EWG**, followed by a number. As many substituent libraries as desired may be attached to a molecule. Each library is given a unique label, that can be changed prior to list generation using the **Substituent Properties** dialog. A substituent library may be removed from the molecule by selecting **Delete** from the **Build** menu and then *clicking* on the library icon.

> A molecule with attached substituent libraries may be saved prior to list generation just as any other document. Any queries (bond distances, angles, etc.) and calculations refer to the unsubstituted molecule.

List Generation

Generation of a list of substituted molecules follows specification and (optionally) editing of one or more substituent libraries and attachment of each of these libraries at one or more positions in a molecule. Duplicates are eliminated. *Clicking* on **Generate List** at the bottom of the model kit, leads to the **Generate List** dialog.


Generate List

Name Template: EWG1-pyridine

cyano-pyridine

Substituent List:

Label	
EWG1	

☐ Generate Nulls.

Generate in:
○ New Document
● Current Document

☑ Use names from database where possible.

A box at the top of the dialog allows the user to specify (or modify) a **Name Template**, from which the names of substituted molecules will be derived. Upon entry, this takes the form.

Ax-By-Cz-molecule name

A, B, C are the names of the substituent libraries (**R**, **EWG**, etc.), x, y, z are integers and molecule name is the name of the unsubstituted molecule if and as it appears in the Spartan Molecular Database (SMD). If the unsubstituted molecule is not in the database, then the box below **Name-Template** will be blank. If the substituted molecule is in SMD, its name in the database may be used (instead of the name generated from the template) by *checking* the box to the left of **Use names from database where possible**.

Nulls are molecules with less than the full complement of substituents, for example, monosubstituted molecules in the case where two different positions have be substituted. These will not be included in the list of substituted molecules unless **Generate Nulls** is checked.

The list may either be written to a **New Document** or appended to the end of the **Current Document**.

Accessing ChemDraw (NAL, NAM)

The ChemDraw program may be seamlessly accessed inside of ***Spartan***[*] allowing chemical drawings to be produced in a familiar environment and then brought over as 3D structures[**]. The conversion is unambiguous as long as all stereochemical cues are in place in the 2D drawing.

To access ChemDraw, enter the builder, *click* on the **2D** tab and *click* on **Edit** at the bottom of the panel that results. ChemDraw will appear. To return to ***Spartan***, close ChemDraw. The 2D drawing will appear at the center of the panel and manipulatable 3D rendering will appear at the top of the panel. *Clicking* on screen will move the 3D rendering into ***Spartan's*** main window.

General Molecule Building Functionality

Additional capabilities are available with **Add Fragment** selected:

Multiple Fragments

Multiple fragments may result either from bond breakage (see **Break Bond** later in this chapter) or from use of the **Insert** button or **Insert** key (**alt** key on Mac). A fragment is selected by *clicking* on it, following which the associated free valences are colored gold

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[*] ChemDraw is not provided with ***Spartan*** but must be obtained from CambridgeSoft at http://www.cambridgesoft.com.

[**] Transfer is one directional only. 3D structures may not be transferred back to ChemDraw.

(free valences for any non-selected fragments are colored white). All builder functions apply to the selected fragment only. Rotation and translation also apply to the selected fragment, but may be made to apply to the entire set of fragments by holding down the **Ctrl** key while carrying out these operations.

Fragments may be attached using **Make Bond** (see discussion later in this chapter).

Bond Rotation/Bond Stretching

In addition to molecule rotation, translation and scaling, the mouse is used to rotate about and stretch bonds not incorporated into rings. This is accomplished via the following sequence of operations:

(i) *Clicking* on the bond, which is then marked by a red cylindrical arrow. (The bond connecting the last atom, group, ring or substituent added to the molecule is automatically selected.)

(ii) Simultaneously holding down the **Alt** key and the left mouse button while *dragging* the mouse up and down, for bond rotation, or the **Alt** key and the right mouse button for bond stretching.

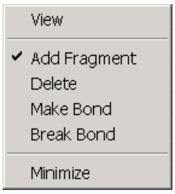
Atom/Fragment Replacement

Another function of the mouse is atom replacement. *Double clicking* on an atom (not a free valence) while an atomic fragment in the organic model kit or an atom icon in the inorganic model kit is highlighted, replaces this atom by the selected atom icon. Atom replacement functions differently in the organic and inorganic model kits. In the organic model kit, free valences are adjusted to accommodate the replacement, for example, replacement of sp^3 carbon by sp^3 oxygen results in two free valences being removed. Atom replacements that violate valence rules or that would disrupt substituents are not permitted. In the inorganic model kit, atom replacement merely changes the atomic number. No changes in the number or arrangement of free valences is made, and no checking is done. Atom replacement is not available in the peptide, nucleotide and substituent model kits.

Chirality Inversion

In the **Add Fragment** mode, *double clicking* on a chiral atom with the **Ctrl** key (**Command** key on Mac) depressed inverts the chirality of the atom (R→S or S→R). This is not available in fused ring systems. *Double clicking* on any atom with both **Ctrl** (**Apple** key on Mac) and **Shift** keys depressed inverts the absolute configuration of the molecule.

Molecule building/editing functions are found under the **Build** menu.



View (V)

This exits build mode, and removes the model kit from the screen.

> Initial entry into build mode is by way of **New** or **New Molecule** under the **File** menu (see **Chapter 10**). **Add Fragment**, **Delete**, **Make Bond**, **Break Bond** and **Minimize** are for modifying existing structures.

Add Fragment (+)

In addition to the capabilities discussed under **General Molecule Building Functionality**, this allows access to the libraries of atomic fragments, groups, rings, ligands and substituents, as well as the file system and the clipboard. *Clicking* on any buttons or menus in the organic, inorganic, peptide, nucleotide or substituent model kits, leads to **Add Fragment**. (If a model kit is not on screen, selection brings up the last-accessed model kit.) A fragment may be used to initiate building by *clicking* anywhere on screen, to add alongside an existing structure on screen by *clicking* on the **Insert** button at the bottom right of the screen or *pressing* the **Insert** key (**alt** key on Mac) followed by *clicking* anywhere on screen, or be added to an existing structure by *clicking* on the appropriate free valence. Fragment addition can be terminated by selection of any other function.

Delete ()

This allows atom, free valence and substituent library removal from a structure. Selection leads to a message at the bottom left of the screen.

Select object to delete.

Subsequent *clicking* on an atom, free valence or substituent library results in its deletion. Deletion of an atom results in deletion of all of its associated free valences. Free valences for any atoms to which the deleted atom was previously connected are restored. Note that atom deletion may result in one or more detached fragments. *Clicking* inside a selection box results in deletion of everything inside the box. Selection of **Delete** does not bring up a model kit nor does it remove a model kit that is present on screen. **Delete** may be terminated by selection of any other function.

> **Delete** may also be used to delete CFD's and pharmacophore elements as well as spectra and plots (or individual curves that make up plots).

Deletion may also be accomplished by holding down on the **Delete** key while *clicking* on the item to be deleted.

Make Bond ()

This allows bonds to be drawn between free valences and/or atoms on different centers. Selection leads to a message at the bottom left of the screen.

Select two free valences.

Clicking on two free valences (on different atoms) will cause these atoms to be linked by a single bond. Alternatively, *double clicking* on each of two atoms will bond them, and *clicking* on a free valence on one atom and *double clicking* on a different atom will bond the two atoms. Where available, free valences are consumed as a result of bond formation, irrespective of whether free valences or atoms are selected.* If the selected atoms are already bonded, this will result in the bond order being increased by one, that is, single → double, double → triple. Selection of **Make Bond** does not bring up a model kit nor does it remove a model kit that is already present on screen. **Make Bond** may be terminated by selection of any other function.

---

* Note that free valences can be "protected" without altering the molecule by adding hydrogens to them (-H from the organic model kit).

Break Bond ()

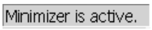
This allows breaking an existing bond resulting in free valences. Selection leads to a message at the bottom left of the screen.

Select bond to break.

Clicking on a bond breaks it and restores free valences. Note that bond breaking may result in detached fragments. Selection of **Break Bond** does not bring up a model kit nor does it remove a model kit that is present on screen. **Break Bond** may be terminated by selection of any other function.

Minimize (↓E)

This uses molecular mechanics to refine the geometry. Selection leads to a message at the bottom left of the screen.



Minimizer is active.

The molecular mechanics strain energy in kJ/mol, displayed at the bottom right of the screen, is continually updated during the minimization process. Minimization may be stopped at any time by *clicking* on the STOP icon at the bottom right of the screen. Any geometrical constraints imposed on the structure (see **Constrain Distance**, **Constrain Angle**, **Constrain Dihedral** in **Chapter 13**) are enforced during minimization. NOE's are not taken into account. Also, any frozen atoms in the structure (see **Freeze Center** under the **Geometry** menu; **Chapter 13**) remain frozen.

Following completion, **Minimize** reverts back to **Add Fragment** only if a model kit is on screen.

Chapter 15

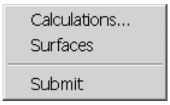
The Setup Menu

This chapter describes functions available under the ***Setup*** *menu.* ***Calculations*** *is used to specify molecular mechanics calculations, semi-empirical calculations, Hartree-Fock molecular orbital calculations, and correlated calculations, including local density calculations, density functional calculations, Møller-Plesset calculations, coupled cluster calculations and quadratic configuration interaction calculations for ground-state species, and configuration interaction calculations, local density calculations and (time dependent) density functional calculations for excited-state species. Tasks include calculation of energy, equilibrium structure and conformation, transition-state structure and constructing energy profiles, although not all tasks are available for some methods. A wide variety of all-electron Gaussian basis sets are supported for Hartree-Fock and correlated calculations as are pseudopotentials for calculations on molecules incorporating heavy elements. Also provided are a number of thermochemical recipes, including G3 and G3(MP2), as well as a new (and more economical) parameterized scheme.* ***Calculations*** *also requests IR, NMR and UV/visible spectra, and calculation and printing of a variety of molecular properties. Finally,* ***Calculations*** *identifies libraries and specifies conditions for identifying similar molecules, based either on molecular structure or chemical functionality, as well as for identifying molecules that are compatible with a pharmacophore.*

Surfaces *designates graphical surfaces, including electron and spin densities, electrostatic potentials, local ionization potentials and molecular orbitals, for later display as surfaces, property maps and contour plots. Accessible regions on electron density surfaces and property maps based on these surfaces may be demarked.*

Submit *directs jobs for calculation, either locally or on a remote Linux server.*

The **Setup** menu provides access to dialogs for specifying molecular mechanics and quantum chemical calculations, for specifying conditions for similarity analysis as well as specifying graphical displays and for submitting jobs for calculation.



Calculations...

Calculations modules perform: molecular mechanics calculations using the SYBYL and MMFF force fields, the latter of which may be corrected for the effects of aqueous solvent*; MNDO (MNDO/d where second-row and heavier elements are involved), AM1, RM1 and PM3 semi-empirical calculations, including PM3 calculations on transition-metal inorganic and organometallic systems; Hartree-Fock molecular orbital calculations; local density calculations; BP, BLYP, EDF1 and B3LYP density functional calculations; MP2 and RI-MP2 Møller-Plesset calculations; configuration interaction calculations (for excited-state species). These are all applicable to energy calculation, equilibrium and transition-state geometry determination, conformational searching and making an energy profile, although some methods may not yet be practical for some tasks. Also available for energy calculations only are a series of high-order correlated models, including MP3 and MP4 Møller-Plesset models, coupled cluster models and quadratic configuration interaction models. A wide selection of basis sets is available, ranging from the STO-3G minimal basis set (Hartree-Fock models only), to the 3-21G split-valence basis set (Hartree-Fock models only), to 6-31G*, 6-311G*, and cc-pVDZ, cc-pVTZ and cc-pVQZ polarization basis sets. In addition, pseudopotentials for very heavy elements are available. All basis sets, except STO-3G and 3-21G may be supplemented with polarization functions on hydrogen, additional and/or higher-order polarization functions on heavy atoms and/or diffuse functions on hydrogens and/or heavy atoms.

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* Note that solvent correlations in MMFF are applied to energies only. Equilibrium geometries and vibrational frequencies are unaffected, as are properties derived from the wavefunction.

Finally, a series of recipes for estimating heats of formation are available. These include the G3 and G3 (MP2) recipes as well as a new scheme based on G3(MP2), but two to three orders of magnitude less costly in terms of computation.

> The Essential Edition of ***Spartan'06*** permits calculations on ground-state species only, and with molecular mechanics, semi-empirical and Hartree-Fock models only. STO-3G, 3-21G, 6-31G* and 6-311G* basis sets only, with extensions for additional polarization functions and/or diffuse functions are supported. Conformer library generation, alignment based on chemical functionality, similarity analysis and intrinsic reaction coordinate (IRC) are not supported. Differences between the full and essential edition of ***Spartan'06*** are detailed at the end of this section.

Discussion of molecular mechanics and quantum chemical methods in general, focusing on the specific methods available in ***Spartan,*** is provided in ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***. This guide also provides a brief discussion of ways in which the different methods may be effectively and efficiently combined, and a description of graphical models and modeling techniques.

Quantum chemical calculations, in particular, also result in a variety of atomic and molecular properties as well as IR, UV/visible and NMR spectra. These are available for selected models. Finally, the **Calculations** dialog accesses a procedure to quantify the extent to which two molecules or a molecule and a pharmacophore are similar. This does not involve either molecular mechanics or quantum chemical calculations but depends only on molecule (pharmacophore) geometry.

Selection of **Calculations...** results in the **Calculations** dialog*.

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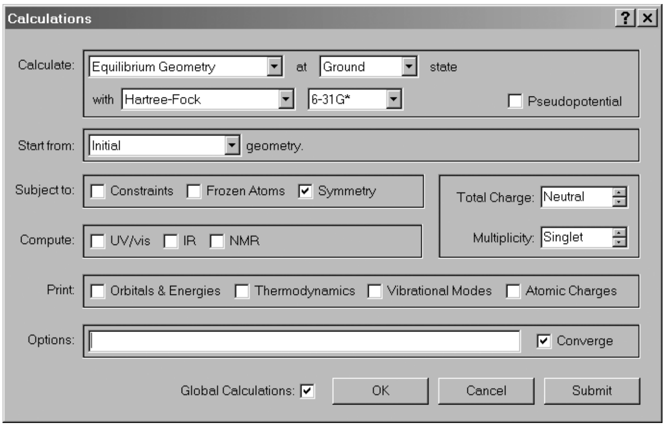
* The dialogs associated with similarity analysis and with conformer library generation are different from that associated with the other entries under the **Calculate** menu. They will be presented later in this section.



Calculations

Calculate: Equilibrium Geometry at Ground state
with Hartree-Fock 6-31G* ☐ Pseudopotential

Start from: Initial geometry.

Subject to: ☐ Constraints ☐ Frozen Atoms ☑ Symmetry

Total Charge: Neutral

Multiplicity: Singlet

Compute: ☐ UV/vis ☐ IR ☐ NMR

Print: ☐ Orbitals & Energies ☐ Thermodynamics ☐ Vibrational Modes ☐ Atomic Charges

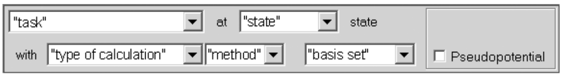
Options: ☑ Converge

Global Calculations: ☑

This contains a number of pull-down menus, buttons and text boxes:

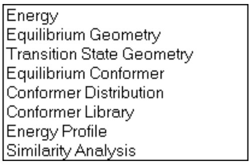
Calculate

This section contains a series of menus and check boxes that specify the task to be accomplished, and where appropriate, the electronic state (ground or excited) the type of calculation, method and basis set to be employed, as well as details specific to each calculation type.



"task" at "state" state
with "type of calculation" "method" "basis set" ☐ Pseudopotential

Specification of **Task** is by way of a pull-down menu:



Energy
Equilibrium Geometry
Transition State Geometry
Equilibrium Conformer
Conformer Distribution
Conformer Library
Energy Profile
Similarity Analysis

Energy specifies calculation of energy (and in the case of quantum chemical methods, a wavefunction) at a single geometry.

Spartan reports energies from molecular mechanics calculations as strain energies in kJ/mol, from semi-empirical calculations and from thermochemical recipes as heats of formation in kJ/mol, and from Hartree-Fock and correlated calculations as total energies in atomic units (hartrees).

The molecular mechanics energy comprises two parts: the strain energy and the non-bonded energy. The strain energy is the difference in energy between a molecule and its “strain free” analog. It is nearly always positive and less than a few hundred kJ/mols in magnitude. The non-bonded energy accounts for attraction or repulsion between atomic centers that are not connected due to van der Waals and Coulombic interactions. Because the strain energy of every molecule relates to a different standard, molecular mechanics energies cannot be used to obtain reaction energies.

The heat of formation is to the enthalpy at 298K of a balanced chemical reaction in which a molecule is converted to a set of standard products. For example, the heat of formation of ethylene is given by reaction,

$$C_2H_4 + \rightarrow 2C\ (\text{graphite}) + 2H_2\ (\text{gas})$$

where graphite and hydrogen molecule are the carbon and hydrogen standards, respectively. In practice, the actual measurement is typically carried out for a combustion reaction, for example, for ethylene:

$$C_2H_4 + 3O_2 \rightarrow 2CO_2 + 2H_2O$$

Heats of formation may either be positive or negative quantities and generally span a range of only a few hundred kJ/mol.

Heats of formation are not suitable for presenting energy data from quantum chemical calculations, simply because the standards for several important elements (most notably, carbon) are not well-defined isolated species. In its place is the energy of a reaction that splits a molecule into its isolated nuclei and electrons, for example, for ethylene:

$$C_2H_4 \rightarrow 2C^{+6} + 4H^{+} + 14e^{-}$$

Total energies, as the energies of such reactions are termed, are always negative and may be very large (tens of thousands of kJ/mol). They are most commonly given in atomic units (hartrees).

$$1 \text{ atomic unit} = 2625 \text{ kJ/mol}$$

Aside from a difference in units, it makes no difference whatsoever which standard is employed to investigate thermochemistry.

To summarize, the heat of formation differs from the total energy both with regard to the standard reaction and with regard to units. Either provides a suitable basis for thermochemical calculations.

Equilibrium Geometry specifies that the nearest energy minimum will be located, and **Transition State Geometry** that the nearest saddle point (transition state) will be located. **Equilibrium Conformer**, **Conformer Distribution** and **Conformer Library**

attempt to characterize the conformers available to a molecule based on different criteria (see discussion following). **Energy Profile** steps along a user-defined coordinate. **Similarity** quantifies the likeness among molecules or between molecules and a template (a pharmacophore).

Three different conformational analysis procedures are available in ***Spartan***. The first two (**Equilibrium Conformer** and **Conformer Distribution**) may be employed with a variety of molecular mechanics and quantum chemical models (although practical concerns may limit application to molecular mechanics), while the third (**Conformer Library**) is restricted to the MMFF molecular mechanics model.

Equilibrium Conformer replaces the initial conformer of a molecule by the lowest-energy conformer. This procedure is typically used to get a good guess at the best (lowest-energy) conformer for calculation of properties using quantum chemical methods.

Conformer Distribution provides a list of low-energy conformers. This procedure is typically used to obtain a set of accessible conformers either for calculation of average properties using quantum chemical methods or to assess similarity of a molecule to one or more molecules in a library.

Except for molecules with very few degrees of conformational freedom where systematic searches are practical, the procedure used to find the equilibrium conformer and to establish a conformer distribution is a so-called Monte-Carlo algorithm. Here, the search follows a path that biases in favor of low-energy conformers (but that does not completely exclude high-energy conformers). While there is no guarantee that the lowest-energy conformer (global minimum) will be located, it can be shown that the set of conformers examined (and kept) constitute a Boltzmann distribution. (This is strictly true only for the hypothetical case of an infinite number of search steps, but is closely approximated for searches with reasonable numbers of steps.)

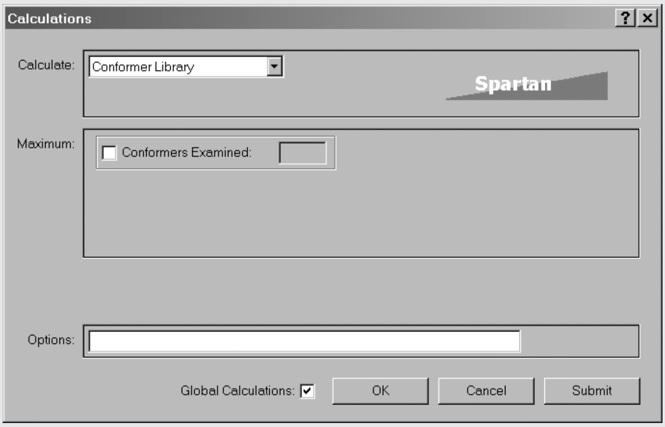
Conformer Library replaces the initial conformer of a molecule by the lowest-energy conformer and attaches the coordinates of a set of conformers spanning all shapes accessible to the molecule. This procedure is typically used to build libraries that will later be used to access similarity of new molecules.

The following recipe is used to generate a conformer library:

1. Step through all possible conformers in a systematic manner and calculate equilibrium structures and energies for each using the MMFF force field. Eliminate duplicates and very high-energy conformers.
2. Place spheres on each nitrogen, and oxygen atom and at the center of each hydrophobic region for each conformer.
3. Find the smallest set of conformers for which spheres do not overlap, that is, eliminate any conformer for which all of its spheres overlap with the corresponding spheres on another conformer.

This procedure involves a systematic search of all possible conformers. A set of conformer assignment rules that eliminate degrees of freedom that are unlikely to produce significant shape changes are available. See **Set Torsions** under the **Geometry** menu (**Chapter 13**) and **Settings Preferences** under the **Options** menu (**Chapter 18**). A limit may be placed on the total number of conformers actually considered. This is done by first calculating the fraction of conformers that are to be kept (total number of conformers to be examined/total number of systematic conformers), and then randomly deciding to examine or skip each conformer in a systematic search in order to enforce this fraction. Such a procedure is different from the Monte-Carlo method, in that it strives to span all possible shapes open to a flexible molecule without consideration of energy.

Selection of **Conformer Library** results in a different dialog.



Calculate: Conformer Library

Maximum: ☐ Conformers Examined:

Options:

Global Calculations: ☑

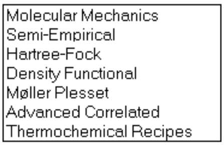
The only control, **Conformers Examined**, allows for setting the maximum number of conformers that are to be considered.

Energy applies to all methods. **Equilibrium Geometry**, **Equilibrium Conformer**, **Conformer Distribution** and **Energy**

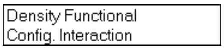
Profile apply to all methods except those listed under **Advanced Correlated** and **Thermochemical Recipes** (see below). **Transition State Geometry** applies to all methods except molecular mechanics methods and those listed under **Advanced Correlated** and **Thermochemical Recipes**. **Conformer Library** applies only to MMFF molecular mechanics, and **Similarity Analysis** does not involve either molecular mechanics or quantum chemical calculations.

Specification of **State** (electronic state) is by way of a pull-down menu. The default setting **Ground** may be changed to **Excited** by *clicking* on ▲ to the right of the box and back again to **Ground** by *clicking* on ▼. Different methods are available to handle ground and excited state species. Hartree-Fock, Møller-Plesset as well as a variety of advanced correlated methods are available only for ground-state species, while configuration interaction methods are available only for excited-state species. Density functional methods are available for both ground and excited state species. **State** is ignored for molecular mechanics calculations, and semi-empirical calculations are limited to the ground state.

Specification of **Type of Calculation** is by way of a pull-down menu. Selections in the menu depend on electronic state. For ground-state species:

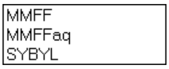

Molecular Mechanics
Semi-Empirical
Hartree-Fock
Density Functional
Møller Plesset
Advanced Correlated
Thermochemical Recipes

For excited-state species:

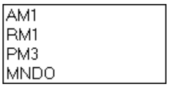

Density Functional
Config. Interaction

All calculation types except for Hartree-Fock require specification of additional information:

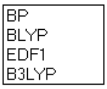
Molecular Mechanics


MMFF
MMFFaq
SYBYL

Semi-Empirical

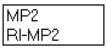

AM1
RM1
PM3
MNDO

Density Functional[*]



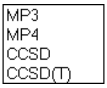
BP
BLYP
EDF1
B3LYP

Møller-Plesset



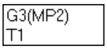
MP2
RI-MP2

Advanced Correlated[**]



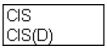
MP3
MP4
CCSD
CCSD(T)

Thermochemical Recipes[***]



G3(MP2)
T1

Configuration Interaction



CIS
CIS(D)

The most important application of molecular mechanics models is conformational searching, in particular, for molecules with several degrees of conformational freedom. In these cases, even the simplest quantum chemical models may not be practical. The MMFF force field is known to properly assign equilibrium conformation in a variety of simple molecules for which experimental data are available. It also has been shown to provide a reasonable account of conformational energy differences in larger organic molecules as obtained from high-level quantum chemical calculations. Aside from conformational energy differences, molecular mechanics models are not suitable for thermochemical calculations.

Semi-empirical models are simplest methods based on quantum mechanics. They are easily applicable to molecules containing 100 - 200 atoms, but not to molecules containing thousands of atoms, for example, proteins. The AM1, RM1 and PM3 models generally provide geometries that are in good accord with experimental structures. This makes them suitable for evaluation of such properties as polar surface area that depend solely on geometry. However, neither model is suitable for the calculation of relative energies as might be required to conclude, whether a chemical reaction is weakly or strongly *exothermic*, thermoneutral or weakly or strongly *endothermic*, or whether one isomeric product of a reaction is likely to be more or less stable than another, or to identify the lowest-energy tautomer. Also, neither method reliably accounts for conformational energy differences, as would be required to establish whether a particular conformer has a good chance at actually being present or to calculate the average value of a property based on the relative (Boltzmann) populations of different conformers.

---

[*] Local and EDF2 functionals are available and may be entered directly into the **Options** box.

[**] A number of other advanced correlated methods are available, and may be entered directly into the **Options** box: CCSD(2), OD, OD(T), QCCD, QCCD(2), QCISD and QCISD (T).

[***] G2 and G3 recipes are available and may be entered into the **Options** box.

Hartree-Fock models follow from the Schrödinger equation by requiring that the electrons be independent particles. This is known as the **Hartree-Fock approximation**. Here, the motions of electrons in molecules (molecular orbitals) are approximated by a sum of the motions of electrons in atoms (atomic orbitals). A second approximation, termed the **LCAO** or **L**inear **C**ombinations of **A**tomic **O**rbital **approximation**, distinguishes different Hartree-Fock models. Different models use different basis sets, that is, different numbers and kinds of atomic orbitals. For example, the model with the 3-21G split-valence basis set uses one atomic orbital to describe each non-valence electron and two atomic orbitals to describe each valence electron, that is, it comprises one 1s atomic orbital and two sets of 2s and 2p atomic orbitals.

$$\begin{gathered} 1s \\ 2s,\ 2p_x,\ 2p_y,\ 2p_z \\ 2s',\ 2p_x',\ 2p_y',\ 2p_z' \end{gathered}$$

The model with the 6-31G* polarization basis set increases the flexibility by including d type atomic orbitals that, while not occupied in the atom, are used in molecules.

$$\begin{gathered} 1s \\ 2s,\ 2p_x,\ 2p_y,\ 2p_z \\ 2s',\ 2p_x',\ 2p_y',\ 2p_z' \\ d_{xx},\ d_{xy},\ d_{xz},\ d_{yy},\ d_{yz},\ d_{zz} \end{gathered}$$

Larger basis sets involving additional basis functions, inclusion of even higher-order (f and g type) functions and diffuse functions can and have been defined and are available in ***Spartan***.

Both 3-21G and 6-31G* models provide good accounts of the geometries of organic molecules. This extends to unusual or unstable systems for which experimental data may be limited (and hence may be poorly represented in parameterization of the PM3 semi-empirical model). The 6-31G* model (and to a lesser extent, the 3-21G model) also properly accounts for thermochemistry, at least insofar as being able to say whether a particular reaction is weakly or strongly *exothermic* or weakly or strongly *endothermic*. It is also able to properly order the stabilities of isomeric products and to reliably identify the lowest-energy tautomer. Finally, 6-31G* calculations provide a qualitatively correct account of the relative stabilities of different conformational arrangements. Hartree-Fock models with larger basis sets show similar behavior.

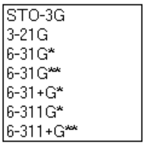
The most conspicuous and most important flaw of Hartree-Fock models (even with very large basis sets) is their inability to properly account for the energetics of bond dissociation. This can be traced to the Hartree-Fock approximation which in effect replaces interactions between electrons by interactions between one electron and the average field created by all other electrons. As a consequence, electrons "get in each other's way" to a greater extent than they should. This leads to overestimation of the electron-electron repulsion energy, most significantly for electrons that are paired. Because bond dissociation reduces the number of electron-pairs (by one), the overestimation will be greater for reactants than for products and the calculated dissociation energy will be too small.

Models that do away with the Hartree-Fock approximation, or at least lessen its effect, are termed **correlated models**. These divide into two broad categories, density functional models and wavefunction-based models. **Density functional models** explicitely introduce an approximate correlation term. They are not much more costly in terms of computation time than Hartree-Fock models, although it is not apparent how to improve on a particular choice of correlation correction. Wavefunction-based models, typified by **Møller-Plesset models** and **configuration interaction models** extend the flexibility of Hartree-Fock models by mixing ground-state and excited-state wavefunctions. They are significantly more costly than both Hartree-Fock and density functional models, but offer the advantage over the latter of a clear path to improvement. In the limit of complete mixing, wavefunction-based models lead to the exact result, although in practice this limit cannot be reached.

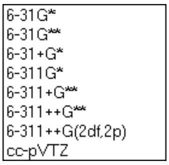
Density functional and wavefunction-based correlated models make use of the same basis sets as Hartree-Fock models, except that 3-21G (and smaller) basis sets do not yeild satisfactory results. Among the most popular models are the B3LYP/6-31G* density functional model and the MP2/6-31G* (second-order) Møller-Plesset model. The primary use of these models (and other correlated models) is to obtain thermochemistry, including for reactions in which bonds are made or broken and including activation energies.

Except for semi-empirical methods, either **restricted** or **unrestricted scf methods** may be used. The former restricts paired electrons to the same spacial orbital, whereas the latter allows spin up and down electrons to occupy different orbitals. The default (singlets are described using restricted methods and non-singlets are described using unrestricted methods) may be overridden using the **Scf** keyword (see **Appendix C**).

Except for molecular mechanics and semi-empirical methods and for thermochemical recipes, a basis set needs to be specified.[*] For Hartree-Fock methods:



For all other methods:



3-21G refers to use of the 3-21G representation for first row, main-group elements as well as for transition metals, but invoke the 3-21G$^{(*)}$ basis set that incorporates a set of d-type functions for second-row and heavier main-group elements. 6-311++G (2df,2p) invokes the 6-311++G (3d2f,2p) basis set for second-row elements.

The combination of a method, for example, B3LYP, and a basis set, for example, 6-31G*, constitutes a **theoretical model** or more simply a **model**. The nomenclature is to separate method and basis set by a "/", for example, B3LYP/6-31G*. By convention, specification of Hartree-Fock (HF) as a method is optional and specification of basis set alone refers to Hartree-Fock models, for example, both HF/6-31G* and 6-31G* refer to combination of the Hartree-Fock method and the 6-31G* basis set. Methods without basis sets, for example, MMFF (molecular mechanics) and PM3 (semi-empirical) are themselves models.

An additional control, **Density**, appears only where an energy using either MP2 or CIS models has been requested. If *checked*,

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[*] A number of other basis sets are available, and may be entered directly into the **Options** box: 6-31G or 6-311G followed by: (idjf) or (idjf, kpld) where i, j, k, l = 0, 1, 2, 3. If 0 eliminate p, d, f; if 1 eliminate the number; 6-31G or 6-311G with "+" or "++" inserted before G; cc-pVDZ and cc-pVQZ.

Density signifies that the post-Hartree-Fock density matrix is to be evaluated (in addition to the energy). This leads to a significant increase in computation time, but is required if properties (dipole moments, charges, etc.) or graphical surfaces are to be based on the post-Hartree-Fock wavefunction (rather than on the Hartree-Fock wavefunction). Post-Hartree-Fock density matrix evaluation is required (and is performed automatically) for equilibrium and transition-state geometry determination.

If *checked*, **Pseudopotential** signifies that a pseudopotential is to replace the all-electron basis set for heavy elements. In effect, this limits description of heavy elements to valence electrons only. Pertains to Hartree-Fock, density functional, MP2 and advanced correlated calculations only, and only for third-row and heavier elements. Does not pertain to STO-3G and 3-21G basis sets. For availability and description of pseudopotentials in ***Spartan***, consult the help facility (**Chapter 19**).

If *checked*, **Dual Basis** signifies that a Hartree-Fock, density functional, MP2 or RI-MP2 energy calculation with the 6-311+G**, 6-311++G**, 6-311++G (2df, 2p), or cc-pVTZ basis set will be approximated by a calculation in which scf convergence is first achieved using the smaller 6-311G* basis set and then corrected pertubatively for the effects of basis set extension. Use of dual basis has only a small effect on calcuated relative energies, but can reduce the cost of large basis set energy calculations by two to ten times (depending on the choice of the large basis set).

Other combinations of small and large basis sets may be specified under **Options** (see discussion following).

An additional control, **IRC** (**I**ntrinsic **R**eaction **C**oordinate), appears when a transition-state geometry has been requested. If *checked*, **IRC** signifies that the resulting transition state will be used to generate a pathway (an intrinsic reaction coordinate) leading first to reactant and then to product. (It is advisable, although not necessary, to compute the IR spectrum prior to calculation of an intrinsic reaction coordinate.) The full sequence of steps: reactant → transition state → product, will be placed in a file **xyz.label** where **xyz** is the label assigned to a molecule. The default number of steps in the sequence (40) may be changed using the keyword **IRCSteps** (see **Appendix C**). **IRC** is not available for semi-empirical models.

While geometry is well described with simple quantum chemical models, energy (or more precisely relative energy) has proven to be more difficult to calculate accurately. Hartree-Fock models properly describe the energies of *isodesmic* reactions, where formal bond count is maintained but are less successful for reactions in which reactants and products have markedly different bonding. Indeed, high level correlated calculations with large underlying basis sets are needed to properly account for the energetics of bond breaking or to relate the energies of reactants to that of a transition state.

A number of thermochemical recipes or combinations of different quantum chemical methods have been formulated for the purpose of providing accurate thermochemical data. The goal has been to be able to reproduce experimental heats of formation to within 4-8 kJ/mol. (Except for very simple molecules, experimental thermochemical data are seldom determined more accurately than this.) G3(MP2) is perhaps the most successful of the recipes that have been formulated. In terms of mean absolute error, it reproduces experimental heats of formation for a wide variety of small molecules to within 6 kJ/mol, with only a small number of systems showing errors twice this amount. The problem with G3(MP2) and other schemes of this type is its large computational cost, and closely associated, with severe limits on the size of systems that can be dealt with. In practice, G3(MP2) may easily be applied to molecules comprising ten heavy (non-hydrogen) atoms and only with great difficulty to molecules comprising fifteen or more heavy atoms.

Three different energies are required in the G3(MP2) recipe:

E_A MP2/6-31G* using the MP2/6-31G* equilibrium geometry
E_B MP2/6-311++G(2df, 2p) using the MP2/6-31G* equilibrium geometry
E_C QCISD(T)/6-31G* using the MP2/6-31G* equilibrium geometry

These are added together in order to take into account both the effects of increased basis set size and of electron correlation beyond the MP2 level.

$$E_D = E_A + (E_B - E_A) + (E_C - E_A)$$

Note, that the two effects are treated independently in order to avoid having to perform a QCISD(T) calculation using a large basis set.

Two corrections are needed to bring this energy in line with what is actually measured experimentally: a correction for zero-point energy; $E_{zero\text{-}point}$, and a correction to the enthalpy (energy) to account for finite temperature (298K), $\Delta H(T)$.

$$E_{zero\text{-}point} = \frac{1}{2} h \sum_{i}^{vibrations} \nu_i$$

$$H(T) = H_{trans}(T) + H_{rot}(T) + H_{vib}(T) + RT$$

$$H_{trans}(T) = \frac{3}{2} RT$$

$$H_{rot}(T) = \frac{3}{2} RT \text{ (RT for a linear molecule)}$$

$$H_{vib}(T)^{*} = H_{vib}(T) - H_{vib}(T) - H_{vib}(0)$$

$$= Nh \sum_{i}^{vibrations} \frac{\nu_i}{(e^{h\nu_i/kT} - 1)}$$

h is Planck's constant, k is the Boltzmann constant, R is the gas constant and N is Avogadro's number. Both zero-point and temperature corrections require the full set of vibrational frequencies. In the G3(MP2) recipe, these are obtained from Hartree-Fock/6-31G* calculations and require the corresponding equilibrium geometry.

To summarize, the G3(MP2) recipe requires two equilibrium geometry calculations (at HF/6-31G* and MP2/6-31G*), a HF/6-31G* frequency calculation, a MP2/6-311++G (2df, 2p) energy calculation and a QCISD(T)/6-31G* energy calculation. The QCISD(T) calculation dominates with increasing molecular size and also requires the most temporary memory and disk storage. The next most costly term is likely to be the MP2/6-31G* geometry optimization, although both the large basis set MP2 energy and the HF/6-31G* frequency calculation may also be significant.

A simplified recipe based on G3(MP2) and intended to closely reproduce G3(MP2) heats of formation has been developed. It eliminates the QCISD(T)/6-31G* energy calculation (E_C), the zero-point energy calculation ($E_{zero\text{-}point}$) and the temperature correction to the enthalpy ($\Delta H(T)$), and replaces the large basis set MP2 energy calculation with a dual basis set RI-MP2 calculation, where G3MP2large is the large basis set (the same basis set that is used in the G3(MP2) recipe) and 6-311G* is the small basis set. To compensate, an empirical correction based on the RI-MP2 energy, the number of each kind of bond and Mulliken bond orders is introduced. This follows from a linear regression analysis involving G3(MP2) heats of formation for ≈1,050 diverse molecules. T1 uses HF/6-31G* equilibrium geometries, instead of MP2/6-31G* geometries in G3(MP2).

---

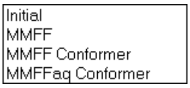
* Note, that the expression for $\Delta H_{vib}(T)$ goes to RT instead of 1/2 RT as ν_i goes to zero. This requires that contributions that would exceed 1/2 RT be set to 1/2 RT.

Start from

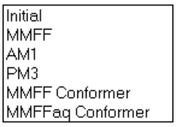
Energy and equilibrium geometry calculations (only) from one model may be preceded by equilibrium geometry calculations at another (simpler) model. Choices depend on the method selected:

Molecular Mechanics — not applicable

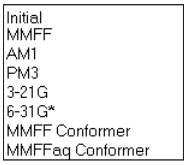
Semi-Empirical


Initial
MMFF
MMFF Conformer
MMFFaq Conformer

Hartree-Fock


Initial
MMFF
AM1
PM3
MMFF Conformer
MMFFaq Conformer

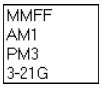
Density Functional, Møller-Plesset, Advanced Correlated, Thermochemical Recipes


Initial
MMFF
AM1
PM3
3-21G
6-31G*
MMFF Conformer
MMFFaq Conformer

Selection of MMFF conformer or MMFFaq conformer signifies that geometry optimization will follow a search for the lowest-energy conformer. These lead to an additional menu specifying the level of geometry optimization.

Molecular Mechanics, Semi-Empirical — not applicable

Hartree-Fock


MMFF
AM1
PM3
3-21G

Density Functional, Møller-Plesset,
Advanced Correlated, Thermochemical Recipes

MMFF
AM1
PM3
3-21G
6-31G*

Start from is missing for transition-state geometry, equilibrium conformer, conformer distribution and energy profile calculations. For equilibrium conformer it has been replaced by **Maximum Conformers Examined** and for conformer distribution by **Maximum Conformers Examined** and **Maximum Conformers Kept**.

Subject to

Spartan allows calculations to be carried out in the presence of geometrical constraints or with atoms which have been frozen in place. In addition, ***Spartan*** attempts to make full use of symmetry.

If *checked*, **Constraints** signifies use of any previously defined constraints on distances, angles and dihedral angles into equilibrium and transition-state geometry optimization, conformation searching and generation of energy profiles. Does not apply to energy calculation, conformer library generation or similarity analysis. See **Chapter 13** for information about constraining geometrical parameters.

NOE data are not treated as constraints, but rather as post-calculation filters in establishing conformer distributions.

If *checked*, **Frozen Atoms** signifies that the coordinates of any atoms that have previously been frozen will not be moved during equilibrium and transition-state geometry optimization, conformation searching and generation of energy profiles. Does not apply to energy calculation, conformer library generation or similarity analysis. See **Chapter 13** for information about freezing atoms. See also discussion in **Chapter 17** regarding the freezing of heavy atoms in structures resulting from a search of the Cambridge Structural Database.

If *checked*, **Symmetry** signifies that molecular symmetry is to be employed wherever possible to simplify the calculation. By default **Symmetry** is checked.

Compute

Entries under this section request calculation of a number of important spectral quantities. Other quantities such as the dipole moment, the estimated aqueous solvation energy* and LogP** that are calculated automatically, whereas calculation of still others may be requested from the **Options** box (see discussion following).

UV/vis

If *checked*, specifies that a single-point excited-state calculation will be performed (following a ground-state calculation) and that state-to-state energy differences will be reported. A UV/visible spectrum may be displayed using **Spectra** under the **Display** menu (see **Chapter 16**).

UV/visible spectra calculations are restricted to Hartree-Fock models (where the CIS model is used for the excited state) and density functional models (where the corresponding time-dependent density functional model is used for the excited state).

IR

If *checked*, calculates vibrational frequencies and corresponding normal modes of vibration. These are then available in the output (**Output** under the **Display** menu, see **Chapter 16**) along with selected thermodynamic properties (entropies*** and Gibbs energies). Vibrational modes may be animated and an IR spectrum displayed from the **IR** dialog accessible from **Spectra** under the **Display** menu (see **Chapter 16**).

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* The aqueous solvation energy is estimated using the SM5.4 procedure of Cramer, Truhlar and co-workers (C.C. Chambers, G.D. Hawkins, C.J. Cramer and D.G. Truhlar, *J. Phys. Chem.,* **100**, 16385 (1996)). This is added to the gas phase total energy and written to the output. This sum is also available in the spreadsheet (see **Chapter 16**).

** LogP is estimated both according to the method of Ghose, Pritchett and Crippen (*J. Computational Chem*., **9**, 80 (1988)), and of Villar (*J. Computational Chem*., **6**, 681 (1991); *Int. J. Quantum Chem*., **44**, 203 (1992)), and written to the output. Both Ghose-Crippen and Villar LogP values may also be brought into the spreadsheet (see **Chapter 16**).

*** Note that the linear harmonic oscillator approximation incorrectly leads to a vibrational contribution to the entropy that goes to ∞ as frequency goes to 0. Vibrational entropy contributions from frequencies below 300 cm^{-1} should be treated with caution.

Second derivatives required for frequency calculation are evaluated analytically for molecular mechanics, semi-empirical, Hartree-Fock and density functional models. Frequency evaluation with MP2 models involves numerical differentiation of analytical gradients, and is more costly.

NMR

If *checked*, specifies that NMR chemical shifts will be calculated. These are then available in the output (**Output** under the **Display** menu, see **Chapter 16**) as well as from the **Atom Properties** dialog (**Display** menu) and as atom labels (**Configure...** under the **Model** menu; **Chapter 12**). ^{13}C (proton decoupled) and ^{1}H (shifts only) spectra from Hartree-Fock or density functional calculations may be displayed from the **NMR** dialog accessible from **Spectra** under the **Display** menu (see **Chapter 16**)[*]. In both cases, line intensities are assumed to be proportional to the number of equivalent carbons or hydrogens. Coupling constants associated with ^{1}H spectra are not presently available.

Total Charge

Total charge. The default setting **Neutral** may be changed either by *clicking* on ⬍ to the right of the box, and selecting **Anion**, **Dianion**, **-3**, etc. from the menu which appears, or by replacing any menu entry by a numerical value. **Total Charge** is ignored for molecular mechanics calculations.

Multiplicity

Spin multiplicity. The default setting **Singlet** may be changed either by *clicking* on ⬍ to the right of the box, and selecting instead **Doublet** or **Triplet** from the menu which appears, or by replacing any menu entry by a numerical value. Multiplicity is 1 for singlets, 2 for doublets, 3 for triplets, 4 for quartets, etc. **Multiplicity** is ignored for molecular mechanics calculations.

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[*] Chemical shifts for other nuclei are available in the **Output** dialog (**Output** under the **Display** menu) and may also be attached as labels (**Configure...** under the **Model** menu).

Print

If *checked*, writes the quantity to the output window. Text output may be seen by selecting **Output** from the **Display** menu (**Chapter 16**) and printed by first selecting the output dialog and then selecting **Print Output** from the **File** menu (**Chapter 10**). Additional printing may be requested from the **Options** box (see discussion following).

Orbitals & Energies

If *checked*, writes the orbitals and energies to the output. Orbital energies are also available in the spreadsheet (**Chapter 16**).

Thermodynamics

If *checked*, writes thermodynamic quantities to the output. Requires that vibrational frequencies (**IR** under **Compute**) have been calculated. Selected thermodynamic quantities are also available in the spreadsheet (**Chapter 16**).

Vibrational Modes

If *checked*, writes vibrational frequencies and normal modes to the output. Requires that vibrational frequencies (**IR** under **Compute**) have been calculated.

Atomic Charges

If *checked*, writes Mulliken, natural and electrostatic-fit charges to the output. Atomic charges are also available from the **Atom Properties** dialog (**Display** menu; **Chapter 16**), in the spreadsheet (**Chapter 16**) and as atom labels (**Configure...** under the **Model** menu; **Chapter 12**). Atomic charges are not available for calculations using advanced correlated models or for thermochemical recipes.

Options

Program options may be specified using keywords entered into the **Options** box. Keywords may be either single words or expressions. Keyword=N indicates an integer argument, and keyword=F indicates a real argument. **Appendix C** contains a listing of commonly-used keywords.

Converge

If *checked*, invokes procedures to assist in convergence of quantum chemical calculations. Use of **Converge** may lead to an increase in computation time.

Similarity

Spartan provides a procedure to assess and quantify the similarity of one or more molecules in a document to one or more molecules in one or more different documents. Similarity may either be based on molecular structure (geometry) or on chemical function descriptors (CFD's). ***Spartan*** also assesses the similarity of one or more pharmacophores in a document to one or more molecules in one or more different documents.

Three different permutations of similarity analysis are available. Here, **template** refers to the selected document in the graphical user interface and **library** refers to one or more different documents specified in the **Calculations** dialog.

template	**library**
pharmacophores	molecular structures for which CFD's are assigned on-the-fly
molecular structures	molecular structures
CFD's from molecular structures	molecular structures for which CFD's are assigned on-the-fly

Two types of libraries are supported for molecular structures (and CFD's generated on-the-fly from molecular structures). In the first, each entry represents a single molecule. In the second, each entry represents a selection of different conformers of a single molecule and spanning all possible shapes that the molecule may take on. The latter are generated using **Conformer Library** under the **Calculate** menu (see discussion earlier in this chapter), and ***may only be used as library entries in similarity analysis and not as templates***.

Of the three cases for similarity analysis, only the second makes direct use of molecular structures (selected atomic centers for the molecules in the template) as a similarity measure. The other two libraries make use of CFD's generated and (optionally) edited for the template and generated on-the-fly in the library. Selection of structure or CFD as the basis of similarity measure must be explicitely stated (see discussion following).

Seven different chemical function descriptors (CFD's) are recognized by the similarity analysis procedure, the first six of which are attributes of a molecule while the seventh derives from knowledge of a molecule bound to a protein or nucleic acid.

hydrophobe (sterically crowded region)
aromatic hydrophobe (aromatic ring)
hydrogen-bond donor
hydrogen-bond acceptor
positive ionizable site
negative ionizable site
excluded volume

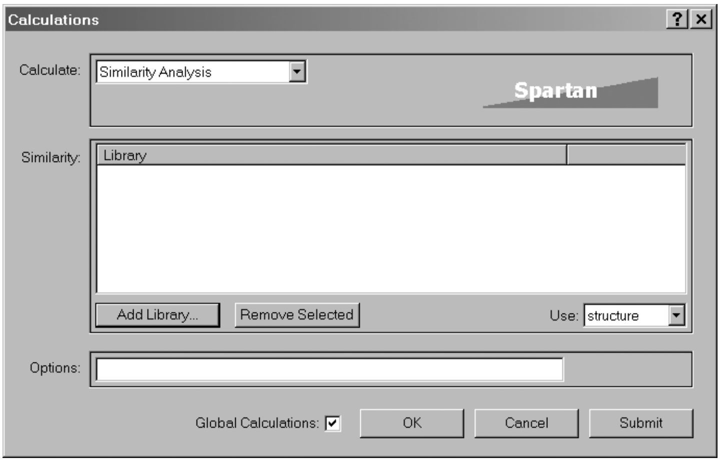
Discussion of CFD types has already been provided (see **CFD's** under the **Model** menu; **Chapter 12**).

The individual CFD's for molecules in the template (only) may either be used or ignored in the similarity procedure. This is specified from **Set Similarity Centers** under the **Geometry** menu (**Chapter 13**). The **CFD Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**) allows for changing or extending the definition of a CFD For example, the nitrogen in a dimethylamino group might initially be assigned as a hydrogen bond acceptor CFD, but could be changed to a positive ionizable site (as such a center could become positively-charged at biological pH) or could be extended to cover both possibilities.

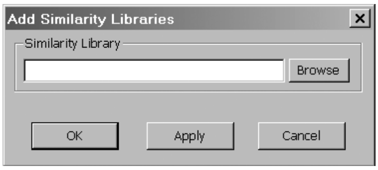
Spartan assumes that any chiral molecules in a library are unresolved (they comprise an equal mixture of enantiomers). By default, similarity comparisons are carried out on both the library molecules as they are stored and (if the molecules are chiral) for their mirror images. The default procedure may be overridden (providing comparisons only to the stored molecules) by way of the **Single Enantiomer** keyword entered in **Options** in the **Calculations** dialog. See discussion later in this chapter and also **Appendix C**.

Note that only a single enantiomer of a chiral template molecule is considered. If comparisons involving both enantiomers are desired, the second enantiomer must be added to the query.

Selection of **Similarity** from the **Calculate** menu with either a molecule or pharmacophore (list of molecules/pharmacophores) leads to a dialog for setting up a similarity analysis.


Calculations
?
Calculate:
Similarity Analysis
Spartan
Similarity:
Library
Add Library...
Remove Selected
Use:
structure
Options:
Global Calculations: ☑
OK
Cancel
Submit

One or more libraries need to be identified. This is accomplished by *clicking* on the **Add Library...** button, and gives rise to the **Add Similarity Libraries** dialog.


Add Similarity Libraries
Similarity Library
Browse
OK
Apply
Cancel

A library may then be requested by *clicking* on the **Browse** button to pull up a file browser. Once selected, *clicking* on **Apply** (at the bottom of the **Add Similarity Libraries** dialog) adds the library to the list of templates and leaves the dialog open. *Clicking* on **OK** (instead of **Apply**) also adds the library to the list but closes the **Add Similarity Libraries** dialog. A library may be deleted from the list by *clicking* on its name in the list and *clicking* on the **Remove Selected** button at the bottom of the dialog. **Shift** and **Ctrl** keys function in the usual manner in both library addition and removal.

Prior to starting a similarity analysis, you need to select either **structure** or **CFD** from the **Use** menu near the bottom of the **Calculations** dialog.

Similarity analysis is most valuable where the template molecule is conformationally flexible, and it is not apparent which (if any) of the different shapes it adopts might match a particular target in a library. It becomes indispensable where the target is also flexible and its conformation is not established. Here, the process must be repeated for every template conformer - target conformer pair, that is, thousands or tens of thousands of times.

This process can be shortened if the purpose is simply to identify which target molecules a particular template molecule might match, irrespective of conformer. In this case, the first good match concludes the analysis, and the user is left with the knowledge that template and target can be made to match (together with an example of a match).

The similarity algorithm incorporated in ***Spartan*** attempts to examine template-target pairs that are most likely to lead to matches before examining pairs that are less likely. It also allows early termination upon finding a single good match, or a user-specified number of good matches*. Taken together, these can lead to one or two orders of magnitude speedup in the analysis.

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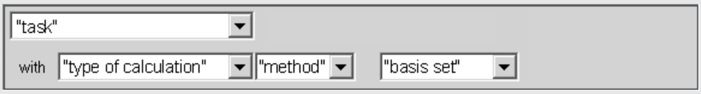
* Criteria for early termination are specified using program options. See **Similarity Analysis Options** in **Appendix C**.

Global Calculations

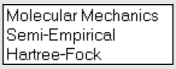
If *checked*, signifies that settings in the **Calculations** dialog are to be applied to all molecules in the document.

The **Calculations** dialog may be exited by clicking on **Submit**, **Cancel** or **OK** at the bottom right of the dialog, or on at the top right. (**Submit** and **OK** are not available if the job is already executing.) Clicking on **OK** or on **Submit** overwrites any previous information. Additionally, **Submit** enters the job in the execution queue (see discussion later this chapter). Clicking on **Cancel** or on ☒ exits the **Calculations** dialog without saving any changes.

The **Calculations** dialog in the Essential Edition of ***Spartan'06*** (**NAL**) differs primarily in the **Calculate** section.



The **Task** menu is the same except that **Conformer Library** and **Similarity** are missing. The **Type of Calculation** menu is restricted to molecular mechanics, semi-empirical and Hartree-Fock models under the **Method** menu.



The **Basis Set** menu (Hartree-Fock models only) is identical. Note that pseudopotentials are not available.

Additionally, intrinsic reaction coordinate (**IRC**) calculations and UV/visible and NMR spectra (**UV/vis** and **NMR** under **Compute**) are not available in the essential edition. IR spectra (**IR** under **Compute**) are available, but the required second-derivative calculations are performed numerically rather than analytically and are significantly slower than in the full edition.

Surfaces

Spartan allows graphical display of the HOMO and LUMO among other molecular orbitals, the electron density, the spin density for molecules with unpaired electrons, the electrostatic potential and the local ionization potential.

The ***electron density*** is the number of electrons found at a point in space. It is the quantity measured in an X-ray diffraction experiment that is then used to locate atomic positions, that is, most electrons are closely associated with atoms. While the electron density is non-zero everywhere, it is possible to define surfaces of constant density. The most important of these contains most of a molecule's electrons and that roughly corresponds to a space-filling model, that is, a van der Waals surface. This is generally referred to simply as an ***electron density***, and is interesting because it reveals overall molecular size and shape and demarks the steric barrier seen by encroaching molecules. Another important surface, referred to as a ***bond density***, contains fewer electrons in total and demarks atomic connectivity.

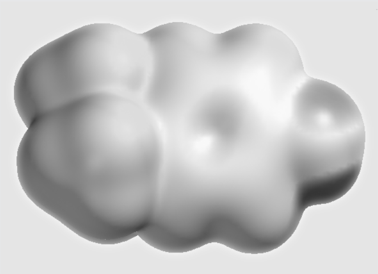
The ***spin density*** is the difference in the number of electrons of α and β spin at a point in space. It indicates the location of the unpaired electron in a radical or unpaired electrons in a triplet or higher multiplicity state.

The ***electrostatic potential*** is the energy of interaction of a positive charge with a molecule. It represents a balance between repulsive interactions involving the positively-charged nuclei and attractive interactions involving the negatively-charged electrons. Regions where the balance tips toward attraction are said to be electron rich (basic) and subject to attack by electrophiles, while regions where the balance tips toward repulsion are said to be electron poor (acidic) and subject to attack by nucleophiles. Electron-rich regions such as lone pairs are typically located outside the van der Waals surface. As such, they may be easily identified by constructing a surface of negative (attractive) electrostatic potential. While interesting electron-poor areas such as acidic hydrogens also lie outside the van der Waals surface, the electrostatic potential is also positive (repulsive) throughout the region inside this surface.

The ***local ionization potential*** indicates the ease or difficulty of electron removal (ionization). Like the negative regions of the electrostatic potential, regions of low local ionization potential are likely to be subject to attack by electrophiles.

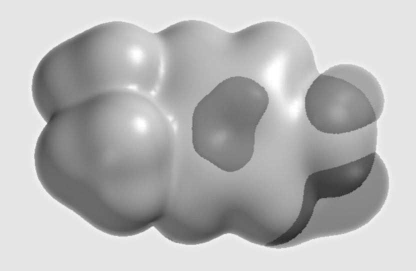
Additionally, any one of the quantities listed above (except the electron density) may be mapped onto any surface (except a molecular orbital surface). In practice, the only maps to have received widespread attention are those based on the electron density surface (depicting overall molecular size and shape). Most important are the electrostatic potential map, the local ionization potential map and the LUMO map.

The ***electrostatic potential map*** paints the value of the electrostatic potential onto an electron density surface. By convention, colors toward red depict negative potential, while colors toward blue depict positive potential, and colors in between (orange, yellow, green) depict intermediate values of the potential. Thus, an electrostatic potential map for *p*-*tert*-butylphenol will show oxygen to be red, its attached (acidic) hydrogen to be blue, the π faces of benzene to be orange or yellow and the *tert*-butyl group to be green.



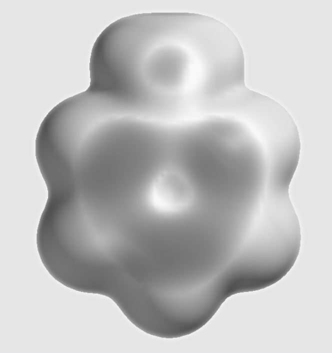
The main advantages of this presentation are its clarity and its compactness. The main disadvantage is that it provides information only about the contact surface and does not reveal how far electron-rich and electron-poor areas extend beyond the surface.

An alternative to an electrostatic potential map, referred to as an ***exposed electrostatic potential surface***, is a composite of three different surfaces: an electron density surface depicting overall molecular size and shape, a negative electrostatic potential surface identifying electron-rich regions and a positive electrostatic potential surface identifying electron-poor regions. These surfaces need to be generated and then displayed simultaneously. The electron density may either be displayed as an opaque solid or as a transparent solid (in order that the molecular skeleton may be seen inside). The two potential surfaces are best represented as transparent solids, the negative surface colored red and the positive surface colored blue. The exposed electrostatic potential surface for *p*-*tert*-butyl phenol is shown on the next page.

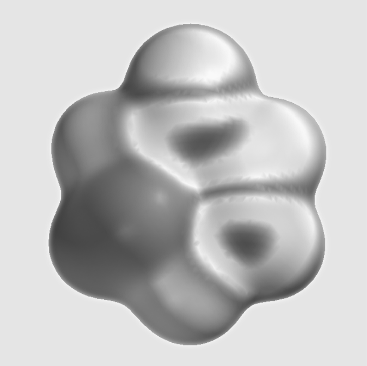


Note that the exposed electrostatic potential surface provides the same information as the electrostatic potential map. Red areas in the map correspond to regions when the negative electrostatic potential surface is likely to protrude from the electron density while blue areas correspond to regions where the positive electrostatic potential surface is likely to stick out. There is broad similarity of this graphic to CFD representations discussed previously (see CFD's under the **Model** menu in **Chapter 12**). Hydrogen-bond acceptors and/or positive ionizable sites are associated with protruding negative potential surfaces, whereas hydrogen-bond donors and/or negative ionizable sites are associated with protruding positive potential surfaces.

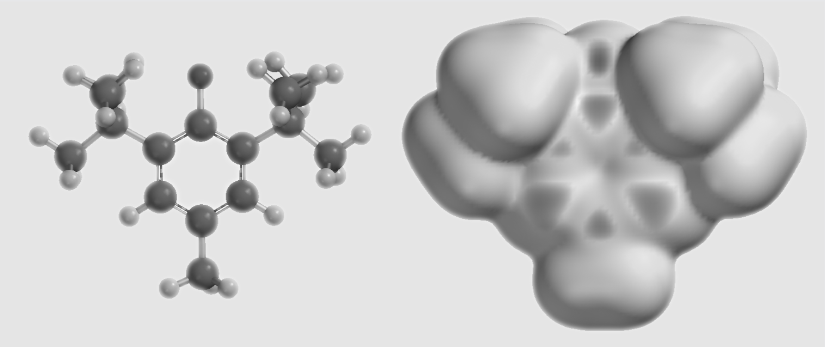
The ***local ionization potential map*** paints the value of the local ionization potential onto an electron density surface. By convention, colors toward red indicate low ionization potential, while colors toward blue indicate high ionization potential. Thus, the local ionization potential map for aniline shows that the *ortho* and *para* ring positions have a lower ionization potential than the *meta* positions, consistent with the known directing ability of an amino group in electrophilic aromatic substitution.



The ***LUMO map*** paints the absolute value of the lowest-unoccupied molecular orbital (the LUMO) onto an electron density surface. By convention, colors near blue indicate high concentration of the LUMO, while colors near red indicate low concentration. Given that the LUMO designates space available for a pair of electrons, a LUMO map indicates where nucleophilic attack would likely occur. For example, a LUMO map for cyclohexenone shows concentration in two regions, one over the carbonyl carbon and the other over the β carbon, consistent with both carbonyl addition and Michael (conjugate) addition.



The ***spin density map*** paints the value of the spin density onto an electron density surface. By convention, colors near blue indicate high concentration of spin density, while colors near red indicate low concentration. For example, a spin density map for the radical resulting from loss of hydrogen from 3,5-di-*tert*-butylhydroxytoluene (BHT) shows that the spin has delocalized from oxygen onto the *ortho* and *para* ring positions.



This radical would be expected to be particularly stable, which explains why BHT acts as an antioxidant (scavenging less favorable localized radicals).

All of these maps use an electron density surface and to delineate overall molecular size and shape. Not all regions on this surface are accessible and therefore available for interaction with their environment (or with an incoming reagent). ***Spartan*** allows these regions to be identified.*

---

* A region on a density surface is designated as inaccessible if a sphere of radius 1.0 Å centered on a line normal to the surface and touching a point in the middle of the region, impinges on any other regions of the density surface. The default radius may be changed in the **Settings Preferences** dialog (**Preferences** under the **Options** menu; **Chapter 8**).

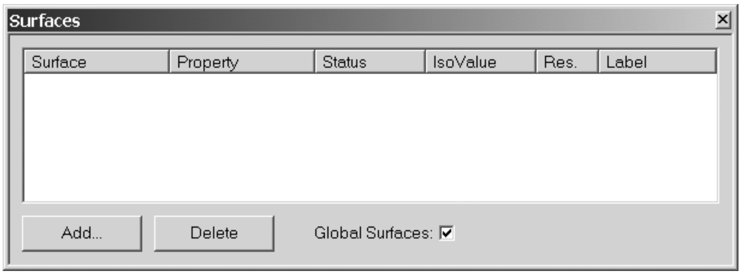
Surfaces (including those underlying maps) connect point of equal value (they are isosurfaces), and may be displayed as an arrangement of dots, a mesh, or an opaque or translucent solid. Examples of graphical output in orthogonal projection are provided in **Figure 15-1**. Surfaces (and maps) may also be rendered in perspective (see **Chapter 12**) and in stereo (see **Chapter 2**).

Calculated quantities may also be displayed as two dimensional contour plots (slices). Unlike surfaces and maps, these can be manipulated (translated and rotated) independently of the molecular skeleton. An example of a slice display is provided in **Figure 15-1**.

Several different surfaces, maps and slices may be simultaneously displayed. In addition, any of the usual structure models may be displayed along with the graphic. The total display can become very complex, and selective use of meshes and/or translucent solids (as opposed to opaque solids) may facilitate visualization.

Discussion of the utility of graphical models for describing molecular structure and chemical reactivity is provided in ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***.

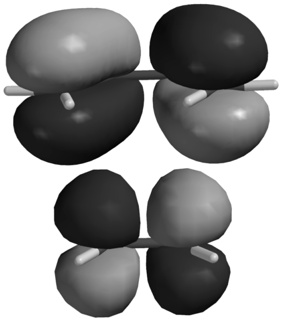
Selection of **Surfaces** from the **Setup** menu results in display of the **Surfaces** dialog.



The box at the top of the dialog identifies graphical surfaces for later calculation and display. The **Add...** button at the bottom of the dialog is used to specify new graphical surfaces. *Clicking* on it leads to the **Add Surface** dialog that contains three menus and a check box:

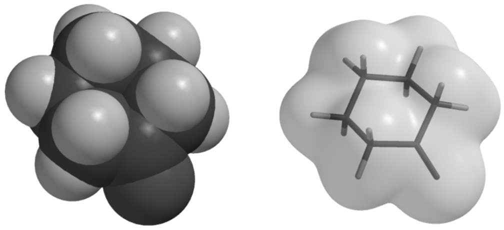
Figure 15-1: Examples of Graphical Displays Available in *Spartan*

Frontier orbitals for a symmetry-allowed Diels-Alder reaction,



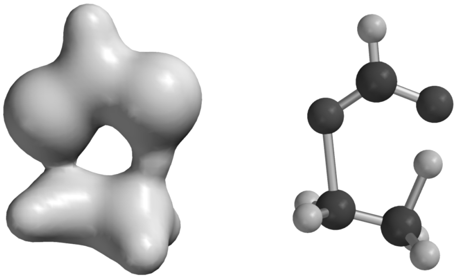
showing interaction of the HOMO of 1,3-butadiene and the LUMO of ethylene.

Space-filling model and electron density surface of cyclohexanone,



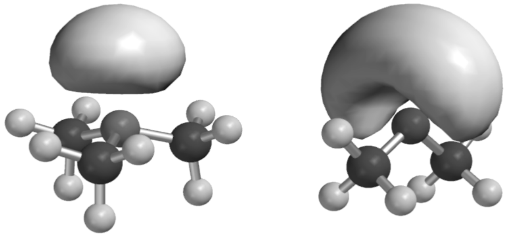
showing overall molecular size and shape.

Electron density surface (0.08 electrons/au^3) of transition structure for pyrolysis of ethyl formate,



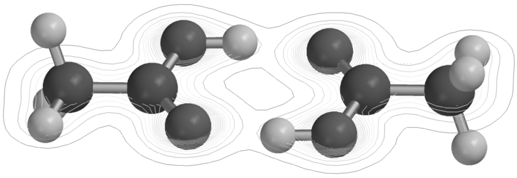
showing bonding in the transition state.

Electrostatic potential surfaces (-40 kJ/mol) of trimethylamine (left) and dimethyl ether (right),



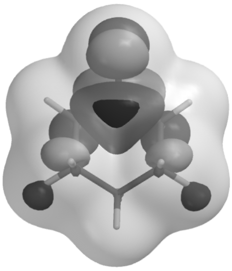
showing the lone pairs on nitrogen and oxygen, respectively.

Electron density slice for acetic acid dimer,

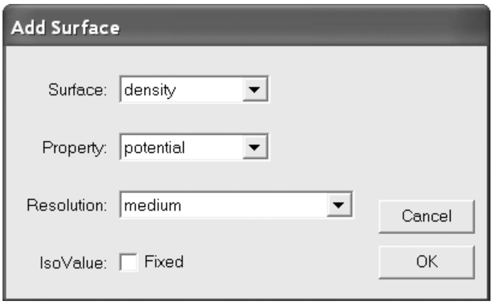


showing hydrogen bonding.

Simultaneous display of the LUMO and the electron density surfaces of cyclohexanone,



showing accessibility for nucleophilic attack.


Add Surface

Surface: density

Property: potential

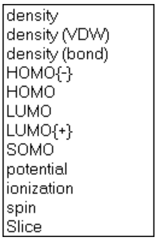
Resolution: medium

IsoValue: ☐ Fixed

Cancel
OK

Surface

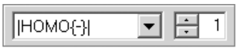
Available surface types appear under the **Surface** menu.


density
density (VDW)
density (bond)
HOMO{-}
HOMO
LUMO
LUMO{+}
SOMO
potential
ionization
spin
Slice

Density portrays overall molecular size, ***density (bond)*** locates bonds, ***density (VDW)*** approximates ***density*** with van der Waals spheres, ***HOMO{-}, HOMO, LUMO, LUMO{+}, SOMO***[*] are molecular orbitals, ***potential*** is the electrostatic potential, ***ionization*** is the local ionization potential and ***spin*** is the spin density[*].

> The local ionization potential does not go to zero with increasing distance. This makes its use as a surface problematic.

Selection of **HOMO{-}** and **LUMO{+}** results in display of a box to decrement the HOMO and increment the LUMO. This allows any molecular orbital to be specified..



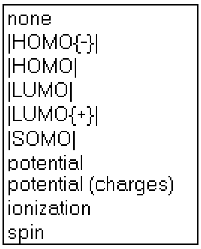
Slice designates that a plane will cut through the graphic defined by **Property** (see discussion following).

---

[*] These entries are available only for molecules with unpaired electrons.

Property

Properties for maps appear in the **Property** menu.

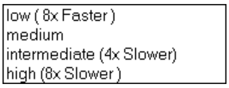


Available properties are the molecular orbitals (**HOMO{-}**, **HOMO**, **LUMO**, **LUMO{+}**, **SOMO***), the electrostatic potential (**potential**), an approximate electrostatic potential based on (electrostatic) charges (**potential (charges)**), the local ionization potential (**ionization**) and the spin density (**spin**)*. **none** indicates that no property is to be mapped onto the surface). As with **Surface** above, selection of **HOMO{-}** and **LUMO{+}** leads to a decrement (increment) box.

A **Spin** button will be displayed if **Multiplicity** (in the **Calculations** dialog) is set to a value other than **Singlet**, or if **Scf=unrestricted** has been specified in the **Options** box (**Calculations** dialog) and if **HOMO{-}**, **HOMO**, **LUMO** or **LUMO{+}** has been selected for **Surface** or for **Property**. *Clicking* on **Spin** toggles it between **Alpha** and **Beta**. **Alpha** designates that the molecular orbital either to be displayed as a surface or mapped as a property corresponds to α spin; **Beta** designates that the molecular orbital corresponds to β spin.

Resolution

Selection of surface resolution is from the **Resolution** menu.



Medium resolution generally is intended for routine work, low resolution is used to get rough images very quickly, while intermediate and high resolution may be employed to obtain publication quality graphics. Both calculation time and disk storage increase significantly with increasing resolution.

---

* These entries are available only for molecules with unpaired electrons.

IsoValue

This allows a fixed isosurface to be generated in place of a three-dimensional grid of points (from which different isosurfaces, and/or slices can be constructed). Fixed isosurfaces are particularly attractive for property maps (that are generally based on a density surface representing molecular size and shape) as they require less computer time and disk storage.

Checking the box to the left of **Fixed** leads to display of the isovalue (0.002 electrons/au^3 in the case of density). This value may be changed. **Fixed** may not be specified in conjunction with **Slice** as a **Surface**.

Following **Surface**, **Property**, **Resolution** and (optionally) spin selection, *clicking* on **OK** adds the requested graphic to the list and removes the (**Add Surface**) dialog. *Clicking* on **Apply** adds the requested graphic to the list but leaves the dialog on screen. *Clicking* on **Cancel** does not add a graphic to the list but removes the (**Add Surface**) dialog.

The process (*clicking* on **Add...**, surface and property selection, *clicking* on **OK** or **Apply**) may be repeated as required.

An existing graphic may be deleted from the list by first highlighting (*clicking* on) it and then *clicking* on **Delete**.

Global Surfaces, if *checked*, signifies that the requested surfaces will be calculated for all members of the list.

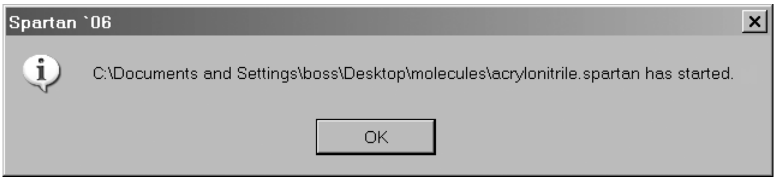
Only one copy of the **Surfaces** dialog may appear on screen, and any actions relate to the currently selected molecule. The dialog may be removed by *clicking* on ☒.

Submit

Following setup of a molecular mechanics or quantum chemical calculation, or a similarity analysis, as well as any requests for properties, spectra and/or graphical displays, the required calculations will begin when **Submit** is selected. If the job has not previously been named, selection of **Submit** triggers a request for a name.

> In addition to the local (Windows, Macintosh or Linux) machine, ***Spartan's*** computational codes may run on a remote (licensed) Linux server. If remote submission has been set up (see **Hosts** from the **Preferences** dialog under the **Options** menu; **Chapter 18**), selection of **Submit** will also request a name for the destination machine.

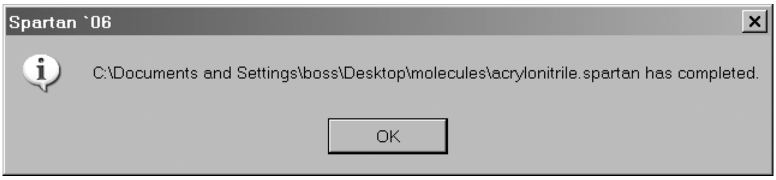
After a name has been provided (or if a name already exists) a dialog appears indicating that the job has actually been submitted.*



C:\Documents and Settings\boss\Desktop\molecules\acrylonitrile.spartan has started.

Click on **OK** to remove it. After a job has started, and until it has completed, all associated files will be designated read only.

Another dialog appears following completion of a calculation.



C:\Documents and Settings\boss\Desktop\molecules\acrylonitrile.spartan has completed.

Click on **OK** to remove it.

Upon completion, conformer distribution and energy profile jobs, as well as jobs that request generation of an intrinsic reaction coordinate, lead to an additional document being created for each molecule in the original document. These new documents are named **xyz.label** where **xyz** is the name of the original document (assigned as a result of saving or job submission) and **label** identifies a molecule inside of the original document. Unless otherwise specified, **label** is **M001**, **M002**, ... for the first, second, ... molecule in the original document. Labels can be specified (to molecule names, for example) by entering them into the **Labels** box in the **Molecule Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**).

---

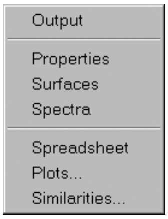
* The job is submitted to a job queue and will be submitted for execution only when released from this queue. See **Monitor** under the **Options** menu (**Chapter 18**) for discussion.

These new documents are not opened but rather stored in the same directory as the original document.

Chapter 16

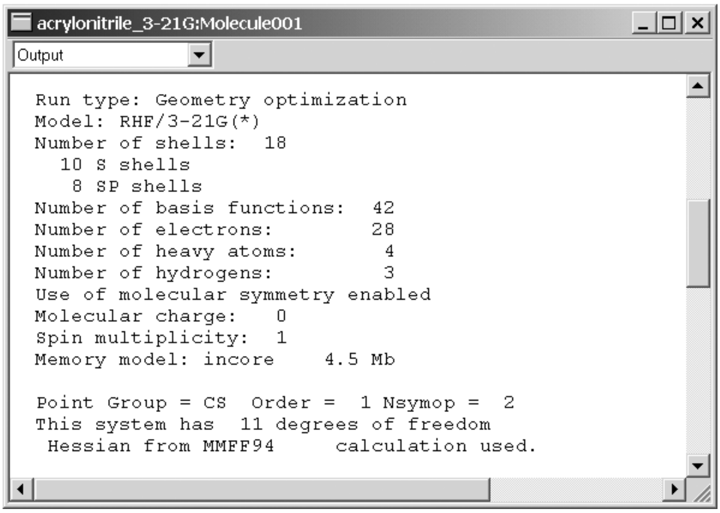
The Display Menu

Functions available under the ***Display*** *menu provide for text, dialog, spreadsheet and graphical displays following structure/property calculation, conformational analysis or similarity analysis. Functions are also available to query a variety of on-screen objects, display IR, UV/visible and NMR spectra, animate vibrational motions, perform linear regression and prepare plots from spreadsheet data, and display similarities between molecular structures and between molecular structures and pharmacophores.*



Output

Selection of **Output** opens a window.



```
Run type: Geometry optimization
Model: RHF/3-21G(*)
Number of shells:  18
  10 S shells
   8 SP shells
Number of basis functions:  42
Number of electrons:        28
Number of heavy atoms:       4
Number of hydrogens:         3
Use of molecular symmetry enabled
Molecular charge:   0
Spin multiplicity:  1
Memory model: incore    4.5 Mb

Point Group = CS  Order =  1 Nsymop =  2
This system has  11 degrees of freedom
 Hessian from MMFF94     calculation used.
```

A menu at the top left of the window selects the type of output for display.

Output
CSD Data
Job Log

Output provides normal output, **CSD Data** (**NAM**) provides the literature reference and other information for data in the Cambridge Structural Database (CSD), and **Job Log** documents execution errors.

The contents of the output window may be scrolled in the usual manner and may be paged up or paged down by *clicking* above or below the scroll bar. The contents may be printed by selecting **Print Output...** from the **File** menu (this replaces **Print...** when an output window is selected), or copied to the clipboard by selecting **Copy** from the **Edit** menu when an output is selected. **Find...** and **Find Next** functions from the **Edit** menu are also available.

A single output window is associated with each document, and changes focus as different molecules from the document are selected. As many output windows as desired may be simultaneously open on screen. An output window may be closed by *clicking* on ☒ at the top right.

> Except for CSD data, output from jobs that are currently executing or are in the execution queue, is unavailable. Output for jobs that execute locally may be viewed using the **Monitor** under the **Options** menu (**Chapter 18**).

Properties

Spartan provides specialized dialogs for reporting and (in some cases) changing the properties of molecules, atoms, bonds, graphical surfaces and geometrical constraints. They also allow for changing default plot styles and limits, as well as for altering the nature of fitting functions. Finally, they allow editing CFD's and substituent libraries. Only one **Properties** dialog is permitted on screen, and this dialog refers either to the selected molecule (**Molecule Properties**), or to the selected component (atom, bond, etc.) or attribute (spectra, graphical surface, substituent, etc.) of the selected molecule (**Atom Properties**, **Bond Properties**, **Surface Properties**, etc.), or to a plot constructed from data in a spreadsheet (**Plot Properties**, **Curve Properties**, etc.), or to a fitting function (**Regression Properties**). Selection of a different molecule (with a **Properties** dialog on screen) leads to the **Molecule Properties** dialog for the newly selected molecule. Dialogs that refer to components/attributes of the (newly selected) molecule follow by *clicking* on the component/attribute.

Dialog selection operates in toggle mode, with the **Molecule Properties** dialog being in the "neutral" position. In this position (with the **Molecule Properties** dialog on screen), *clicking* on a component/attribute (of the currently selected molecule) brings up the appropriate **Properties** dialog. For example, *clicking* on an atom brings up the **Atom Properties** dialog. *Clicking* on a different component or attribute brings up the **Properties** dialog for this component or attribute. However, *clicking* a second time on the same component reverts back to the **Molecule Properties** dialog.*

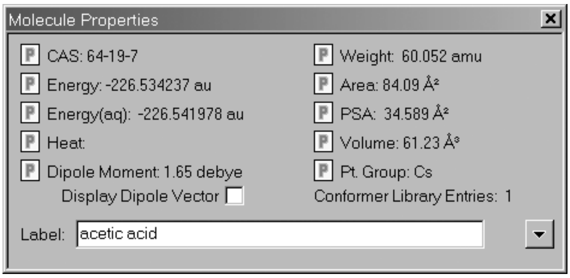
Most **Properties** dialogs have an associated **Utilities** or **Style** dialog. For example, associated with the **Molecule Properties** dialog is a **Molecule Utilities** dialog. These access additional information about the molecule and its components/attributes, or provide style and color controls unique to the selected molecule, component or attribute. This is useful for highlighting (or dehighlighting) a particular molecule, component or attribute. **Utilities**/**Style** dialogs are reached by *clicking* on ▼ at the bottom right of the appropriate **Properties** dialog. Return to the **Properties** dialog follows from *clicking* on ▲ at the bottom right of the associated **Utilities**/**Style** dialog. *Clicking* on a new molecule with a **Utilities**/**Style** dialog on screen leads to the **Molecule Properties** dialog for that new molecule.

The **Properties** (or **Utilities**/**Style**) dialog may be removed from the screen by *clicking* on ☒.

---

* The exception to this involves *clicking* on a property map to obtain the value of the property. *Clicking* a second time on the property map will report a new value. *Clicking* on the background leads to the **Molecule Properties** dialog. This is different behavior than exhibited in previous versions of ***Spartan***.

Molecule Properties



Molecule Properties

CAS: 64-19-7

Energy: -226.534237 au

Energy(aq): -226.541978 au

Heat:

Dipole Moment: 1.65 debye

Display Dipole Vector ☐

Weight: 60.052 amu

Area: 84.09 Å²

PSA: 34.589 Å²

Volume: 61.23 Å³

Pt. Group: Cs

Conformer Library Entries: 1

Label: acetic acid

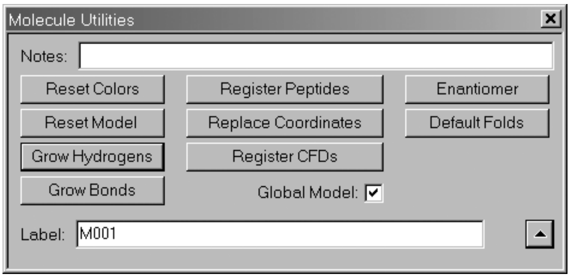
The **Molecule Properties** dialog displays the energy (in au) of a Hartree-Fock, density functional, Møller-Plesset or other correlated calculation, the heat of formation (in kJ/mol) of a semi-empirical calculation or thermochemical recipe, or strain energy (in kJ/mol) of a molecular mechanics calculation, the energy (heat of formation, strain energy) corrected for an aqueous environment (in the same units as the non-corrected quantity), dipole moment (in debyes), molecular weight (in amu), surface area, polar surface area* and volume of a space-filling model** (in $Å^2$ and $Å^3$, respectively), the point group and (if available) the experimental heat of formation (in kJ/mol) and the CAS number. These may be posted to the spreadsheet using the P buttons to the left of their values. Also provided is the number of conformers generated for the molecule using **Conformer Library**. **Label** identifies the molecule in a document. It appears in the first column of the spreadsheet (see **Spreadsheet** later in this chapter) and is the name given to the molecule in the Spartan Molecular Database. Finally, the dialog permits display of the dipole moment vector by *checking* the box to the right of **Display Dipole Vector**.

Clicking on ▼ at the bottom right of the **Molecule Properties** dialog brings up the **Molecule Utilities** dialog (*clicking* on ▲ at the bottom right of this dialog returns to the **Molecule Properties** dialog).

---

* Polar surface area is defined as the area due to nitrogen and oxygen and any hydrogens attached to nitrogen and oxygen.

** Area and volume calculations are not performed for molecules with more than 500 atoms.


Molecule Utilities
Reset Colors
Register Peptides
Enantiomer
Reset Model
Replace Coordinates
Default Folds
Grow Hydrogens
Register CFDs
Grow Bonds

Notes:

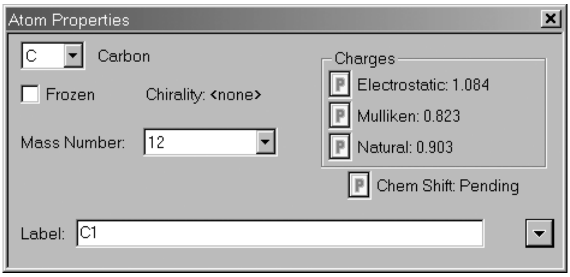
Global Model: ☑

Label: M001

Notes provides for entering text that will be reproduced in the output. Controls allow resetting model color and style, adding missing hydrogens and missing bonds to the model, providing information about amino acids in polypeptides and about CFD's, replacing coordinates by those based on atomic connectivities, changing enantiomers and resetting single-bond and ring conformer selections to default values.

Atom Properties

Selection of an atom with a **Properties** dialog on screen, or selection of **Properties** following selection of an atom, leads to the **Atom Properties** dialog.


Atom Properties
Charges
P
P
P
P

C Carbon

☐ Frozen

Chirality: <none>

Mass Number: 12

Electrostatic: 1.084

Mulliken: 0.823

Natural: 0.903

Chem Shift: Pending

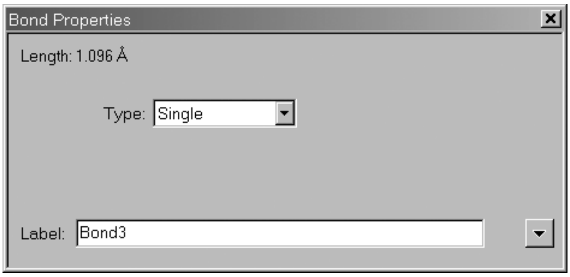
Label: C1

This displays the element name and allows for changing of element type, R/S chirality, Mulliken, electrostatic-fit and natural charges (in electrons) and chemical shifts (in ppm relative to the appropriate standards) if the NMR spectrum has been requested. It also allows the atom to be **Frozen** (see **Freeze Center** in **Chapter 13**), as well as changing its **Mass Number** and the default atomic **Label**. Atomic charges and the chemical shift may be posted to the spreadsheet.

Clicking on ▼ at the bottom right of the **Atom Properties** dialog brings up the **Atom Style** dialog (not shown). This contains controls for selecting atom color and changing model style. *Clicking* on ▲ at the bottom right of this dialog returns to the **Atom Properties** dialog.

Bond Properties

Selection of a bond with a **Properties** dialog on screen, or selection of **Properties** following selection of a bond leads to the **Bond Properties** dialog.



Bond Properties

Length: 1.096 Å

Type: Single

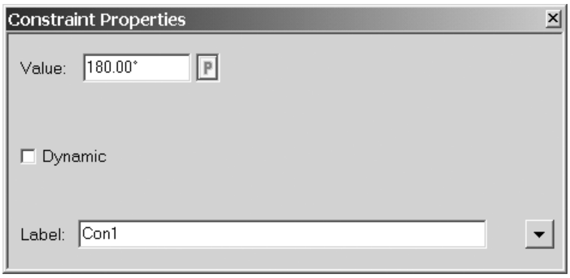
Label: Bond3

This displays the bond length and bond type (and allows changing of bond type).

Clicking on ▼ at the bottom right of the **Bond Properties** dialog brings up the **Bond Style** dialog (not shown). This contains controls for changing bond color. *Clicking* on ▲ at the bottom right of this dialog returns to the **Bond Properties** dialog.

Constraint Properties

Selection of a constraint marker with a **Properties** dialog on screen, or selection of **Properties** following selection of a constraint marker, leads to the **Constraint Properties** dialog.



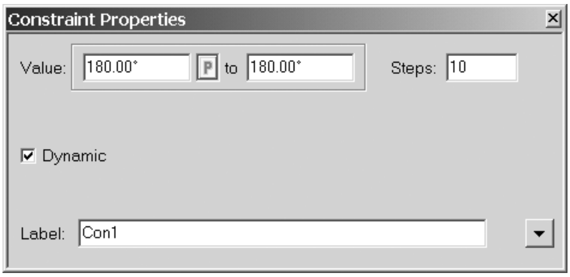
Constraint Properties

Value: 180.00°

☐ Dynamic

Label: Con1

This allows setting the **Value** of a constraint, posting it to the spreadsheet and changing the default constraint **Label**. *Checking* **Dynamic** leads to an expanded dialog.



Value: 180.00° P to 180.00°

Steps: 10

☑ Dynamic

Label: Con1

This allows specifying a sequence of constraints for an energy profile (see **Calculations...** in **Chapter 15**). The value of the constraint for the first member is given in the lefthand box to the right of **Value**, and the value of the constraint for the last member is given in the righthand box to the right of **Value**. The number of members in the sequence is given in the box to the right of **Steps**. Initially, the numbers in both boxes to the right of **Value** will be the same, and **Steps** will be set to **1**. These may be altered by typing the desired numbers into the appropriate boxes and then *pressing* the **Enter** key (**return** key on Mac). An energy profile may involve constraints on more than one geometrical variable (changed in lock-step with one another). In this case, the constraint ranges for the individual variables need to be selected, but the number of steps must be the same for each variable.

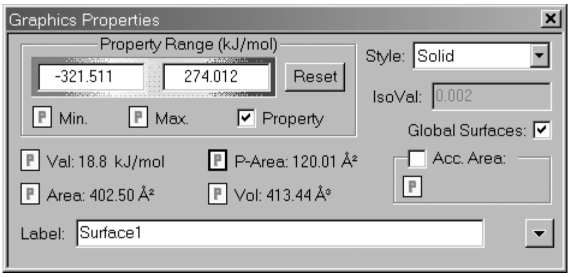
Clicking on ▼ at the bottom right of the **Constraint Properties** dialog brings up the **Constraint Style** dialog (not shown). This contains controls for selecting the color of the constraint marker. *Clicking* on ▲ at the bottom right of this dialog returns to the **Constraint Properties** dialog.

Point and Plane Properties

Selection of a user-defined point or plane with a **Properties** dialog on screen, or selection of **Properties** from the **Display** menu following selection of a point or plane, leads to the **Point Properties** or **Plane Properties** dialog (not shown). These allow changing point or plane labels. *Clicking* on ▼ at the bottom right of the **Point** (**Plane**) **Properties** dialog gives rise to the **Point** (**Plane**) **Style** dialogs (not shown). These contain controls for adjusting point and plane colors, respectively. *Clicking* on ▲ at the bottom right of this dialog returns to the **Point** or **Plane Properties** dialog.

Surface Properties

Selection of a graphical display with a **Properties** dialog on screen, or selection of **Properties** following selection of a graphical display, leads to the **Surface Properties** dialog.



Graphics Properties

Property Range (kJ/mol): -321.511 274.012 Reset

P Min. P Max. ☑ Property

Style: Solid

IsoVal: 0.002

Global Surfaces: ☑

P Val: 18.8 kJ/mol

P P-Area: 120.01 Å²

P Area: 402.50 Å²

P Vol: 413.44 Å³

☐ Acc. Area:

Label: Surface1

This allows changing display style, turning "on" mapped properties, setting the range of electrostatic potential and local ionization potential maps, displaying accessible area of surfaces and maps and changing the default surface labels. The dialog also reports the area and volume of the graphic, the accessible area[*], the polar area of an electrostatic potential map[**], the maximum and minimum value of the mapped property and its value at the cursor position[***]. These quantities may be posted to the spreadsheet using P buttons. If *checked*, **Global Surfaces** designates that the settings apply to all molecules in the document.

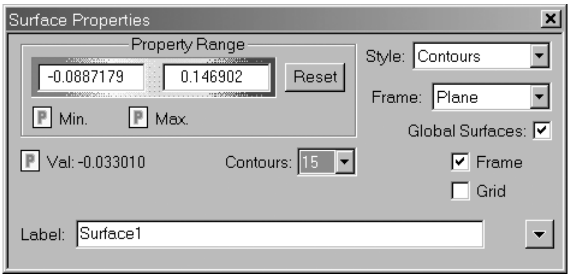
---

[*] A region on a density surface is designated as inaccessible if a sphere of radius 1.0 Å centered on a line normal to the surface and touching a point in the middle of the region, impinges on any other regions of the density surface. The default radius may be changed in the **Settings Preferences** dialog (**Preferences** under the **Options** menu; **Chapter 18**).

[**] This is defined as that part of the surface area for which the absolute value of the electrostatic potential is > 80 kJ/mol.

[***] To determine property value at another position *click* on it. To bring up the **Molecule Properties** dialog, *click* on the background. This is different behavior than exhibited in previous versions of ***Spartan***.

In the event that the selected graphical surface is a slice, a different **Surface Properties** dialog appears.


Surface Properties

Property Range: -0.0887179 0.146902

Style: Contours

Frame: Plane

Global Surfaces: ☑

Val: -0.033010

Contours: 15

☑ Frame

☐ Grid

Label: Surface1

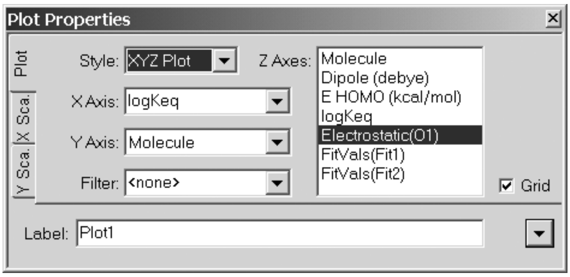
Range, **Min**, **Max** and **Val** controls are repeated. **Style** selections apply to slices rather than surfaces, **Frame** allows choosing the type of slice (plane, cylinder or sphere) and **Contours** sets the number of lines. Check boxes allow for a frame around the slice and for a grid.

Clicking on ▼ at the bottom right of the **Surface Properties** dialog brings up the **Surface Style** dialog (not shown). This contains controls for selecting surface color. *Clicking* on ▲ at the bottom right of this dialog returns to the **Surface Properties** dialog.

Curve and Plot Properties

Plots created using data from the spreadsheet (see discussion under both **Spectra** and **Plots...** later in this chapter) may be edited using a set of closely-related dialogs. These refer to curves, meaning a single relationship between variables, and plots meaning a set of relationships that share variables.

Selection of a plot frame with a **Properties** dialog on screen, or selection of **Properties** following selection of a plot frame, leads to the **Plot Properties** dialog (XY plot case shown).


Plot Properties

Style: XYZ Plot

X Axis: logKeq

Y Axis: Molecule

Filter: <none>

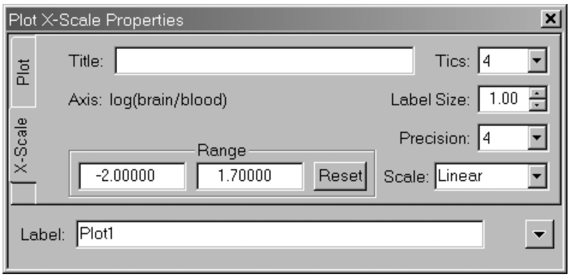
Z Axes: Molecule, Dipole (debye), E HOMO (kcal/mol), logKeq, Electrostatic(O1), FitVals(Fit1), FitVals(Fit2)

☑ Grid

Label: Plot1

The **X Axis** menu and the **Y Axes** list duplicate functionality under the **Plots** dialog (see **Plots...** later in this chapter). They allow specification of a molecular property to serve as the X axis of the plot and one or more properties to serve as the Y axes. Initial selections may be altered as desired (by selecting a new property from the **X Axis** menu and/or adding or deleting properties from the **Y Axes** list). In addition, a **Grid** can be added to the plot, and the default **Label** can be changed.

The scale along the X (horizontal) axis may be altered from default settings by *clicking* on the **X Sca.** tab at the left of the dialog. This brings up the **Plot X-Scale Properties** dialog (*clicking* on the **Plot** tab at the left of this dialog returns to the **Plot Properties** dialog).


Plot X-Scale Properties

Title:

Axis: log(brain/blood)

Tics: 4

Label Size: 1.00

Precision: 4

Range: -2.00000 1.70000

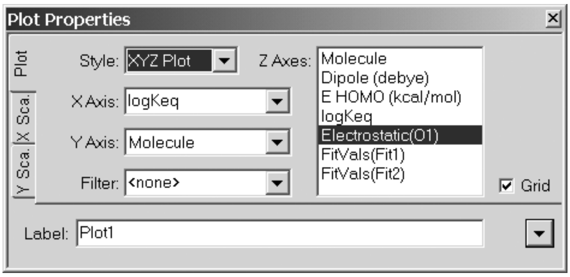
Scale: Linear

Label: Plot1

To alter the scale, edit the values inside the **Range** boxes. You need to *press* the **Enter** key following each entry. Controls are also available to alter the number of tic marks on the X axis (**Tics**), the **Label Size** and **Precision**.

Clicking on ▼ at the bottom right of either the **Plot Properties** or **Plot X-Scale Properties** dialog brings up the **Plot Style** dialog (not shown). This contains controls for selecting the color of the plot frame, as well as the **Label** associated with the X axis. *Clicking* on ▲ at the bottom right of this dialog returns to either the **Plot Properties** or **Plot X-Scale Properties** dialog.

The **Style** menu in the **Plot Properties** dialog allows shifting between 2D (XY) and 3D (XYZ) plots. Selection of **XYZ Plot** leads to an extended **XYZ Plot Properties** dialog.



Style: XYZ Plot

X Axis: logKeq

Y Axis: Molecule

Filter: <none>

Z Axes: Molecule, Dipole (debye), E HOMO (kcal/mol), logKeq, Electrostatic(O1), FitVals(Fit1), FitVals(Fit2)

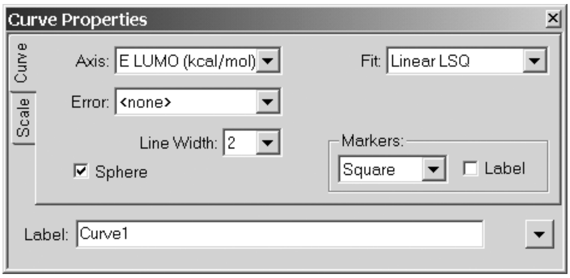
☑ Grid

Label: Plot1

This is identical to the **XY Plot Properties** dialog, except that it includes an additional menu (**Y Axis**) from which one property needs to be selected. In addition, the **Y Axes** list in the **XY Plot Properties** dialog has been renamed to **Z Axes**.

Scales along X and Y axes may be adjusted by *clicking* on **X Sca.** and **Y Sca.** tabs to the left of the dialog. This leads to the **Plot X-Scale** (**Plot Y-Scale**) **Properties** dialog (*clicking* on the **Plot** tab at the left of this dialog returns to the **Plot Properties** dialog). These are analogous to the (**Plot X-Scale Properties**) dialog discussed for XY plots.

Selection of an individual curve in a plot with a **Properties** dialog on screen, or selection of **Properties** from the **Display** menu following selection of an individual curve, leads to the **Curve Properties** dialog.



Axis: E LUMO (kcal/mol)

Error: <none>

Line Width: 2

☑ Sphere

Fit: Linear LSQ

Markers: Square ☐ Label

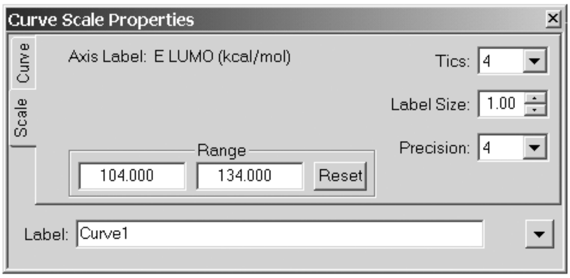
Label: Curve1

This allows changing the presentation format for the curve specified from the **Axis** menu. This includes designation of the kind of **Markers** for the data points[*], request for **Marker Labels**, designation of the kind of **Fit** to the data points and the **Line Width** of the fitting curve. If *checked*, **Sphere** designates the selected molecule by a sphere on the curve. **Error** bars on the individual data points (drawn from a column on the spreadsheet) may also be included.

---

[*] Fitting functions include linear, quadratic and cubic least square, a Fourier series, a Lorentzian or a Gaussian. The data points may also be connected by straight lines (point-to-point) or by a smooth curve (cubic spline) or be presented as a skyline. Finally, the fitting curve can be removed.

The scale along the Y axis (vertical axis) in the case of an XY plot (or Z axis in the case of a XYZ plot) may be altered from default settings (from the minimum to maximum value of the Y or Z variable) by *clicking* on the **Scale** tab at the left of the dialog. This brings up the **Curve Scale Properties** dialog.


Curve Scale Properties

Axis Label: E LUMO (kcal/mol)

Tics: 4

Label Size: 1.00

Precision: 4

Range: 104.000 134.000

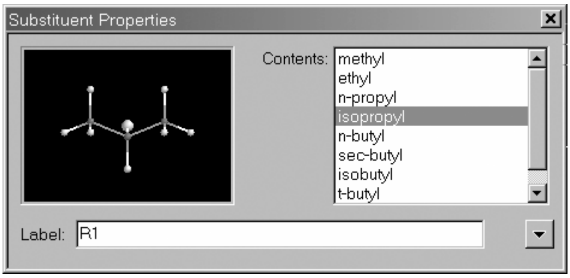
Label: Curve1

To alter the scale, type in new values inside the boxes underneath **Range**. You need to *press* the **Enter** key (**return** key on Mac) following each entry. Controls are also available to alter characteristics of labels associated with the Y or Z axis: **Tics** (the number of tic marks on the axis), **Label Size** and **Precision**.

Clicking on ▼ at the bottom right of either the **Curve Properties** or **Curve Scale Properties** dialog brings up the **Curve Style** dialog (not shown). This contains controls for selecting the color of the curve (and the **Label** associated with the Y (or Z) axis). *Clicking* on ▲ at the bottom right of this dialog returns to the original dialog.

Substituent Properties

Selection of a substituent icon with a **Properties** dialog on screen, or selection of **Properties** following selection of a substituent icon, leads to the **Substituent Properties** dialog.



Substituent Properties

Contents:
- methyl
- ethyl
- n-propyl
- isopropyl
- n-butyl
- sec-butyl
- isobutyl
- t-butyl

Label: R1

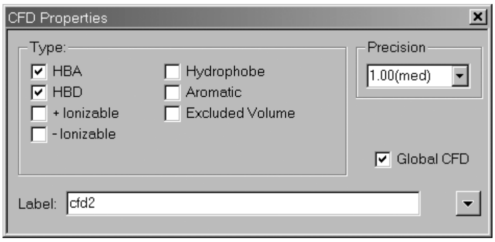
This allows substituent libraries already attached to a molecule to be edited, and the label on the substituent icon to be changed. It does not allow for attachment points to be reassigned. The dialog comprises a scroll box (listing the names of the substituents) on the right, a viewing window (showing a model of the substituent) on the left and a label field at the bottom.

To delete a substituent from the library, *click* on its name in the scroll box, then right *click* and select **Delete** from the menu that appears. **Ctrl** and **Shift** keys may be used in the usual way to remove several substituents at once. To add a new substituent that has been copied to the clipboard to the library, *click* inside the scroll box, then right *click* and select **Paste** from the menu that appears. Note, that if the clipboard contains several molecules, all will be added to the substituent library. A substituent (or list of substituents) can also be added by *dragging* the document that contains the substituent(s) from an external window into the scroll box.

Clicking on ▼ at the bottom right of the **Substituent Properties** dialog brings up the **Substituent Style** dialog (not shown). This contains controls for selecting substituent (icon) color. *Clicking* on ▲ at the bottom right of this dialog returns to the **Subtituent Properties** dialog.

CFD Properties

Selection of a chemical function descriptor (CFD) or of an element of a pharmacophore (which is functionally the same as a CFD) with a **Properties** dialog on screen, or selection of **Properties** (**Display** menu) following selection of a CFD or pharmacophore element, leads to the **CFD Properties** dialog.


CFD Properties

Type:
☑ HBA
☑ HBD
☐ + Ionizable
☐ - Ionizable
☐ Hydrophobe
☐ Aromatic
☐ Excluded Volume

Precision: 1.00(med)

☑ Global CFD

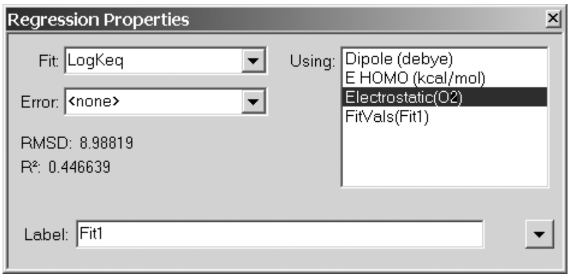
Label: cfd2

This allows changing the definition of the CFD, changing the label on the CFD and the precision of the fit (by changing the radius of the CFD; the bigger the radius, the less precise the fit). If *checked*, **Global CFD** specifies that CFD definitions will apply to all molecules in the document.*

Clicking on ▼ at the bottom right of the **CFD Properties** dialog brings up the **CFD Style** dialog (not shown). This contains controls for selecting CFD color. *Clicking* on ▲ at the bottom right of this dialog returns to the **CFD Properties** dialog.

Regression Properties

Following a linear regression analysis (see discussion later in this chapter), a new row, labeled **Fit1****, appears near the bottom of the spreadsheet. This contains information about the fit. *Clicking* on this line with a **Properties** dialog on screen, or selecting **Properties** (**Display** menu) after *clicking* on the line, leads to the **Regression Properties** dialog.


Regression Properties

Fit: LogKeq

Error: <none>

RMSD: 8.98819

R^2: 0.446639

Using:
Dipole (debye)
E HOMO (kcal/mol)
Electrostatic(O2)
FitVals(Fit1)

Label: Fit1

This reports RMSD and R^2 error statistics related to the fit, as well as allows for changing what is to be fit (**Fit** menu) and what it is to be fit to (list to the right of **Using**). Following selection of either or both, the error statistics will update, allowing the user immediate feedback.

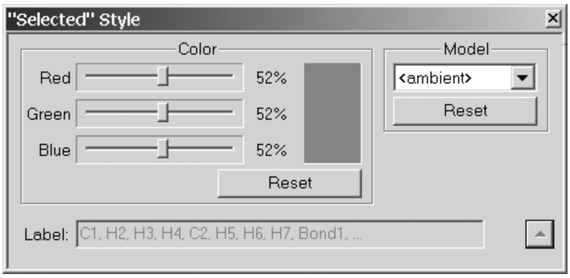
---

* This is generally applicable only where the molecules are conformers, or the CFD labels have been adjusted to associate positions on different molecules. Label reassignment is accomplished using the **Atom Properties** dialog (see discussion earlier in this chapter).

** More precisely, a row will be written for each fit, and labelled **Fit1**, **Fit2**, ...

“Selected” Style

In addition to **Style** dialogs associated with several **Properties** dialogs, there is **“Selected” Style** dialog. This is accessed either by defining a selection box (see discussion under **Mouse and Keyboard Operations** in **Chapter 2**) with a **Properties** dialog on screen, or by selecting **Properties** from the **Display** menu after defining a selection box.



Red 52%
Green 52%
Blue 52%
<ambient>
Label: C1, H2, H3, H4, C2, H5, H6, H7, Bond1, ...

This dialog contains controls for changing the color and model type of whatever is included in the selection box.

Surfaces

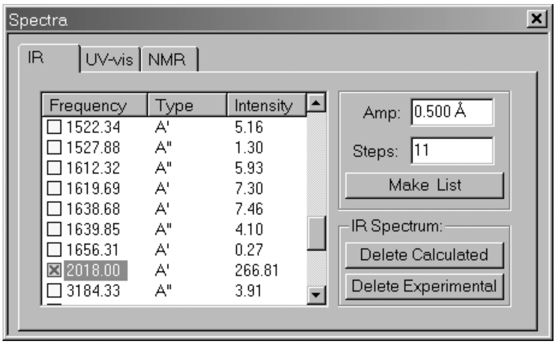
This accesses the same dialog already described in **Chapter 15**.

Spectra

Spartan provides for display of calculated IR, UV/visible and NMR spectra. (All of these need to have been previously requested from the **Calculations** dialog under the **Setup** menu; see **Chapter 15**.) In addition, it allows on-line access and display of experimental spectra from publicly available collections. This allows direct visual comparison of calculated and experimental spectra. Access to spectra display is via a series of tabbed dialogs.

IR

Clicking on the **IR** tab leads to the **IR Spectra** dialog that not only provides for display of a calculated and (if available) experimental infrared spectra, but also allows for animated display of the vibrational modes as well as for generation of a sequence of structures along a vibrational coordinate.



Frequency	Type	Intensity
☐ 1522.34	A'	5.16
☐ 1527.88	A"	1.30
☐ 1612.32	A"	5.93
☐ 1619.69	A'	7.30
☐ 1638.68	A'	7.46
☐ 1639.85	A"	4.10
☐ 1656.31	A'	0.27
☒ 2018.00	A'	266.81
☐ 3184.33	A"	3.91

Amp: 0.500 Å

Steps: 11

This contains an ascending list of frequencies (in cm^{-1})[*] together with (infrared) intensities and symmetry labels. A frequency is selected for display by *clicking* on it. *Clicking* again deselects it.

The amplitude of vibrational motion (the maximum displacement away from equilibrium of any pair of atoms) may be changed from the default amplitude (0.5Å which is much larger than appropriate for vibrational motion at room temperature) by altering the contents of the box to the right of **Amp**. The default number of steps that make up the display (11) may be changed by altering the contents of the box to the right of **Steps**[**]. The greater the number of frames, the slower will be the vibration.

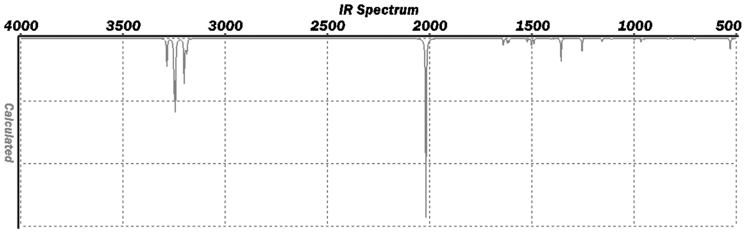
Make List creates a list containing a sequence of structures corresponding to motion along the selected normal mode. The original molecule is not closed, and several sequences (corresponding to different vibrations) can be created.

---

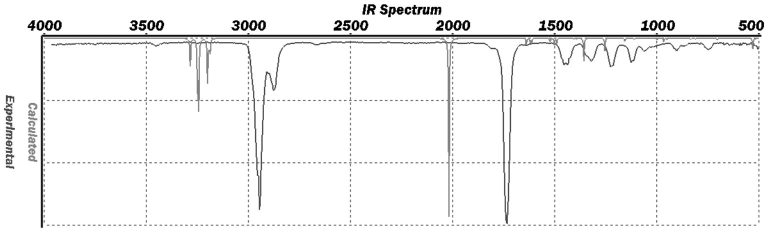
[*] Imaginary frequencies, for example, corresponding to the reaction coordinate for a transition state, will appear first in the list, and will be designated by the letter **i** in front of the frequency value.

[**] It is recommended that the number of steps be odd ensuring that the center point corresponds to the actual equilibrium or transition-state structure.

The calculated spectrum may be drawn by *clicking* on **Draw Calculated**.



The corresponding experimental spectrum (if it is available) may be drawn on top of the calculated spectrum by *clicking* on **Draw Experimental**. (It may also be drawn independently of the calculated spectrum.)



Draw operations for both calculated and experimental IR spectra, apply to all molecules in the list (not just the selected molecule).

> Experimental IR spectra are accessed from the NIST (National Institute of Standards and Technology) website (http://webbook.nist.gov/chemistry). This comprises approximately 14,000 IR spectra, primarily for organic molecules. ***Spartan*** keeps an index to facilitate retrieval but the actual data are on the website.

The default range for both calculated and experimental IR spectra is from 4000 cm^{-1} to 500 cm^{-1}. This corresponds to the range commonly measured and reported. This range may be changed by selecting **Properties** from the **Display** menu, *clicking* on the horizontal axis to bring up the **Plot Properties** dialog, *clicking* on the **X Sca.** tab at the left of the dialog and editing the values under **Range**. The spectrum is treated like any other graphical object, and may be translated and scaled using the appropriate mouse operations. It may not be rotated.

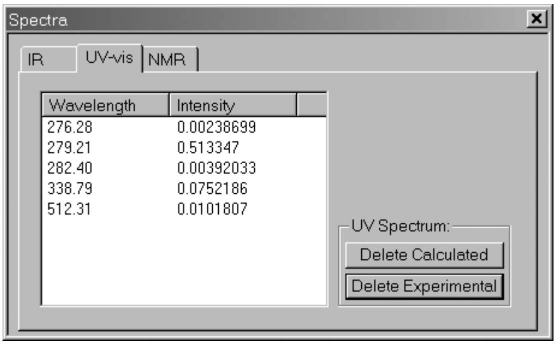
The calculated spectrum may be removed by *clicking* on **Delete Calculated** (that has replaced **Draw Calculated**) in the dialog. Similarly, the experimental spectrum may be removed by *clicking* on **Delete Experimental** (that has replaced **Draw Experimental**). The last spectrum (calculated or experimental) removed will also cause removal of the plot axes. These operations apply to all molecules in the list (not just the selected molecule). An individual (calculated or experimental) spectrum or entire plot may be removed by selecting **Delete** from the **Build** menu and then *clicking* on a spectrum or on the plot axes, respectively. Holding down the **Delete** key while *clicking* on the spectrum or plot axes has the same effect.

Calculated IR frequencies often exhibit systematic (as opposed to random) errors. For example, frequencies obtained from (limiting) Hartree-Fock models are typically 10-12% larger than measured frequencies. Systematic errors may be revealed (and quantified) by first simultaneously displaying calculated and experimental spectra and then scaling one of the spectra to provide a best visual fit. To scale, *click* on the spectra (not on an axis) to select and move the mouse up and down while simultaneously depressing the **Shift** and **Alt** keys in addition to the right button. The scale factor (multiplying the frequency) will be displayed on the vertical axis. Scaling applies uniformly to all molecules in the list (not just the selected molecule).

A scaling factor may be applied to frequencies, and to all properties that make use of frequencies, prior to reporting using the **FSCALE** keyword typed into the **Options** box in the **Calculations** dialog (**Calculations...** under the **Setup** menu, **Chapter 15**).

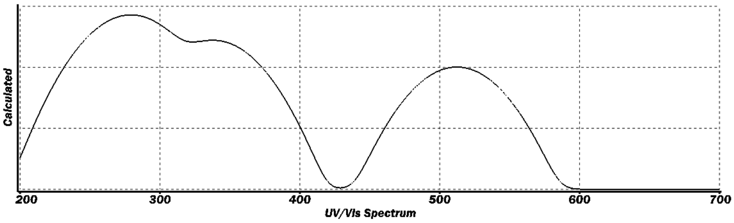
UV/vis

Clicking on the **UV/vis** tab leads to the **UV/vis Spectra** dialog that provides for display of both calculated and (if available) experimental UV/visible spectra.

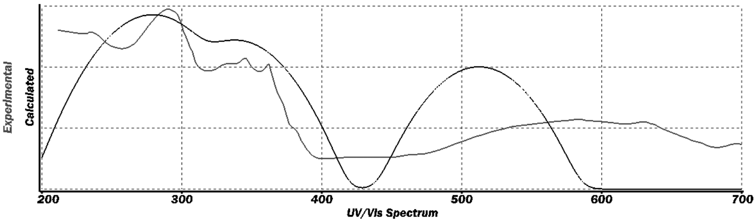


Wavelength	Intensity
276.28	0.00238699
279.21	0.513347
282.40	0.00392033
338.79	0.0752186
512.31	0.0101807

This lists absorption wavelengths (from lowest to highest) together with intensities. The calculated UV/visible spectrum may be drawn by *clicking* on **Draw Calculated**.



The corresponding experimental spectrum (if it is available) may be drawn on top of the calculated spectrum by *clicking* on **Draw Experimental**. (It may also be drawn independently of the calculated spectrum.)



Draw operations for both calculated and experimental UV/visible spectra and apply to all molecules in the list (not just the selected molecule).

Experimental UV/visible spectra are accessed from the NIST (National Institute of Standards and Technology) website (http://webbook.nist.gov/chemistry). This comprises approximately 1,500 UV/visible spectra, primarily for organic molecules. ***Spartan*** keeps an index to facilitate retrieval but the actual data are on the website.

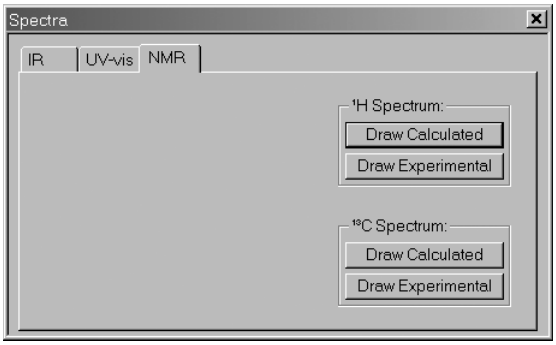
The default range for both calculated and experimental UV/visible spectra is from 200 nm to 700 nm. This corresponds to the range commonly measured and reported. This range may be changed by selecting **Properties** from the **Display** menu, *clicking* on the horizontal axis to bring up the **Plot Properties** dialog, *clicking* on the **X Sca.** tab at the left of the dialog and editing the values under **Range**. The spectrum is treated like any other graphical object, and may be translated and scaled using the appropriate mouse operations.

The calculated spectrum may be removed by *clicking* on **Delete Calculated** (that has replaced **Draw Calculated**) in the dialog. Similarly, the experimental spectrum may be removed by *clicking* on **Delete Experimental** (that has replaced **Draw Experimental**). The last spectrum removed will also cause removal of the plot axes. These operations apply to all molecules in the list (not just the selected molecule). An individual (calculated or experimental) spectrum or entire plot may be removed by selecting **Delete** from the **Build** menu (or holding down the **Delete** key) and then *clicking* on the spectrum or on the plot axes, respectively.

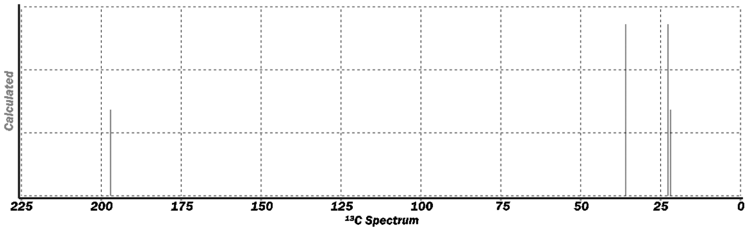
Differences between calculated and experimental UV/visible spectra may be revealed by simultaneously displaying both spectra and then scaling one of the spectra to provide a best visual fit. To scale, *click* on the spectra (not on an axis) to select and move the mouse up and down while simultaneously depressing the **Shift** and **Alt** keys in addition to the right button. The scale factor will be displayed on the vertical axis. Scaling applies uniformly to all molecules in the list (not just the selected molecule).

NMR

Clicking on the **NMR** tab leads to the **NMR Spectra** dialog that provides for display of both calculated and (if available) experimental ^{1}H and ^{13}C NMR spectra.*


Spectra
IR
UV-vis
NMR
¹H Spectrum:
Draw Calculated
Draw Experimental
¹³C Spectrum:
Draw Calculated
Draw Experimental

Calculated proton and ^{13}C spectra may be drawn by *clicking* on their respective **Draw Calculated** buttons.



The corresponding experimental ^{13}C spectrum (if it is available) may be drawn on top of the calculated spectra by *clicking* on the **Draw Experimental** buttons, respectively. (It may also be drawn independently of the calculated spectrum.) A suitable collection of experimental proton spectra is not presently available on-line.

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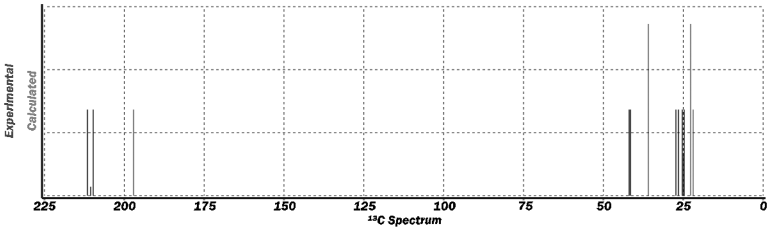
* At present, only chemical shifts are calculated. Coupling constants are not available and relative intensities are assumed to be in proportion to the number of equivalent nuclei. Chemical shifts for nuclei other than hydrogen and carbon may be displayed as labels (see **Configure...** under the **Model** menu; **Chapter 12**).



Draw operations for both calculated and experimental NMR spectra apply to all molecules in the list (not just the selected molecule).

> Experimental ^{13}C spectra are accessed from http://almost.cubic.uni-koeln. This comprises approximately 15,000 experimental ^{13}C spectra, all for organic molecules. ***Spartan*** keeps an index to facilitate retrieval but the actual data are on the website.

The default range for both calculated and experimental proton spectra is from 0 ppm to 10 ppm (relative to TMS), whereas the default range for ^{13}C spectra is from 0 ppm to 225 ppm (again relative to TMS). These correspond to ranges typically measured and reported. These ranges may be changed by selecting **Properties** from the **Display** menu, *clicking* on the horizontal axis to bring up the **Plot Properties** dialog, *clicking* on the **X Sca.** tab at the left of the dialog and editing the values under **Range**. ^{1}H and ^{13}C spectral plots are treated like any other graphical object, and may be translated and scaled using the appropriate mouse operations. They may not be rotated.

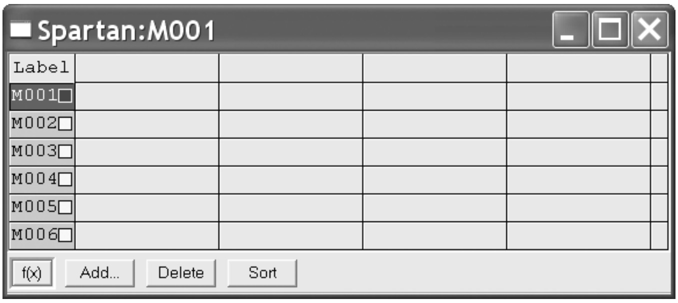
The calculated spectrum may be removed by *clicking* on **Delete Calculated** (that has replaced **Draw Calculated**) in the appropriate section of the dialog. Similarly, the experimental (^{13}C) spectrum may be removed by *clicking* on **Delete Experimental**). The last spectrum removed will also cause removal of the plot axes. These operations apply to all molecules in the list (not just the selected molecule). An individual (calculated or experimental) spectrum or entire plot may be removed by selecting **Delete** from the **Build** menu and then *clicking* on the spectrum or on the plot axes, respectively. Holding down the **Delete** key while *clicking* on the spectrum or plot axes has the same effect.

Systematic errors in chemical shifts may be revealed (and quantified) by first simultaneously displaying calculated and experimental spectra and then scaling of the spectra to provide a best visual fit. To scale, *click* on the spectra (not on an axis) to select and move the mouse up and down while simultaneously depressing the **Shift** and **Alt** keys in addition to the right button. The scale factor (multiplying the chemical shifts) will be displayed on the vertical axis. Scaling applies uniformly to all molecules in the list (not just the selected molecule).

Only a single copy of one of the dialogs under **Spectra** may appear on screen; scaling will relate to the currently selected molecule. The dialog may be removed by *clicking* on ☒.

Spreadsheet

Associated with each ***Spartan*** document (including documents comprising a single molecule) is a spreadsheet. This may be displayed by selecting **Spreadsheet**.



Label				
M001☐				
M002☐				
M003☐				
M004☐				
M005☐				
M006☐				

The spreadsheet comprises a series of rows (corresponding to different molecules in the document) and columns (corresponding to different molecular properties). This gives rise to cells, the number of which is the product of the number of rows (molecules) and the number of columns (molecular properties). The spreadsheet may be expanded or contracted by positioning the cursor at one of the corners, *pressing* the left mouse button and *dragging* the mouse.

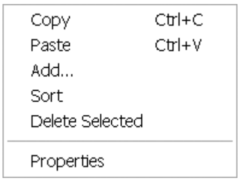
Only one molecule from one document may be selected (although several molecules may be simultaneously displayed). Molecule selection follows either by *clicking* on the spreadsheet cell containing the label, or by using the ◀ and ▶ buttons or the scroll bar at the bottom left of the screen. Molecules may be animated (stepped through in succession) using the ▶ button at the bottom left of the screen. Animation speed may be adjusted from the **Settings Preferences** dialog (**Preferences** under the **Options** menu; **Chapter 18**). Molecule selection (for members of a document) results in deselection of the previously selected molecule. A molecule (in a document) may be designated for permanent display by *checking* the box to the right of its label (left-most column) in the spreadsheet. The molecules in a document may either be translated and rotated in concert or manipulated independently. This is controlled by **Coupled** under the **Model** menu (**Chapter 12**). By default (**Coupled** checked) molecules move in concert. *Uncheck* **Coupled** to move them independently.

Upon initial entry into the spreadsheet, all columns except the leftmost column, are blank. The leftmost column contains a label that may be changed either by directly typing a new label into the spreadsheet or into the **Label** box in the **Molecule Properties** dialog (see discussion earlier in this chapter).

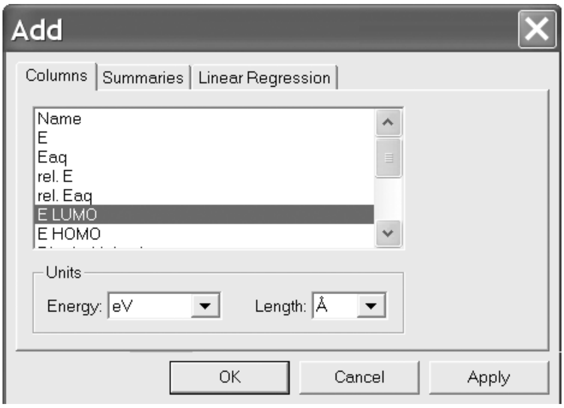
Information may be added to the spreadsheet in several different ways:

From the Add Dialog

A selection of molecular properties may be entered into the spreadsheet by first *clicking* on the header cell of an empty column, and then *clicking* on **Add...** at the bottom of the spreadsheet. An alternative is to right *click* (following *clicking* on the header cell) and then to select **Add...** from the menu that results.



This leads to the **Add Columns** dialog that lists available properties.



Energy: eV

Length: Å

Name	molecule name as it appears in SMD
Formula	molecular formula
E	energy (heat of formation, strain energy)
E_{aq}	aqueous energy (heat of formation, strain energy)
rel. E	energy (heat of formation, strain energy) relative to selected molecule
rel. E_{aq}	aqueous energy (heat of formation, strain energy) relative to selected molecule
E HOMO	energy of highest-occupied molecular orbital
E LUMO	energy of lowest-occupied molecular orbital
Dipole	dipole moment (in debyes)
CPK Area	area of a space-filling molecule
CPK Volume	volume of a space-filling molecule
PSA	polar surface area (N,O + attached hydrogens)
Molecular Weight	molecular weight (in amu)
HBD Count	number of hydrogen-bond donors[*]
HBA Count	number of hydrogen-bond acceptors[*]
+ Ionizable Count	number of positive ionizable centers[*]
- Ionizable Count	number of negative ionizable centers[*]
H°	enthalpy at room temperature
S°	entropy at room temperature
G°	Gibbs energy at room temperature

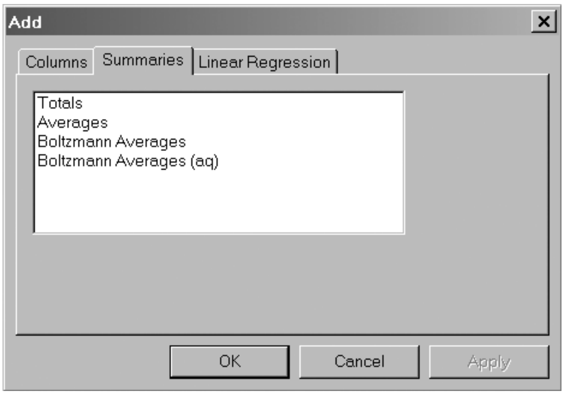
---

[*] Counts of hydrogen-bond donors and acceptors and positive and negative ionizable sites derive from CFD assignments. These in turn follow from atomic connectivity together with special case designations for common organic functional groups. CFD's assignments may be modified on a case-by-case basis using the **CFD Properties** dialog (**Properties** under the **Display** menu; **Chapter 16**).

ZPE	zero-point energy
Boltzmann Distribution	Boltzmann distribution based on energy
Boltzmann Distribution (aq)	Boltzmann distribution based on aqueous energy
Alignment Scores	1-R^2/N, where R^2 is the root mean square distance and N is the number of alignment centers. 1 is a perfect score

One or more properties may be added to the spreadsheet by *clicking* on their entries, then specifying appropriate units from the **Energy** and **Length** menus, and finally *clicking* on **OK** or on **Apply**. In the former case, the dialog is dismissed and in the latter it is left on screen. *Clicking* on **Cancel** or on ☒ removes the dialog without further affecting the contents of the spreadsheet. (Any previous additions to the spreadsheet as a result of *clicking* on **Apply** are maintained.)

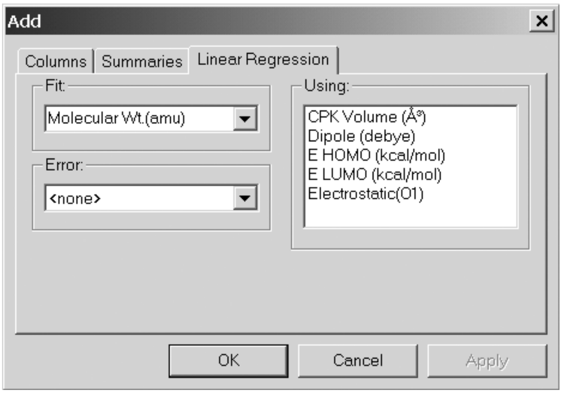
Column totals, averages and Boltzmann-weighted averages may be accessed by *clicking* on the **Summaries** tab. This leads to the **Add Summaries** dialog.


Add
Columns
Summaries
Linear Regression
Totals
Averages
Boltzmann Averages
Boltzmann Averages (aq)
OK
Cancel
Apply

Totals	sum of column values
Averages	average of column values
Boltzmann Averages	Boltzmann weighted average of column values
Boltzmann Averages (aq)	Boltzmann weighted average of column values based on energies corrected for aqueous environment

Clicking on one or more of these followed by *clicking* on **OK** or **Apply**, leads to the requested summaries as rows at the bottom of the spreadsheet, identified as **Totals**, **Averages**, etc. (one row for each summary). Note, that this dialog can be brought up directly by *clicking* on an empty row header (instead of an empty column header) inside the spreadsheet prior to *clicking* on **Add...**.

Finally, a linear regression analysis may be performed on the data in the spreadsheet. First *click* on the **Linear Regression** tab to bring up the **Add Linear Regression** dialog.



Fit: Molecular Wt.(amu)

Error: <none>

Using:
CPK Volume (Å³)
Dipole (debye)
E HOMO (kcal/mol)
E LUMO (kcal/mol)
Electrostatic(O1)

Select one entry from the **Fit** menu and one or more entries from the list under **Using**. *Clicking* on **OK** or **Apply** performs the linear regression analysis and places the results in a row at the bottom of the spreadsheet identified by **Fit**. As many analyses as desired may be performed on the data in the spreadsheet. These will each be entered as separate rows in the spreadsheet, with names **Fit1**, **Fit2**, etc. Additional information about the regression analyses is available from the **Regression Properties** dialog (see discussion earlier in this chapter).

Numerical Data

Numerical data may be entered by typing directly into the spreadsheet. A column header first needs to be specified. *Click* on an empty column header cell, type in a name and *press* the **Enter** key. Then, type the data into individual cells of the new column (*press* the **Enter** key following each data entry).

User-Defined Expressions

An expression may be entered either into a header cell (in which case it refers to all entries in a column) or into an individual cell (in which case it refers only to a single entry). Expressions in the column header take the form ***name=formula***, where ***formula*** is made up of arithmetic operations (**Table 16-1**), specialty functions (**Table 16-2**), calculated quantities (**Table 16-3**), conversion factors and constants (**Table 16-4**) in addition to numerical values. References to specialty functions, molecular mechanics and quantum chemical quantities and conversion factors and constants must be preceded by @. For example, ***mu = @DIPOLE*** typed into a header cell gives the dipole moment. Some quantities have arguments, for example, ***c1*** and ***c2*** in the expression ***c12= @DISTANCE (c1,c2)*** refer to atoms c1 and c2, while ***3*** in the expression ***orbitalE=@HOMO (-3)*** designates the energy of the molecular orbital three orbitals below the HOMO. It is necessary to *press* the **Enter** key (**return** key on Mac) following entry of the expression into a cell. The leading ***name=*** is optional for entries in an individual (non-header) cell. Examples of user-defined expressions are provided in **Table 16-5**.

From Post (P) Buttons

Post buttons found in a number of properties dialogs provide an alternative method to the **Add** dialog for entering calculated properties into the spreadsheet. Note that some properties

Table 16-1: Arithmetic and Boolean Operations and Mathematical Functions

arithemetic operations		**boolean operations**	
+	addition	>	greater than
_	subtraction	>=	greater than or equal to
*	multiplication	<	less than
/	division	<=	less than or equal to
^	raise to a power	==	equal to
		!=	not equal to
		|	or
		&	and

mathematical functions			
ABS(x)	absolute value	LN(x)	natural logarithm
ACOS(x)	inverse cosine	LOG(x)	log (base 10)
ASIN(x)	inverse sine	SIN(x)	sine
ATAN(x)	inverse tangent	SQRT(x)	square root
COS(x)	cosine	TAN(x)	tangent
EXP(x)	exponential		

Table 16-2: Specialty Functions

AVG (column name)	average of values in column
FITVAL (fit name)	column of fit values from regression analysis
MIN (column name)	minimum of values in column
MAX (column name)	maximum of values in column
NUM (column name)	number of defined entries in column
ROW	the number of the row in the spreadsheet
ROW(molecule name)	the number of the row of molecule
REF(i, x)	the value of the x referenced to row i
STDEV (column name)	standard deviation of values in column
SUM (column name)	sum of values in column

Table 16-3: Calculated Quantities

ANGLE(i, j, k)	angle involving atoms i, j, k (degrees)
AREA	area of a user-defined plane (Å^2)
DIHEDRAL(i, j, k, l)	dihedral angle involving atoms i, j, k, l (degrees)
DISTANCE(i, j)	distance involving atoms i, j (Å)
ELECTRONEGATIVITY	QSAR descriptor -(HOMO+LUMO)/2 (eV)
ELECTROSTATIC (i)	electrostatic charge on atom i (electrons)
HARDNESS	QSAR descriptor -(HOMO-LUMO)/2 (eV)
HOMO(-n)	energy of n^{th} orbital below the HOMO (eV)
HOMOBETA(-n)	energy of the n^{th} orbital below the β HOMO (eV)
HYPERPOLARIZABILITY	beta hyperpolarizability parameter
INTERTIA(i)	principle movements of inertia from largest (i=1) to smallest (i=3)
ISOTOPE(i)	mass number of atom i
LENGTH (i)	length of bond i (Å)
LOGPC	LogP from Crippen model
LOGPV	LogP from Villar model
LUMO(+n)	energy of the n^{th} orbital above the LUMO (eV)
LUMOBETA(+n)	energy of the n^{th} orbital above the β LUMO (eV)
MULLIKEN(i)	Mulliken charge on atom i (electrons)
NATURAL(i)	natural charge on atom i (electrons)
OVALITY	QSAR descriptor area/$[4\pi(3\bullet\text{volume}/4\pi)^{2/3}]$
PAREA (i, j, . . .)	partial surface area of a space-filling model due to all atoms of type i, j, ..., where i, j, ... are either atomic numbers or elemental symbols. i:, j:, ... signifies that attached hydrogens are also included (the surface area due to nitrogen, oxygen and any bonded hydrogen is commonly referred to as the polar surface area) (Å^2)
POLARIZABILITY	alpha polarizability parameter
PVOLUME (i, j, . . .)	partial volume of a space-filling model due to all atoms of type i, j, ..., where i, j, ... are either atomic numbers or elemental symbols. i:, j:, ... signifies that attached hydrogens are also included (Å^3)

Table 16-4: Conversion Factors and Constants

ANGS2AU	Ångstroms to atomic units
AU2ANGS	atomic units to Ångstroms
EV2HART	eV to atomic units (hartrees)
EV2KCAL	eV to kcal/mol
EV2KJ	eV to kJ/mol
HART2KCAL	atomic units (hartrees) to kcal/mol
HART2EV	atomic units (hartrees) to eV
HART2KJ	atomic units (hartrees) to kJ/mol
KCAL2EV	kcal/mol to eV
KCAL2HART	kcal/mol to atomic units (hartrees)
KCAL2KJ	kcal/mol to kJ/mol
KJ2EV	kJ/mol to eV
KJ2HART	kJ/mol to atomic units (hartrees)
KJ2KCAL	kJ/mol to kcal/mol
PI	π

Table 16-5: Examples of User Defined Expressions

E/area = @ENERGY/@AREA	energy divided by surface area
RelE = @ENERGY-@REF (6,@ENERGY)	energy relative to energy of molecule in row 6
Eq = @EXP (-@ENERGY/592.1)	equilibrium constant at room temperature
EnergyFilter = @ENERGY<-99.43	"true" (≠0) for all energies <-99.43
RowFilter = @ROW>10	"true" (≠0) all entries past row 10

may require user specification. These include individual bond distances, angles and dihedral angles (available from **Measure Distance**, **Measure Angle** and **Measure Dihedral** under the **Geometry** menu; **Chapter 13**), bond distance, angle and dihedral angle constraints (available from **Constrain Distance**, **Constrain Angle** and **Constrain Dihedral** under the **Geometry** menu; see discussion in **Chapter 13**), atomic charges and chemical shifts (available from the **Atom Properties** dialog; this chapter), the accessible area of an electron density surface, the polar area of an electrostatic potential map, minimum and maximum property values on a map and the value of the property at a specific location on a property map (available from the **Surfaces Properties** dialog; this chapter). With the exception of the property value on a map, post generates an entire column. Where atom labels are involved, for example, in defining a specific distance, post can be expected to yield consistent results for all molecules in a document only where the molecules are closely related, for example, molecules resulting from a conformational search, or where labels have been explicitly reassigned*. The property value on a map is posted only for the selected molecule. Post buttons are also available for CAS numbers and experimental heats of formation contained in ***Spartan's*** internal database.

From the Clipboard

Properties of one or more molecules in a document may be copied into the clipboard and then pasted into individual spreadsheet cells. These include bond distances, angles and dihedral angles (**Measure Distance**, **Measure Angle** and **Measure Dihedral** under the **Geometry** menu), bond distance, angle and dihedral angle constraints (**Constrain Distance**, **Constrain Angle** and **Constrain Dihedral** under the **Geometry** menu), atomic charges and chemical shifts (**Atom Properties** dialog), infrared frequencies and chemical shifts

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* Label reassignment is accomplished using the **Atom Properties** dialog (see discussion earlier in this chapter).

(**IR Spectra** and **NMR Spectra** dialogs, respectively) and the value of a property on a property map (**Surface Properties** dialog). First, highlight the numerical value of the property in the appropriate screen location (distances, etc.) or dialog (charges, etc.), then select **Copy** from the **Edit** menu, then *click* on the appropriate (destination) cell in the spreadsheet, and finally select **Paste** from the **Edit** menu.

Each row in a spreadsheet corresponds to a molecule in a document, and new rows are automatically added in response to adding new molecules to the document. New molecules are added either by building (**New Molecule** under the **File** menu; **Chapter 10**), by appending one or more existing documents each containing one or more molecules (see **Append Molecule(s)...** under the **File** menu; **Chapter 10**), by using the clipboard, or by *dragging* from the file system. Copy a molecule into the clipboard by first selecting (*clicking* on) it, and then selecting **Copy** from the **Edit** menu. Alternatively, *click* on its label in its spreadsheet, and then select **Copy** from the **Edit** menu. The latter permits several molecules to be selected (and copied) at once using the **Shift** and **Ctrl** keys in the usual manner. Move the contents of the clipboard to its destination by *clicking* on an empty row header in the spreadsheet (for the destination document), and then selecting **Paste** from the **Edit** menu. Copy a document containing one or more molecules from the file system to ***Spartan***, by first selecting the document, and then *dragging* it from the file system onto the open spreadsheet (associated with the destination document) inside of ***Spartan***. Several documents can be selected (and *dragged*) at once using the **Shift** and **Ctrl** keys in the usual manner.

A row (molecule) may be deleted from a spreadsheet, either by first selecting the molecule and then selecting **Delete Molecule** from the **File** menu, or by first *clicking* on its label in the spreadsheet (leftmost column) and then either *clicking* on the **Delete** button at the bottom of the spreadsheet, or by selecting **Delete Selected** from the menu that appears when the right mouse button is pressed (with the cursor over the spreadsheet). In all cases, a warning is provided prior to deletion. An entire column in the spreadsheet may be deleted by first *clicking* on the column header (the title) and then *clicking* on the **Delete** button (or **Delete Selected** from the menu).

Rows in the spreadsheet may be sorted according to the numerical values in any column by first *clicking* on the column header and then either *clicking* on the **Sort** button at the bottom of the spreadsheet or by selecting **Sort** from the menu that appears when the right mouse button is pressed (with the cursor over the spreadsheet). The rows are placed in ascending order, the smallest (least positive) value of the selected property at the top, largest (most positive) value at the bottom. To sort in descending order, hold down the **Shift** key before *clicking* on the **Sort** button.

A button at the bottom right of the spreadsheet toggles between numerical representation of data, **f(x)**, and formula presentation, **=?**.

The spreadsheet may be printed by selecting **Print Spreadsheet...** from the **File** menu (that replaces **Print...** when a spreadsheet is selected).

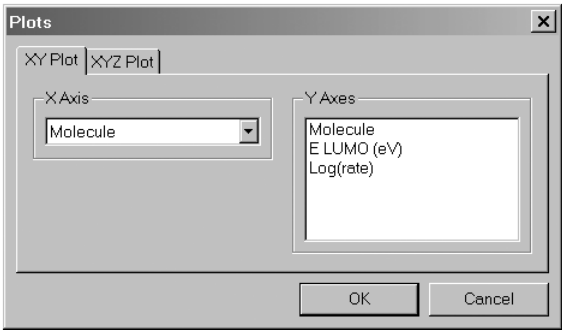
As many spreadsheets as desired (corresponding to different documents) may be open on screen. A spreadsheet is removed when the associated document is closed and may also be removed by *clicking* on ☒.

The contents of the spreadsheet may be brought into Excel™ using the clipboard. Select whatever information is to be copied, select **Copy** from the **Edit** menu (or hold down the right mouse button with the cursor positioned over the spreadsheet and select **Copy** from the menu that appears). **Paste** into Excel.

The contents of an Excel spreadsheet may be brought into ***Spartan***. Copy whatever information is to be transferred to the clipboard, move into ***Spartan***, then *click* on the appropriate cell and select **Paste** from the **Edit** menu (or hold down the right button and select **Paste** from the menu that appears). Note, that information on the clipboard that goes beyond the number of rows in ***Spartan's*** spreadsheet will be ignored.

Plots...

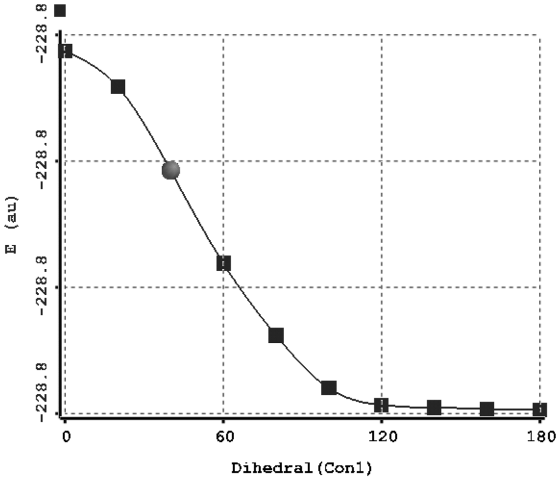
Plots may be constructed from data in a spreadsheet and a variety of simple curves fit to these data. Selection of **Plots...** from the **Display** menu leads to the **Plots** dialog.



A tab at the top of the dialog selects between **XY Plot** (two dimensions) or **XYZ Plot** (three dimensions).

XY Plots

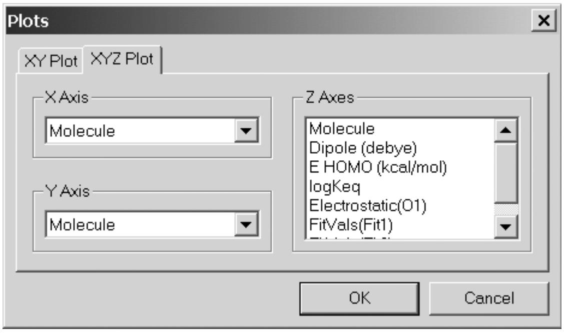
The XY Plot incorporates an **X Axis** menu designating the molecular property to be displayed among the X (horizontal) axis, and a list of properties to be displayed along the Y (vertical) axis. These properties correspond one to one to the columns in the associated spreadsheet. To construct a 2D plot, select an item from the **X Axis** menu, then *click* on one or more items from the **Y Axes** list and finally *click* on **OK**. (Repeated *clicking* on a property in the **Y Axes** list turns it "on" and "off".) The dialog is removed from the screen and a plot appears.



The plot may be moved about the screen. Select (*click* on) either the frame or on one of the curves (it will turn gold in response), then hold down the right mouse button and *drag* the mouse. The plot may also be scaled (expanded or shrunk) by first selecting either the frame or one of the curves and *dragging* the mouse while holding down both the right button and the **Shift** key. The plot may not be rotated.

XYZ Plots

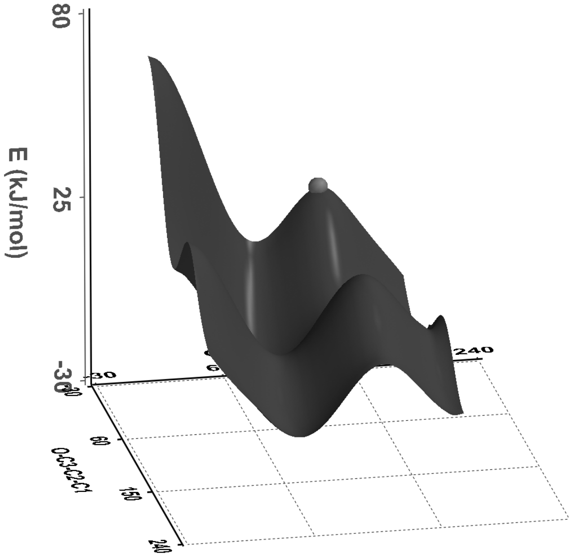
The XYZ Plot is reached by clicking on the **XYZ Plot** tab at the top of the dialog. This leads to a new dialog.


Plots
XY Plot
XYZ Plot
Z Axes
Molecule
Dipole (debye)
E HOMO (kcal/mol)
logKeq
Electrostatic(O1)
FitVals(Fit1)
OK
Cancel

X Axis: Molecule

Y Axis: Molecule

This is very similar to the XY Plot, except that it incorporates **X Axis** and **Y Axes** menus to designate quantities to be displayed along the X and Y axes, respectively, as well as a list of properties to be displayed along the Z axis. To construct a 3D plot, select one item from each of the **X Axis** and **Y Axis** menus, then *click* on one or more items from the **Z Axes** list and finally *click* on **OK**. A plot appears.



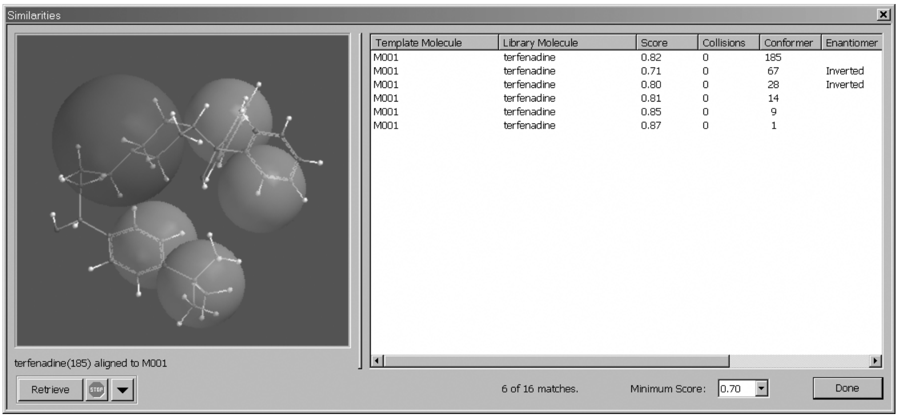
The plot can be moved about the screen. Select (*click* on) either the frame or on one of the curves (it will turn gold in response), then hold down the right mouse button and *drag* the mouse. The plot may also be scaled (expanded or shrunk) by first selecting either the frame or one of the curves and *dragging* the mouse while holding down both the right button and the **Shift** key. Finally, 3D plots (unlike 2D plots discussed earlier) may be rotated, by first selecting either the frame or one of the curves and *dragging* the mouse while holding down the left button.

Plots initially presented connect the data points with cubic splines. A variety of curve fits (linear, least squares, Fourier, etc.) as well as a variety of different presentation formats are available under the **Plot Properties** and associated dialogs (see **Properties** earlier in this chapter).

A plot may be deleted by first selecting (*clicking* on) **Delete** from the **Build** menu, or *clicking* on ✳, or holding down the **Delete** key, and then *clicking* on either the plot frame or on an individual curve. *Clicking* on the frame removes it and all associated curves, while *clicking* on a curve removes only this curve. However, the last curve deleted also deletes the frame. IR, UV/vis and NMR spectral plots may also be removed from the corresponding **Spectra** dialog.

Similarities...

The results of a similarity analysis based either on selected atoms in a structure or on a set of CFD's as a template may be viewed using the **Similarities** dialog.



Template Molecule	Library Molecule	Score	Collisions	Conformer	Enantiomer
M001	terfenadine	0.82	0	185	
M001	terfenadine	0.71	0	67	Inverted
M001	terfenadine	0.80	0	28	Inverted
M001	terfenadine	0.81	0	14	
M001	terfenadine	0.85	0	9	
M001	terfenadine	0.87	0	1	

terfenadine(185) aligned to M001

6 of 16 matches.

Minimum Score: 0.70

The box at the right of the dialog identifies each hit in terms of the identity of the Template, the Library molecule, and in the case where a library molecule has been expanded in terms of a set of diverse conformers, the identity of the conformer. It also provides a score* and, in the case where excluded volume CFD's are present in the template, the number of collisions between these elements and the library molecule. Finally, it indicates whether the enantiomer for the molecule included in the library has been inverted. Entries in the dialog may be sorted by score or number of collisions (as well as by the names of the template and library molecules) by *clicking* on the appropriate column header at the top of the box.

A minimum score can be set from the **Minimum Score** menu at the bottom right of the dialog. The number of matches that satisfy this minimum is reported.

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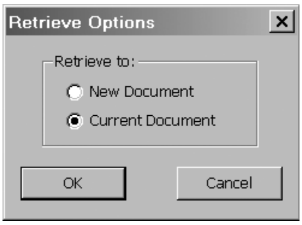
* The score is defined as $[(1-R^2)/N]$-penalty, where R^2 is the root mean square distance between template and library molecule centers and N is the number of similarity centers. Whereas molecule alignment as a prelude to similarity scoring is based on atomic, CFD and pharmacophore centers ***only***, penalties are given for alignments that lead to unfavorable steric interactions between template and library entries or (in the case of molecule alignment by CFD's) to incorrect orientation of hydrogen bond donor or acceptor CFD's. These are subtracted from the score based on R^2. 1 is a perfect score.

As hits are selected by *clicking* on them in the box, the library entry superimposed onto the template will be displayed in the window at the left of the dialog. This graphic may be manipulated (rotated, translated, scaled) with the usual mouse/keyboard commands (the cursor needs to be positioned inside the window). The display style cannot be altered, nor can any measurements be made.

The library entry associated with a particular hit may be retrieved (brought into ***Spartan's*** main window) by first selecting it and then *clicking* on the **Retrieve** button at the bottom of the **Similarities** dialog. The template cannot be retrieved. Retrieval can either be to a New Document or to the Current Document depending on the setting in the **Retrieve Options** dialog accessed by *clicking* on ▼ to the right of the **Retrieve** button.



Retrieve Options

Retrieve to:

○ New Document

● Current Document

Retrieval to the Current Document (that with the template) allows both the template and one or more hits from the library to be displayed simultaneously, with a full range of model styles and display options.

The **Similarities** dialog is closed by *clicking* on the **Done** button.

Chapter 17

The Search Menu

Functions available under the ***Search*** *menu provide substructure searching of the Cambridge Structural Database (CSD) of experimental X-ray structures, replacement from and searching by name, formula, molecular weight, isomer and substructure of the Spartan Molecular Database (SMD) of calculated structures, energies and properties, the Spartan Reaction Database (SRD) of calculated transition states, on-line access to the Protein Data Bank (PDB), extraction of ligands from PDB files, a facility for automatically guessing transition states for reactions based on their similarity to transition states in SRD and a procedure for identifying tautomers.*

✓ Databases
Ligands
Transition States
Tautomers

Databases (📖)

This provides access to the Cambridge Structural Database (CSD) of experimental X-ray crystal structures (**NAM**), the Spartan Molecular Database (SMD) of calculated structures, energies and molecular properties, the Spartan Reaction Database (SRD) of calculated transition states and the Protein Data Bank (PDB).* CSD, SMD and SRD may be searched based on substructure. In addition, both SMD and SRD may be searched by name, formula, molecular weight and isomer and SMD is accessed automatically whenever a database entry is selected on screen. PDB may be searched only by its PDB ID number.

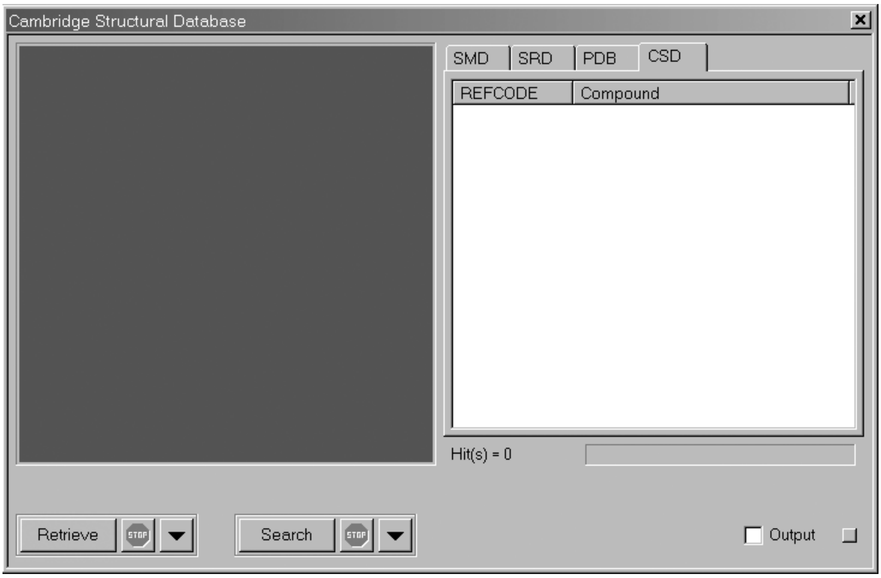
---

* CSD, SMD and SRD may be located on the local machine or on a remote server. Setup details are provided in **Appendix F** for CSD and in **Preferences** under the **Options** menu in **Chapter 18** for SMD and SRD. PDB is available only through web access.

Cambridge Structural Database (CSD)

The Cambridge Structural Database (CSD) is a collection of more than 350,000 experimental X-ray crystal structures for organic and organometallic molecules.* It is maintained by the Cambridge Crystallographic Data Centre (CCDC) and grows approximately 10% per year. CSD not only contains information about the molecular geometry, but also about the manner in which molecules pack in the solid state**. In short, the CSD represents a gold mine of detailed experimental structural information, and also serves to identify molecules that can be (and have been) synthesized and purified through crystallization.

Access to the data in CSD is via a substructure searching procedure. A molecule is first constructed and one or more attachment points are identified. *Clicking* on the **CSD** tab at the top of the **Database** dialog leads to the **CSD** dialog.



This contains a window at the left for previewing structures, a box at the right for listing hits on CSD and buttons at the bottom to control aspects of the search and subsequent transfer of CSD data into the file system. Both the preview window and the text box may be scaled independently. A substructure search is set up by specifying one or more of the following[*]:

---

* CSD is not included with ***Spartan*** but is available by subscription from CCDC (http://www.ccdc.cam.ac.uk/). For installation instructions, see **Appendix F** (**NAM**).

** ***Spartan***'s interface to CSD accesses only molecular information. Additional information may be accessed using CCDC's program ConQuest, that is supplied as part of the CSD subscription.

(i) **Attachment Points**

A free valence is designated as an attachment point by *clicking* on it. It will be marked with an orange cone. *Clicking* again removes the designation and the cone. Anything may be grown off an attachment point (including hydrogen). Free valences not designated as attachment points are assumed to be hydrogens.

(ii) **Wild-Card Atoms**

An atom may be designated as a wild card by *clicking* on it. An orange ball will surround the atom. *Clicking* again removes the designation and the ball. Wild card designation means that element type is unimportant, and use of wild card atoms will result in structures that incorporate variants of the original substructure with different atoms at designated positions.

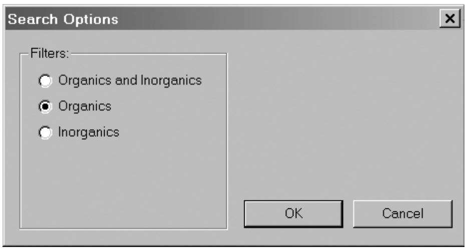
(iii) **Wild-Card Bonds**

A bond may be designated as a wild card by *clicking* on it. An orange cylinder will be drawn around it. *Clicking* on this cylinder removes the wild card designation and the cylinder. Wild-card bond designation means that bond type is unimportant. This is particularly important in certain heterocycles where bond typing may be ambiguous.

To limit a CSD search either to organic molecules only or to molecules containing transition metals only (each about half the total collection), bring up the **Search Options** dialog by *clicking* on ▼ to the right of the **Search** button at the bottom right of the dialog, and select **Organics** or **Inorganics** respectively.

---

[*] If nothing is specified, a search for an exact match is carried out (all free valences are assumed to be hydrogens).



Search Options

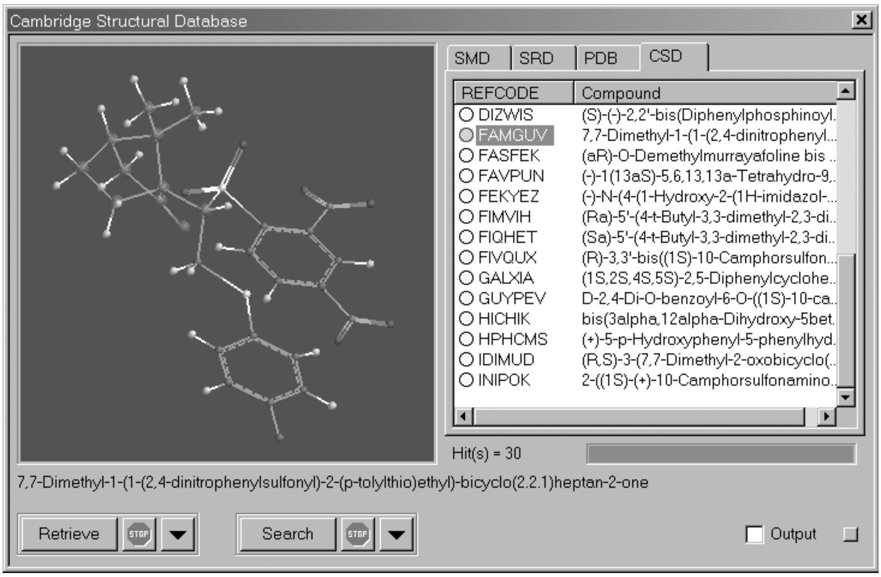
Filters:

○ Organics and Inorganics

● Organics

○ Inorganics

After a substructure has been specified, a search of CSD is initiated by *clicking* on the **Search** button at the bottom right of the dialog. If there are hits to be found, these will appear in the scroll box at the right of the dialog. The search can be terminated at any time by *clicking* on STOP to the right of the **Search** button at the bottom of the dialog. Once completed (or stopped), the CSD reference codes (**REFCODE**) and the names for the hits are displayed in the box and the number of hits is indicated immediately below. Structural data are available only for entries preceded by a filled yellow circle, although experimental references are available for all entries (see **Output** under the **Display** menu; **Chapter 16**). A ball-and-wire model for any entry for which a structure is available may be displayed in the window at the left of the dialog by *clicking* on its name in the box.



Cambridge Structural Database

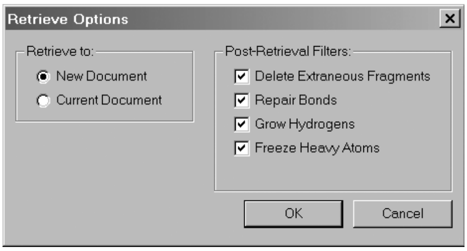
REFCODE	Compound
○ DIZWIS	(S)-(-)-2,2'-bis(Diphenylphosphinoyl.
○ FAMGUV	7,7-Dimethyl-1-(1-(2,4-dinitrophenyl..
○ FASFEK	(aR)-O-Demethylmurrayafoline bis ..
○ FAVPUN	(-)-1(13aS)-5,6,13,13a-Tetrahydro-9,.
○ FEKYEZ	(-)-N-(4-(1-Hydroxy-2-(1H-imidazol-..
○ FIMVIH	(Ra)-5'-(4-t-Butyl-3,3-dimethyl-2,3-di..
○ FIQHET	(Sa)-5'-(4-t-Butyl-3,3-dimethyl-2,3-di..
○ FIVQUX	(R)-3,3'-bis((1S)-10-Camphorsulfon...
○ GALXIA	(1S,2S,4S,5S)-2,5-Diphenylcyclohe..
○ GUYPEV	D-2,4-Di-O-benzoyl-6-O-((1S)-10-ca..
○ HICHIK	bis(3alpha,12alpha-Dihydroxy-5bet.
○ HPHCMS	(+)-5-p-Hydroxyphenyl-5-phenylhyd.
○ IDIMUD	(R,S)-3-(7,7-Dimethyl-2-oxobicyclo(..
○ INIPOK	2-((1S)-(+)-10-Camphorsulfonamino..

Hit(s) = 30

7,7-Dimethyl-1-(1-(2,4-dinitrophenylsulfonyl)-2-(p-tolylthio)ethyl)-bicyclo(2.2.1)heptan-2-one

The model can be manipulated (rotated, translated, scaled) inside the window with the usual mouse/keyboard commands (you need to position the cursor inside the window).

The structure is ***exactly as it appears in CSD***. In particular, it may contain two or more different molecules, two or more different conformations of the same molecule and/or extraneous molecules (most commonly solvent molecules and counterions). Hydrogens will be present only where they have been assigned in the experimental structure. The structure may also contain errors in bonding due to uncertainties in the original data. Modifications to the CSD entry to address these issues may be made prior to transfer to the file system using the **Retrieve Options** dialog. This is accessed by *clicking* on ▼ to the right of the **Retrieve** button at the bottom of the **CSD** dialog.


Retrieve Options

Retrieve to:
● New Document
○ Current Document

Post-Retrieval Filters:
☑ Delete Extraneous Fragments
☑ Repair Bonds
☑ Grow Hydrogens
☑ Freeze Heavy Atoms

(i) **Delete Extraneous Fragments**
If *checked*, deletes any detached molecules that do not contain the original substructure.

(ii) **Repair Bonds**
If *checked*, attempts to fix bonding errors based on the actual geometry in CSD and on normal valence rules.

(iii) **Grow Hydrogens**
If *checked*, grows hydrogens wherever they appear to be missing, based on the actual geometry and on normal valence rules. This function is also available under **Grow Hydrogens** in the **Molecule Utilities** dialog (**Chapter 16**).

(iv) **Freeze Heavy Atoms**
If *checked*, freezes all atoms except for hydrogens. This allows experimental X-ray hydrogen positions to be refined

using molecular mechanics or quantum chemical methods, while maintaining the heavy atom skeleton.*

(v) **Retrieve to:**
Selection of **New Document** means that the search results are to be stored in a new document and leads to a request for a document name, whereas selection of **Current Document** results in the retrieved molecules being appended to the end of the current document.

The **Retrieve Options** dialog is dismissed with all changes to existing settings maintained by *clicking* on **OK**. *Clicking* on **Cancel** or on ☒ also dismissed the dialog but any changes to settings are lost.

Retrieval is accomplished by first selecting (*clicking* on) one or more hits in the scroll box and then pressing the **Retrieve** button at the bottom of the **CSD** dialog. The **Shift** and **Ctrl** keys may be used in the usual way to specify retrieval of multiple hits. Retrieval can be stopped at any time by *clicking* on STOP to the right of the **Retrieve** button at the bottom of the **CSD** dialog.

Spartan Molecular Database (SMD)

The version of the **S**partan **M**olecular **D**atabase (SMD) included with ***Spartan*** comprises two collections. The first ***small molecules*** collection comprises approximately 140,000 molecules, the structures, energies, and selected properties of most of which have been obtained from five different theoretical models: Hartree-Fock models with 3-21G and 6-31G* basis sets, EDF1/6-31G* and B3LYP/6-31G* density functional models and the MP2/6-31G* model. Infrared spectra have been provided for approximately 50,000 molecules at one or more levels of calculation, UV/visible spectra primarily from B3LYP models for approximately 2,000 molecules and NMR spectra from the HF/6-31G* and B3LYP/6-31G* models for approximately 20,000 molecules. In addition, Hartree-Fock, B3LYP and MP2 calculations with larger basis sets (primarily 6-311+G**) are provided for approximately 2,000 molecules. In total, the ***small molecules*** collection in SMD contains about 400,000 data records. It is expected to grow at 25%/year.

---

* Hydrogen positions may be refined using molecular mechanics using **Minimize** under the **Build** menu; **Chapter 14**. Refinement using quantum chemical models is specified in the **Calculations** dialog (**Calculations...** under the **Setup** menu; **Chapter 15**) by way of **Frozen Atoms** (**Freeze Center** under the **Geometry** menu; **Chapter 13**). Additional discussions provided in **Chapter 15**.

The second collection comprises molecules that have been found to bind to proteins or nucleotides (***ligands***) as abstracted from the Protein Data Bank. Each molecule is represented by the conformer (or conformers) found in the protein or nucleotide complex. This collection is intended to be used as a library in similarity analysis.

An entry in SMD is specified by a three-dimensional structure encoded as a one-dimensional (SMILES like) character string together with a theoretical model. Structural isomers, for example, *cis-trans* isomers are distinguished as are diastereomers, but enantiomers are not distinguished.

SMD is open-ended and users may construct their own data collections with additional molecules and/or results from additional theoretical models on existing molecules (see **Appendix G**). Additional collections of organic molecules, each molecule represented in terms of a set of diverse conformers and intended for use in similarity analysis, are available from Wavefunction, Inc.

While the majority of entries in the ***small molecules*** collection are represented in terms of a single (lowest-energy) conformer (see text box below), some entries are represented in terms of two or more conformers. In these cases, the available conformers will be ranked according to energy, and the user needs to choose among them.

The individual entries supplied in the ***small molecules*** collection of SMD have been obtained according to the following recipe.

1. Identify the lowest-energy conformer using molecular mechanics and the MMFF (Merck) force field. Systems with only a few degrees of conformational freedom are searched systematically guaranteeing location of the global minimum, while a Monte-Carlo search is applied to more complicated systems. The latter does not guarantee location of the global minimum.

2. Starting from the best conformer located, perform a geometry optimization using the appropriate quantum chemical model. This generally means that all quantum chemical calculations for a particular molecule will refer to the same conformer.

The ***ligands*** collection in SMD comprises approximately 1250 small molecules bound to proteins/nucleotides contained in the January 6, 2005 snapshot of PDB. It contains approximately 1650 entries in total, and has been constructed according to the following procedure:

1. Restrictions

   H, C, N, O, S and halogens only
   $200 \leq$ molecular weight ≤ 700
   LogP ≤ 7
   number of hydrogen-bond acceptor sites ≤ 14
   number of hydrogen-bond donor sites ≤ 7

   In addition, ligands that are incomplete (according to the compound that is supposed to be incorporated) or are severely distorted have been excluded.

2. Refinement

   Allow atoms to float as much as 0.05A from experimentally assigned positions
   Add hydrogens
   Correct obvious bonding errors

3. Eliminate duplicates, that is, ligands in the same conformation that bond at different sites in a protein/nucleotide or bond to different proteins/nucleotides.

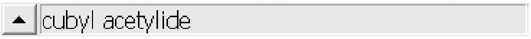
A listing of PDB identification codes for all proteins/nucleotides that incorporate the ligand in a particular conformation may be added to the spreadsheet by typing "PDBids" in an empty column header. A maximum of ten codes are supplied, with the existence of additional codes signaled by the word "more" at the end of the list.

The collections in SMD may be accessed in several ways. Most important for the ***small molecules*** collection is exact replacement of a structure with a database entry corresponding to a particular quantum chemical model, and location of entries in the database (corresponding to one or more quantum chemical models) that contain a particular substructure. The latter is strictly analogous to the way

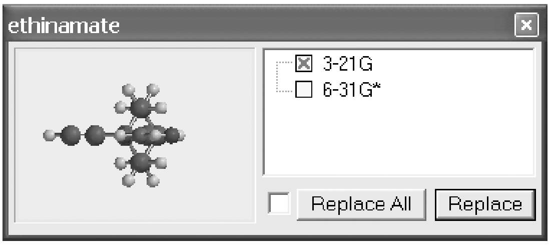
Spartan accesses the Cambridge Structural Database (see previous discussion). The ***small molecules*** collection may also be searched by molecule name, chemical formula, molecular weight and isomer.

Replacement

The existence of one or more entries in the ***small molecules*** collection (corresponding to different quantum chemical models) for the selected molecule is signaled by its name being displayed at the bottom of the screen.



Details are provided by *clicking* on ▲ to the immediate left of the molecule name (it then changes to ▼). This brings up a dialog that comprises a viewing screen on the left and a list of quantum chemical models for which database entries exist on the left.



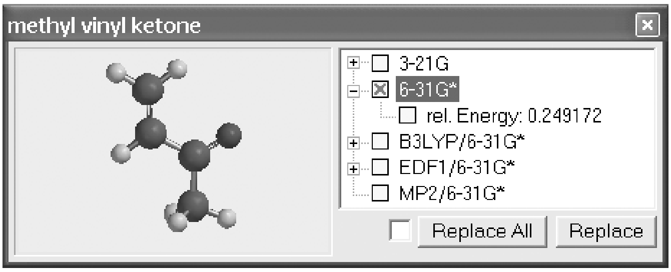
☒ 3-21G
☐ 6-31G*

Upon initial entry, the topmost entry in the list is *checked* and a ball-and-spoke model corresponding to its structure appears in the viewing screen. This model may be rotated, translated and scaled using the usual mouse/keyboard commands (you need to position the cursor inside the viewing area). The model may be made to tumble automatically by *checking* the box to the left of **Replace All** at the bottom of the dialog. Model style may not be changed. A different database entry (corresponding to a different quantum chemical model) may be selected by *checking* the box to the left of the name of the quantum chemical model in the dialog.

The selected (on-screen) molecule may be replaced by the selected database entry by *clicking* on **Replace** at the bottom of the dialog. (Replacement can be undone by selecting **Undo** from the **Edit** menu;

see **Chapter 11**). Note that replacement destroys all information associated with the molecule being replaced.

Some database entries also comprise information on higher-energy conformers (in addition to that on the presumed ground-state conformer). These entries are designated by a ⊞ icon to the left of the check box. *Checking* this icon leads to an expanded entry that allows access to these higher-energy conformers, as well as provides their relative energies (in kJ/mol).



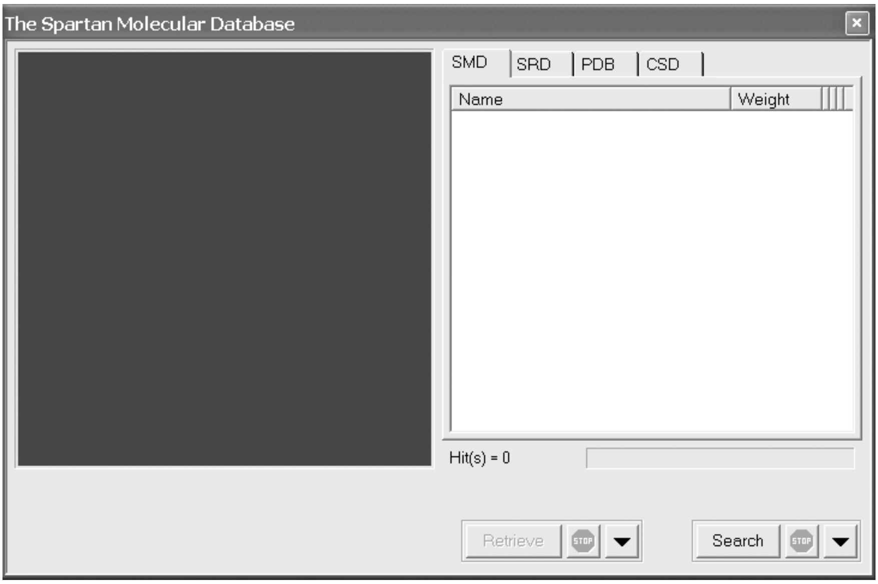
Entries are selected as before, after which they may be examined in the viewing screen or used to replace the on-screen molecule.

In the event that the selected (on-screen) molecule is a member of a list, it is possible to replace all members of the list for which database entries for the specified level of calculation are available. This is accomplished as above except that **Replace All** instead of **Replace** is used. A warning message is provided prior to replacement. Note that the lowest-energy conformer for all other (non-selected) molecules in the list is used even though a higher-energy conformer may be indicated for the selected molecule. (Replacement of list entries with non lowest-energy conformations needs to be done one by one using **Replace** instead of **Replace All**.) Molecules in the list for which there are no database entries at the specified level of calculation are not affected.

Substructure Searching

Substructure searching from SMD is very similar to that from CSD described previously, in that all that is required is a three-dimensional structure and specification of one or more growth points. It differs from CSD in that SMD contains multiple sets of results (corresponding to different theoretical models), and it is necessary to specify prior to the search which model (or which set of models) is requested.

Access to SMD is provided by *clicking* on the **SMD** tab at the top of the **Database** dialog. This gives rise to the **SMD** dialog.

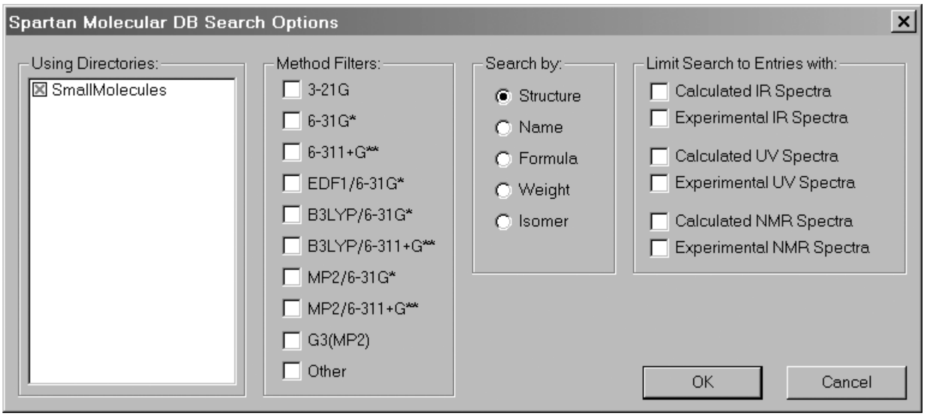


Hit(s) = 0

Like the **CSD** dialog, this dialog contains a window on the left for previewing structures and a box on the right for listing hits on SMD, as well as buttons at the bottom to control various aspects of the search and subsequent transfer of data into ***Spartan***'s file system. Both the preview window and the text box can be sized independently.

A substructure search is set up by specifying one or more attachment points, in the same manner as for CSD (see previous discussion). Wild-card atoms and bonds are not available.

Prior to starting the actual search, it is necessary to verify that a structure search is desired and to specify which theoretical model or set of models are to be included. Optionally, the search can be limited to database entries that contain calculated and/or experimental IR, UV/visible and/or NMR spectra. Model specification and search limitations are set in the **Search Options** dialog that is reached by *clicking* on ▼ to the right of the **Search** button.



Spartan Molecular DB Search Options ☒

Using Directories:
☒ SmallMolecules

Method Filters:
☐ 3-21G
☐ 6-31G*
☐ 6-311+G**
☐ EDF1/6-31G*
☐ B3LYP/6-31G*
☐ B3LYP/6-311+G**
☐ MP2/6-31G*
☐ MP2/6-311+G**
☐ G3(MP2)
☐ Other

Search by:
● Structure
○ Name
○ Formula
○ Weight
○ Isomer

Limit Search to Entries with:
☐ Calculated IR Spectra
☐ Experimental IR Spectra
☐ Calculated UV Spectra
☐ Experimental UV Spectra
☐ Calculated NMR Spectra
☐ Experimental NMR Spectra

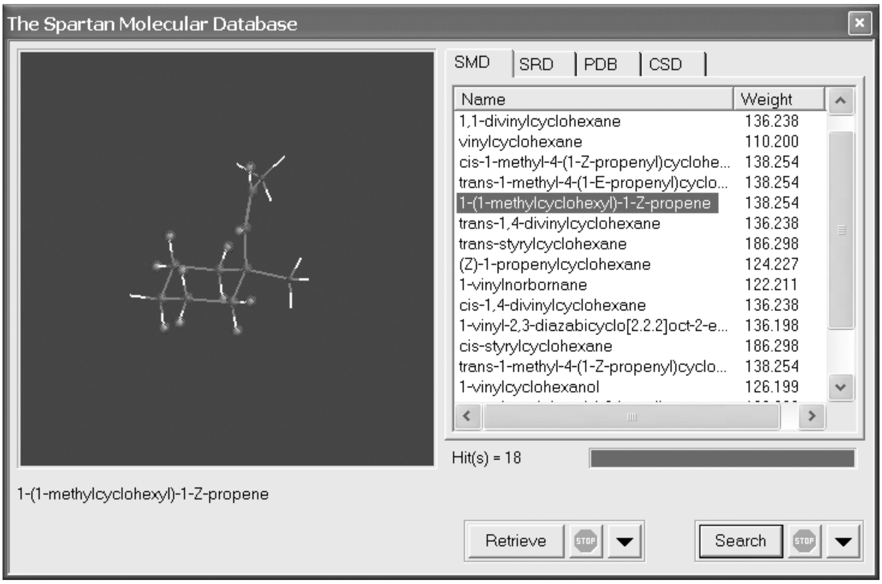
OK Cancel

Checking the appropriate boxes specifies the appropriate model(s). Specification of **Other** provides access to data with theoretical models other than those explicitly mentioned in the dialog.

Check boxes in the **Search Options** dialog allow restriction of the search to database entries that include IR, UV/visible and/or NMR spectra, and/or for molecule where the corresponding experimental spectra are known to exist in on-line databases accessible to ***Spartan***. These restrictions act in an additive manner, for example, *checking* **Calculated IR Spectra** and **Calculated NMR Spectra** restricts the search to database entries containing both of these quantities.

Clicking on **OK** removes the dialog. (*Clicking* on **Cancel** or on ☒ also removes the dialog, but selections are not made.)

Following specification of attachment points and designation of theory level(s) and spectral requirements, a search on SMD is carried out by *clicking* on the **Search** button at the bottom right of the dialog. If there are hits, they will begin to appear in the box at the right of the dialog after a few seconds. The search may be terminated at any time by *clicking* on 🛑 to the right of the **Search** button at the bottom right of the dialog. Database hits are displayed in the box at the right of the dialog[*]. A 3D structure for a particular hit may be previewed by *clicking* on its name in the box. The ball-and-wire model is displayed in the window at the left of the dialog, and its name appears immediately below the window.



Name	Weight
1,1-divinylcyclohexane	136.238
vinylcyclohexane	110.200
cis-1-methyl-4-(1-Z-propenyl)cyclohe...	138.254
trans-1-methyl-4-(1-E-propenyl)cyclo...	138.254
1-(1-methylcyclohexyl)-1-Z-propene	138.254
trans-1,4-divinylcyclohexane	136.238
trans-styrylcyclohexane	186.298
(Z)-1-propenylcyclohexane	124.227
1-vinylnorbornane	122.211
cis-1,4-divinylcyclohexane	136.238
1-vinyl-2,3-diazabicyclo[2.2.2]oct-2-e...	136.198
cis-styrylcyclohexane	186.298
trans-1-methyl-4-(1-Z-propenyl)cyclo...	138.254
1-vinylcyclohexanol	126.199

Hit(s) = 18

1-(1-methylcyclohexyl)-1-Z-propene

The model may be manipulated (rotated, translated, scaled) inside the window in the usual way, but the model style cannot be changed, nor can geometrical measurements be made. These require that selected entries be transferred to ***Spartan***'s file system (see discussion following).

Searching Name, Formula, Weight, Isomer

It is also possible to search SMD by molecule name, by molecule formula, by molecular weight, or by isomer. Specification is provided under **Search by** in **Search Options** dialog.

(i) **Structures**
Search by structures is described earlier in this chapter.

(ii) **Name**
Selection of **Name** followed by *clicking* on **OK** leads to a

---

[*] Normally, only the name of the molecule is visible, but molecular weight and theoretical model may also be displayed by appropriately *sliding* the header cells at the top of the box.

box **By Name** at the bottom right of the **SMD** dialog. The search will return all entries that include whatever text string is entered into this box. For example, typing in ***toluene***, will not only result in toluene, but also molecules like para-toluenesulfonic acid and 4-chloro-2-fluorotoluene.

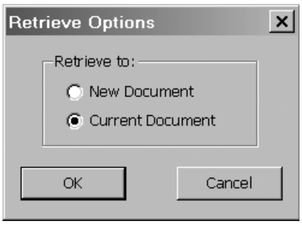
(iii) **Formula**
Selection of **Formula** followed by *clicking* on **OK** leads to a box **By Formula** at the bottom right of the **SMD** dialog. A formula of the form $C_xH_yHet_z$... where C and H stand for carbon and hydrogen respectively and Het stands for other elements (heteroatoms). x, y, z are integers and are required, for example, the formula for nitrobenzene needs to be written as ***C6H5N1O2***. The order of atoms is irrelevant. The search will return all entries with this formula. For example, the formula ***C6H5N1O2*** will return not only nitrobenzene but also molecules like phenyl nitrite and pyridine-4-carboxylic acid. Formula search is one way to gather the isomers of a particular molecule.

(iv) **Weight**
Selection of **Weight** followed by *clicking* on **OK** leads to a text box **By Weight** at the bottom right of the **SMD** dialog. The search will return all entries with the specified molecular weight ± 0.05 amu.

(v) **Isomer**
Selection of **Isomer** followed by *clicking* on **OK** specifies that all isomers of the selected molecule will be returned.

Retrieval

Prior to retrieval of one or more database hits, it is necessary to specify a destination. This is accomplished with the **Retrieve Options** dialog, brought up by *clicking* on ▼ to the right of the **Retrieve** button at the bottom left of the **SMD** dialog.



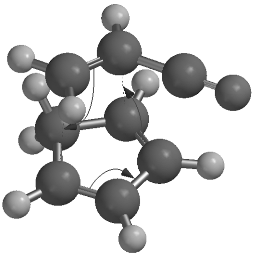
Selection of destination is accomplished by *toggling* between **New Document** and **Current Document**. Selection of the former results in request for a file name; selection of the latter results in the retrieved molecules being appended to the end of the current document. The **Retrieve Options** dialog is dismissed by *clicking* on **OK**. *Clicking* on **Cancel** or on ☒ also dismissed the dialog but any changes to settings are lost.

Retrieval is accomplished by first selecting (*clicking* on) one or more hits in the box and then pressing the **Retrieve** button at the bottom of the **SMD** dialog. The **Shift** and **Ctrl** keys may be used to specify retrieval of multiple hits. A block of entries may be specified by *clicking* on the top (or bottom) entry, then holding down the **Shift** key and finally *clicking* on the bottom (or top) entry. Multiple entries may be specified by *clicking* on each in turn while holding down the **Ctrl** key. Retrieval may be stopped at any time by *clicking* on STOP to the right of the **Retrieve** button at the bottom of the **SMD** dialog.

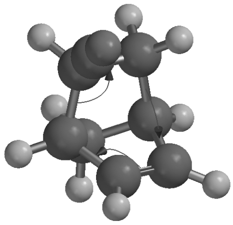
Spartan Reaction Databases (SRD)

The **S**partan **R**eaction **D**atabase (**SRD**) is a collection of transition states for approximately 1,500 organic and organometallic reactions obtained from one or more of the following theoretical models: AM1, PM3, HF/3-21G and HF/6-31G*. In addition to the (transition-state) geometry and the energy (heat of formation for semi-empirical models) each data entry contains the infrared spectrum.

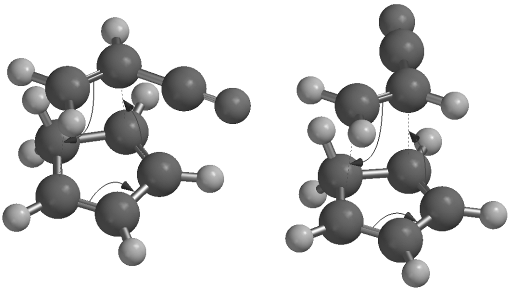
An entry in SRD is in terms of a three-dimensional structure (corresponding to the reactants or the product), together with an appropriate set of reaction arrows (connecting the reactants to the product or vice versa) and designation of theoretical model. For example, an entry for the Diels-Alder reaction of cyclopentadiene and acrylonitrile is as follows:



while that for the corresponding retro Diels-Alder is as follows:



Note, that stereoisomers are distinguished. For example, reactions leading to *endo* and *exo* Diels-Alder adducts are distinct.

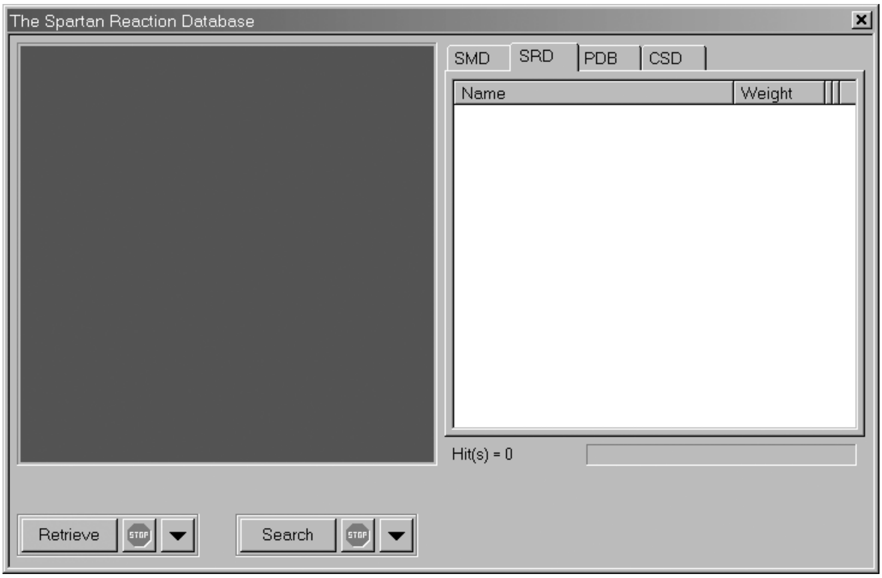


Additional information about drawing reaction arrows is provided later in this chapter under **Transition States**.

SRD is open-ended and users may construct their own data collections with additional reactions and/or results from additional theoretical models on existing reactions (see **Appendix G**).

Substructure Searching

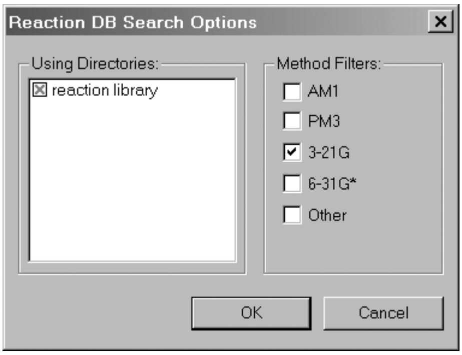
Substructure searching from SRD is very similar to that from SMD described previously. Access to SRD is provided by *clicking* on the **SRD** tab at the top of the **Database** dialog. This gives rise to the **SRD** dialog.



Like the **SMD** dialog, the **SRD** dialog contains a window on the left for previewing structures and a box on the right for listing hits on SRD, as well as buttons at the bottom to control various aspects of the search and subsequent transfer of data into ***Spartan***'s file system. Both the preview window and the text box can be sized independently.

A substructure search is set up by specifying one or more attachment points on the reactant (product) structure that has been augmented with reaction arrows, much in the same manner as for SMD (see previous discussion).

Prior to starting the actual search, it is necessary to verify that a structure search is desired and to specify which theoretical model or set of models are to be included. Model specification and type of search are set in the **Search Options** dialog that is reached by *clicking* on ▾ to the right of the **Search** button at the bottom right of the dialog.


Reaction DB Search Options

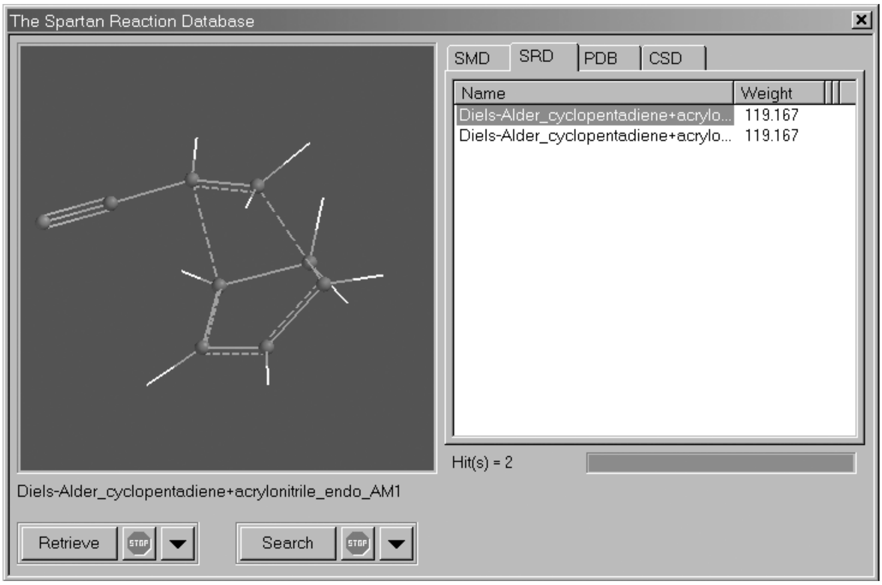
Using Directories:
☒ reaction library

Method Filters:
☐ AM1
☐ PM3
☑ 3-21G
☐ 6-31G*
☐ Other

Checking the appropriate boxes specifies the appropriate model(s).

Clicking on **OK** removes the dialog. (*Clicking* on **Cancel** or on ☒ also removes the dialog, but selections are not made.)

Following specification of structure/reaction arrows, attachment points and designation of theory level(s), a search on SRD is carried out by *clicking* on the **Search** button at the bottom right of the dialog. If there are hits, they will begin to appear in the box at the right of the dialog after a few seconds. The search may be terminated at any time by *clicking* on 🛑 to the right of the **Search** button at the bottom right of the dialog.


The Spartan Reaction Database

Name	Weight
Diels-Alder_cyclopentadiene+acrylo...	119.167
Diels-Alder_cyclopentadiene+acrylo...	119.167

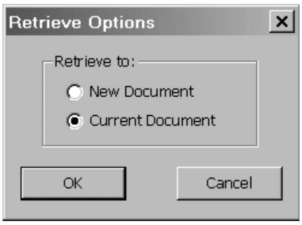
Hit(s) = 2

Diels-Alder_cyclopentadiene+acrylonitrile_endo_AM1

Database hits are displayed in the box at the right of the dialog[*]. A 3D structure for a particular hit may be previewed by *clicking* on its name in the box. A ball-and-wire model of the transition state with bonding consistent with the reactant and associated reaction arrows is displayed in the window at the left of the dialog, and its name appears immediately below the window. The model may be manipulated inside the window in the usual way, but the model style cannot be changed, nor can geometrical measurements be made. These require that selected entries be transferred to ***Spartan***'s file system.

Retrieval

Prior to retrieval of one or more database hits, it is necessary to specify a destination. This is accomplished with the **Retrieve Options** dialog, brought up by *clicking* on ▾ to the right of the **Retrieve** button at the bottom left of the **SRD** dialog.



Retrieve Options

Retrieve to:

○ New Document

● Current Document

Selection of destination is accomplished by *toggling* between **New Document** and **Current Document**. Selection of the former results in request for a file name; selection of the latter results in the retrieved molecules being appended to the end of the current document. The **Retrieve Options** dialog is dismissed by *clicking* on **OK**. *Clicking* on **Cancel** or on ☒ also dismissed the dialog but any changes to settings are lost.

Retrieval is accomplished by first selecting (*clicking* on) one or more hits in the box and then pressing the **Retrieve** button at the bottom of the **SMD** dialog. The **Shift** and **Ctrl** keys may be used to specify retrieval of multiple hits. A block of entries may be specified by *clicking* on the top (or bottom) entry, then holding down the **Shift** key and finally *clicking* on the bottom (or top) entry. Multiple entries may be specified by *clicking* on each in turn while holding down the **Ctrl** key. Retrieval may be stopped at any time by *clicking* on STOP to the right of the **Retrieve** button at the bottom of the **SRD** dialog.

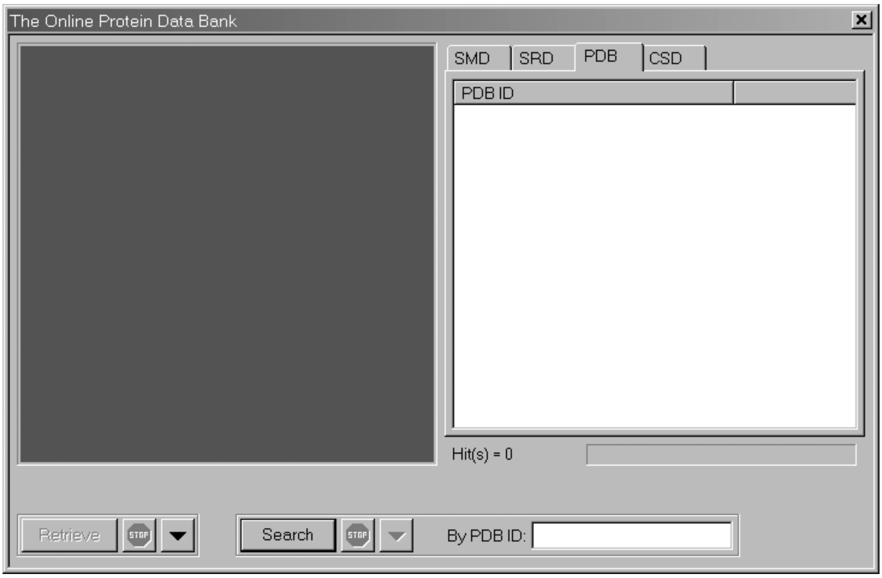
---

[*] Normally, only the name of the reaction is visible, but molecular weight and theoretical model may also be displayed by appropriately *sliding* the header cells at the top of the box.

Protein Data Bank (PDB)

Spartan provides on-line access to the Protein Data Bank (PDB)[*] comprising upwards of 37,000 protein and nucleotide structures.

Access to PDB is provided by *clicking* on the **PDB** tab at the top of the **Database** dialog. This gives rise to the **PDB** dialog.



This contains a window on the left for previewing structures and a scroll box on the right for listing hits on PDB, as well as buttons at the bottom to control transfer of data into the file system.

To access a PDB structure, enter the four character identification code in the box to the right of **By PDB ID** at the bottom of the dialog and *click* on the **Search** button. If the PDB entry contains more than one structure (common with protein structures obtained from NMR spectroscopy) and/or the PDB ID yields more than one entry, all structures will be returned in a single document.

---

[*] The web address is http://www.rcsb.org.

To retrieve a structure, *click* on the PDB ID (or, using the **Ctrl** and **Shift** keys, set of ID's) inside the box in the dialog and then *click* on the **Retrieve** button. The **Retrieve Options** dialog (not shown) designates whether the structure will go into a **New Document** or be appended onto the **Current Document**.

Ligands (▾)

Spartan provides a facility for extracting ligands from PDB files[*] either as molecular structures or as footprints (pharmacophores) that these structures leave behind. The latter is separated into three parts, the first two of which follow from the molecular structure of the ligand and the third which follows from the immediate (protein or nucleotide) environment:

i) hydrogen-bond donor/acceptor sites and positive/negative ionizable sites
ii) hydrophobes
iii) excluded volumes

A pharmacophore can be constructed by requiring (i) to account for hydrogen-bonded and electrostatic interactions and (optionally) ***either*** (ii) or (iii) to account for steric interactions. Selection of (ii) leads to a pharmacophore that is visually simpler, but selection of (iii) may provide a more realistic picture.

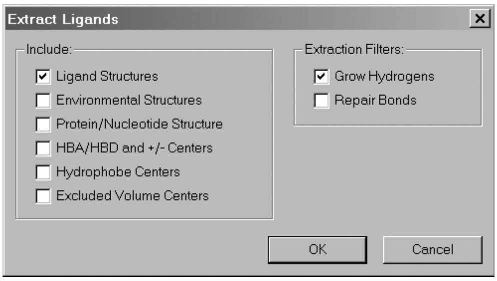
Selection of **Ligands** leads to a message at the bottom of the screen.

Select Ligands.

Ligands in PDB files are represented as a series of transparent spheres much like a space-filling model. *Clicking* on a ligand selects it and displays the PDB **HET name** at the bottom of the screen (if a HET name is available). Multiple ligands may be selected if desired by holding down on the **Ctrl** key. All ligands may be selected by *clicking* on the **Select All Ligands** button at the bottom right of the screen. After one or more ligands have been selected, *clicking* on the **Extract Ligands** button at the bottom right of the screen brings up the **Extract Ligands** dialog.

---

[*] This capability is not restricted to files in PDB, but extends to files written in PDB format.


Extract Ligands

Include:
☑ Ligand Structures
☐ Environmental Structures
☐ Protein/Nucleotide Structure
☐ HBA/HBD and +/- Centers
☐ Hydrophobe Centers
☐ Excluded Volume Centers

Extraction Filters:
☑ Grow Hydrogens
☐ Repair Bonds

This allows selection of whether **Ligand Structures** or one or more pharmacophore elements (**HBA/HBD and +/- Centers**, **Hydrophobe Centers** including aromatic centers, **Excluded Volume Centers**) or ***both*** structure and one or more pharmacophore elements are to be abstracted from the PDB file, and whether amino acid and/or nucleotide residues in close hydrogen-bonding or charge-charge contact with the ligand (**Environmental Structures**) are to be identified. It also allows the **Protein/Nucleotide Structure** (minus all ligands) to be extracted.

In the case of extraction of **Ligand Structures**, the **Extract Ligands** dialog also provides a set of utilities:

(i) **Grow Hydrogens**
If *checked*, grows hydrogens wherever they appear to be missing, based on the actual geometry and on normal valence rules. This function is also available under **Grow Hydrogens** in the **Molecule Utilities** dialog (**Chapter 16**).

(ii) **Repair Bonds**
If *checked*, attempts to fix bonding errors based on the actual geometry in the PDB entry, and on normal valence rules.

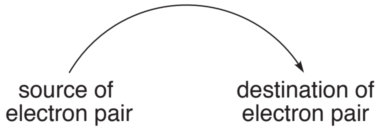
Clicking on **OK** at the bottom of the **Extract Ligands** dialog extracts the ligand(s) or pharmacophore(s), placing them in a single new (unnamed) document. *Clicking* on **Cancel** dismisses the dialog without ligand (pharmacophore) extraction.

Transition States (↷)

Spartan provides a facility for automatically guessing transition state geometries based on the similarity of the reaction of interest with one or more entries in ***Spartan***'s reaction database[*]. An exact hit is possible, in which case the guess will be the exact transition state[**]. More commonly, this will not be the case, and ***Spartan*** will attempt to provide as close a match as possible with a database entry. This will generally involve a less substituted system or one in which substituents differ. Here, ***Spartan*** will use those parts of the structure of the transition state in the database that are common, and will optimize the remaining parts (using molecular mechanics). No conformational searching is performed, and it may be essential for the reactants to be properly oriented to reflect the desired stereochemical outcome of the reaction.

Where a reaction is completely unknown to the database, a fallback technique similar to the linear synchronous transit method is automatically invoked.

Input to ***Spartan***'s transition-state guessing procedure will be very familiar to (organic) chemists, in that it is based on reaction arrows. The reaction is specified using curved arrows, where each arrow identifies the movement of one electron pair. The direction of electron flow follows customary practice:



---

[*] The Spartan Reaction Database (SRD) may also be directly searched by substructure. See discussion earlier in this chapter.

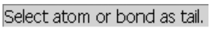
[**] More precisely, the transition state supplied in this case will be exact for the particular theoretical model entered in the database. At the present time, the majority of database entries derive from very simple (semi-empirical and Hartree-Fock) quantum chemical models.

There are two possible sources of an electron pair and three possible destinations, leading to six combinations:

lone pair → lone pair	move lone pair
lone pair → bond	use lone pair to increase bond order
lone pair → space between atoms	use lone pair to create new (single) bond
bond → lone pair	decrease bond order to make lone pair
bond → bond	decrease order of one bond to increase order of another bond
bond → space between atoms	decrease order of one bond to make a new (single) bond

The first of these is a null operation, and its inclusion has no effect.

Selecting **Transition States** results in a message at the bottom left of the screen.



Select atom or bond as tail.

The tail of the arrow corresponds to the source of the electron pair. If the source is a lone pair, then select the appropriate atom. If the source is a bond, then select the appropriate bond. *Clicking* on an atom or bond highlights (colors gold) the atom or bond and leads to a new message at the bottom left of the screen.

Select atom, bond, or two atoms as head. If two atoms hold SHIFT key.

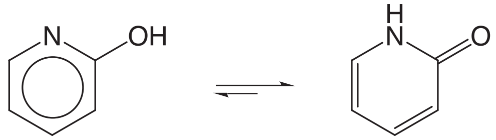
The head of the arrow corresponds to the destination of the electron pair. If the destination is an atom (leading to a lone pair), then select this atom. If the destination is an existing bond (leading to an increase in bond order from single → double → or double → triple), then select the appropriate bond. If no bond presently exists at the destination, *press* the **Shift** key and select the two atoms that will become bonded. These operations result in a curved arrow being drawn on the reactant structure. This extends from an atom, or the center of a bond to an atom, or the center of a bond, or the center of a dotted line that has been drawn between atoms that are to be bonded. The original message returns to the bottom left of the screen.

The process (tail selection followed by head selection) is repeated as necessary to fully define the reaction. Incorrect reaction arrows may be removed by selecting **Delete** from the **Build** menu (✳) followed by *clicking* on the arrow to be deleted. In the latter case, you need to again select **Transition States** (↷) in order to continue arrow selection. Alternatively, *click* on the arrow(s) to be deleted while holding down the **Delete** key

After all reaction arrows have been properly designated, *click* on ⟳ at the bottom right of the screen to replace the reactant with a guess at the transition state. In the event that the guess is unreasonable, this operation may be undone (select **Undo** from the **Edit** menu). This allows you to review your assignment of arrows and make changes as needed.

Tautomers (⚲)

Spartan provides a facility to automatically identify tautomers, that is, isomers arising from (rapid) transfer of hydrogens among heteroatoms. Tautomer identification is especially important in dealing with heterocyclic compounds where two or more different tautomers may exist in equilibrium and the identity of the dominant tautomer may not be obvious, for example.

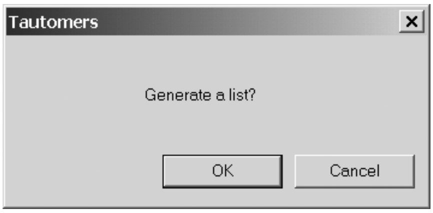


2-hydroxypyridine 2-pyridone

This, of course, has consequences in trying to locate a particular molecule in a database where it may be represented by a different tautomer.

The procedure incorporated into ***Spartan*** is limited to tautomers involving nitrogen, oxygen, phosphorous and sulfur. Tautomers involving carbon, in particular, have been excluded. In addition, zwitterion tautomers, for example, $H_3N^+CH_2CO_2^-$ as a tautomer of glycine, are not considered. Within these limits, all possible tautomers will be identified. Note, however, that there may be duplicates as well as tautomers that are likely to be highly unfavorable.*

The existence of tautomers is automatically sensed and is signaled by the word **Tautomer** displayed at the bottom right of the screen. If tautomers exist, individual structures may be examined or a complete list of structures generated by selecting **Tautomers** from the **Search** menu (or *clicking* on the icon on the top of the screen). Following this, *clicking* on the step buttons at the bottom right of the screen moves through the list of tautomers. Any one of these may be used in place of the original. The full list of tautomers may be generated by *clicking* on ▼ (at the bottom right of the screen). This leads to a dialog.



Generate a list?

Clicking on **OK** dismisses the dialog and leads to a new (unnamed) document containing the full list of tautomers. (The original document is unaffected.) *Clicking* on either **Cancel** or ☒ dismisses the dialog without generating a tautomer list.

As tautomers are generated without consideration of steric crowding, it is a good idea to minimize each in turn (**Minimize** under the **Build** menu; **Chapter 14**) prior to using them for quantum chemical calculations.

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* Of course, once a complete list of tautomers has been generated it is straightforward to calculate their relative energies using quantum chemical models.

Chapter 18

The Options Menu

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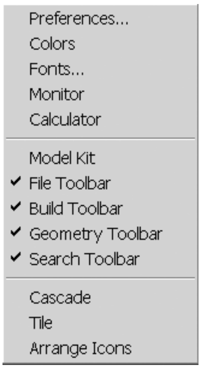
*Functions under the **Options**[*] menu set colors, fonts and user preferences and monitor jobs.*


Preferences...
Colors
Fonts...
Monitor
Calculator
Model Kit
✓ File Toolbar
✓ Build Toolbar
✓ Geometry Toolbar
✓ Search Toolbar
Cascade
Tile
Arrange Icons

Preferences...

This sets up preferences relating to the graphical user interface (**Settings**), to molecule displays (**Molecules**), changing default van der Waals radii (**VDW Radii**). It also specifies the locations for databases (**Paths**) and identifies remote servers (**Hosts**). Selection results in one of five dialogs, depending on which tab has been selected in the previous entry. To exit a **Preferences** dialog *click* on **OK**. *Clicking* on **Cancel** or on ☒ exits the dialog without instituting any changes. The **Preferences** dialog may vary slightly between Windows, Macintosh and Linux versions.

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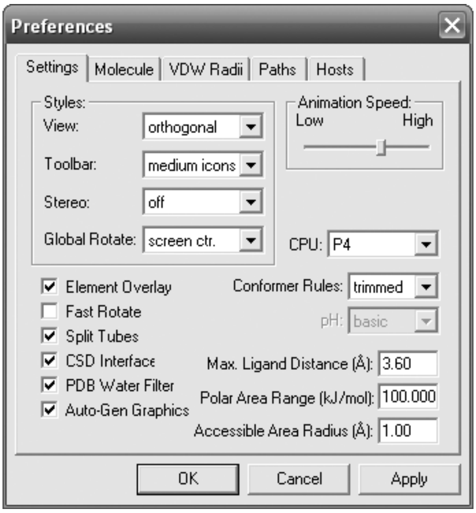
[*] **Preferences** are also under the ***Spartan'06*** menu on the Macintosh version.

Settings



View: orthogonal
Toolbar: medium icons
Stereo: off
Global Rotate: screen ctr.
CPU: P4
☑ Element Overlay
☐ Fast Rotate
☑ Split Tubes
☑ CSD Interface
☑ PDB Water Filter
☑ Auto-Gen Graphics
Conformer Rules: trimmed
pH: basic
Max. Ligand Distance (Å): 3.60
Polar Area Range (kJ/mol): 100.000
Accessible Area Radius (Å): 1.00

(i) **View: Orthogonal/Perspective**
Controls the view of structural models and graphics.

(ii) **Toolbar Style: text/small icons/medium icons/large icons**
Controls presentation style (text vs. icons) and size of the icons.

(iii) **Stereo: off/red-cyan/interlaced**
Turns "off" or selects between color separated (**red-cyan**) or hardware (**NAL**, **NAM**) stereographic display (**interlaced**).

(iv) **Global Rotate: screen ctr./molecule ctr**.
Screen ctr. rotates all molecules about a common center; while **molecule ctr.** rotates each molecule about its own center.

(v) **Animation Speed**
A slider bar controls the maximum speed for animations.

(vi) **Element Overlay**
If *checked*, this highlights elements in the inorganic model kit for which the model specified in the **Calculations** dialog are available.

(vii) **Fast Rotate**
If *checked*, lowers the resolution of structure models during rotation to improve graphics performance.

(viii) **Split-Tubes**
If *checked*, the tubes in tube and ball-and-spoke models are split to designate multiple bonds.

(ix) **CSD Interface**
If *checked*, displays the **CSD** tab in the **Database** dialog (**Database** under the **Search** menu; **Chapter 17**). *Uncheck* if CSD is not installed.

(x) **PDB Water Filter**
If *checked*, removes water molecules from imported PDB files.

(xi) **Auto-Gen Graphics**
If *checked*, performs graphics calculations in the interface.

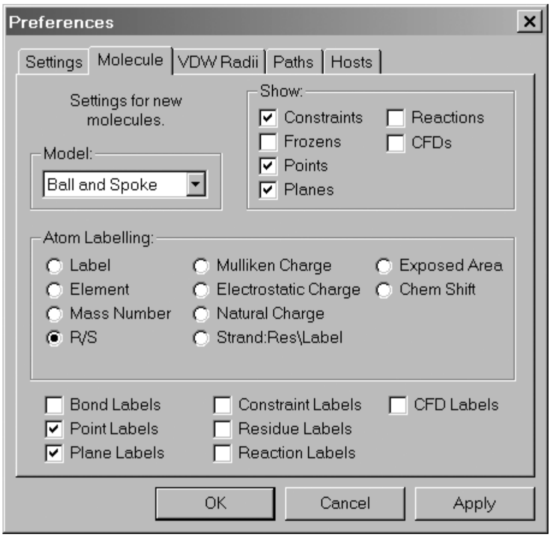
(xii) **Max-Ligand Distance**
Set maximum distance (in Å) for an amino acid to be recognized as bonded to a ligand.

(xiii) **Conformer Rules**
Sets rules for conformational searching. **Normal** should be used for **Equilibrium Conformer** and **Conformer Distribution** where Monte Carlo methods are involved. **Trimmed** eliminates less important degrees of conformational freedom and should be used for **Conformer Library** where systematic searches are carried out.

(xiv) **Polar Area Range**
Set potential (in kJ/mol) for calculating polar area from elecrostatic potential map. Values > | range | contribute to polar area.

(xv) **Accessible Area Radius**
Set sphere radius (in Å) for determining accessible area.

Molecule



Settings for new molecules.

Model: Ball and Spoke

Show:
☑ Constraints
☐ Frozens
☑ Points
☑ Planes
☐ Reactions
☐ CFDs

Atom Labelling:
○ Label
○ Element
○ Mass Number
● R/S
○ Mulliken Charge
○ Electrostatic Charge
○ Natural Charge
○ Strand:Res\Label
○ Exposed Area
○ Chem Shift

☐ Bond Labels
☑ Point Labels
☑ Plane Labels
☐ Constraint Labels
☐ Residue Labels
☐ Reaction Labels
☐ CFD Labels

This specifies default settings for model appearance. These settings may be overridden for a specific molecule (or list of molecules) using entries under the **Model** menu and for specific portions of a molecule using **Utilities/Style** dialogs associated with **Properties** dialogs (**Properties** under the **Display** menu; **Chapter 16**).

(i) **Model: Wire/Ball and Wire/Tube/Ball/Spoke/Space Filling/Line**
Controls default model style.

(ii) **Show: Constraints/Frozens/Points/Planes/Reactions/CFD's**
If *checked*, constraints and frozen markers, points and planes, reaction arrows and CFD's will be shown.

(iii) **Atom Labeling: Label/Element/Mass Number/Mulliken Charge/Electrostatic Charge/Natural Charge/Strand: Residue/Label/R/S/Exposed Area/Chem Shift**
Controls label type.

(iv) **Bond Labels**
If *checked*, bond labels will be shown.

(v) **Point Labels**
If *checked*, point labels will be shown.

(vi) **Plane Labels**
If *checked*, plane labels will be shown.

(vii) **Constraint Labels**
If *checked*, constraint labels will be shown.

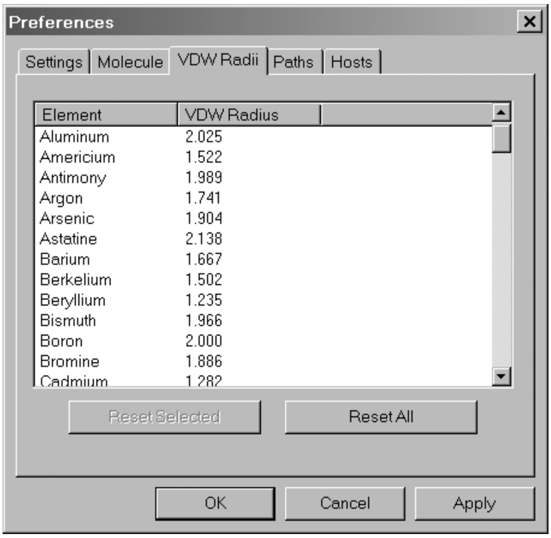
(viii) **Residue Labels**
If *checked*, residue labels will be shown.

(ix) **Reaction Labels**
If *checked*, reaction arrow labels will be shown.

(x) **CFD Labels**
If *checked*, CFD labels will be shown.

VDW Radii

This provides a list of van der Waals radii

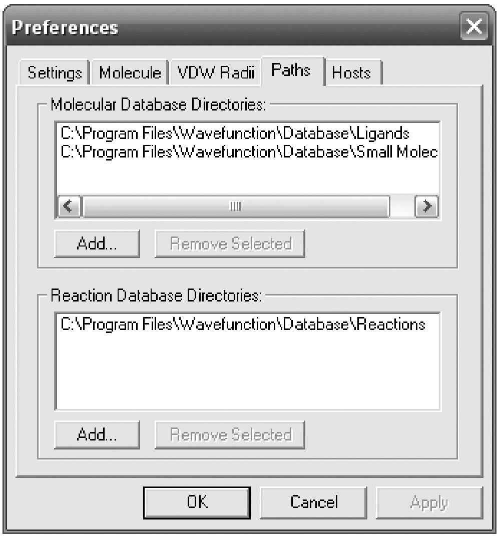


Element	VDW Radius
Aluminum	2.025
Americium	1.522
Antimony	1.989
Argon	1.741
Arsenic	1.904
Astatine	2.138
Barium	1.667
Berkelium	1.502
Beryllium	1.235
Bismuth	1.966
Boron	2.000
Bromine	1.886
Cadmium	1.282

To order the list by element name *click* on **Element**, and by atomic radius *click* on **VDW Radius**. Individual entries may be changed from default values by first *clicking* on the entry and then entering a new value. The currently selected entry may be returned to its default radius by *clicking* on **Reset Selected** at the bottom of the dialog, and the full set of radii may be returned to their default values by *clicking* on **Reset All** at the bottom of the dialog.

Paths

This allows setting up of paths for both SMD and SRD database directories and for similarity directories.


Preferences
Settings
Molecule
VDW Radii
Paths
Hosts
Molecular Database Directories:
C:\Program Files\Wavefunction\Database\Ligands
C:\Program Files\Wavefunction\Database\Small Molec
Add...
Remove Selected
Reaction Database Directories:
C:\Program Files\Wavefunction\Database\Reactions
Add...
Remove Selected
OK
Cancel
Apply

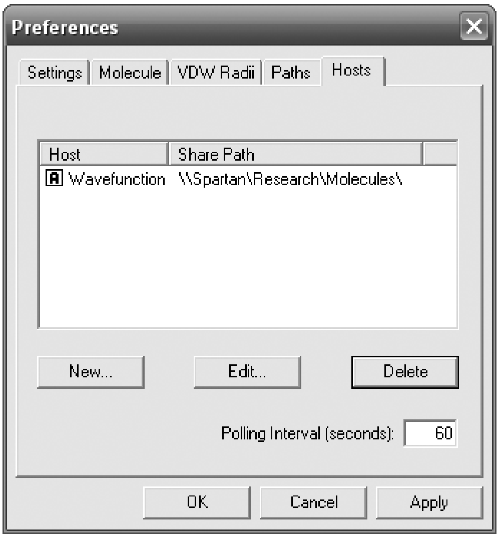
Molecular Database Directories defines the content of SMD and SRD in terms of one or more directories. Multiple directories can be accessed at once. Specification of which directory (or directories) is to be searched in the **Search Options** dialogs associated with SMD (**Databases** under the **Search** menu; **Chapter 16**). The default settings include:

Small Molecules and Ligands	for SMD
Reactions	for SRD

meaning that SMD refers to the collection of small molecules and SRD refers to the reaction library. Other collections may be added. **Appendix G** discusses creation of user-defined databases.

Hosts

This allows specification of one or more computers that may act as servers.


Preferences
Settings
Molecule
VDW Radii
Paths
Hosts
New...
Edit...
Delete
OK
Cancel
Apply

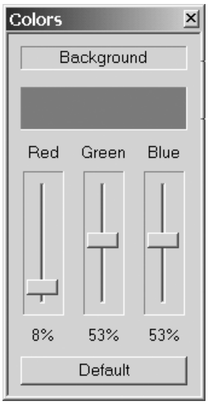
Host	Share Path
Wavefunction	\\Spartan\Research\Molecules\

Polling Interval (seconds): 60

To add a new host, *click* on the **New...** button and follow the directions provided in the **Host** dialog that appears. **Polling Interval** indicates how often ***Spartan*** will query the remote resource for status of ***Spartan*** calculations (**NAM**).

Colors

This alters default colors. Selection leads to the **Colors** dialog.

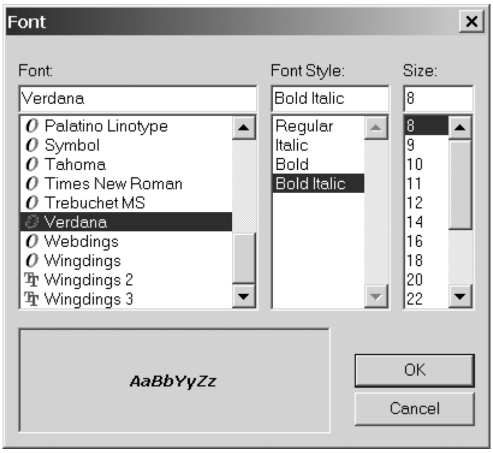

Colors
Background
Default

Red 8%
Green 53%
Blue 53%

After selecting an object, its color may be set by adjusting the **Red**, **Green** and **Blue** slider bars. The default color may be reset by *clicking* on **Default**. Color selection applies to all objects of the same type, for example, all carbon atoms, and not just to the selected carbon. Further control of colors is available from **Utilities/Style** dialogs associated with **Properties** dialogs (**Properties** under the **Display** menu; **Chapter 16**). *Clicking* on ☒ removes the dialog.

Fonts...

This selects fonts, style and size of labels attached to molecules (**Labels** and **Configure...** under the **Model** menu; **Chapter 12**), and plots (**Plots...** under the **Display** menu; **Chapter 16**). Selection leads to the **Fonts** dialog (**NAM**, **NAL**).



Font: Verdana

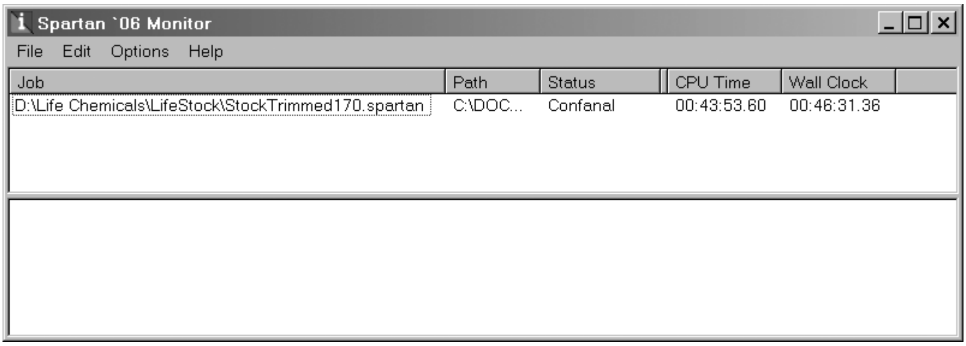
Font Style: Bold Italic

Size: 8

Font
Palatino Linotype
Symbol
Tahoma
Times New Roman
Trebuchet MS
Verdana
Webdings
Wingdings
Wingdings 2
Wingdings 3
Regular
Italic
Bold
Bold Italic
8
9
10
11
12
14
16
18
20
22
AaBbYyZz
OK
Cancel

Selections are made from the **Font**, **Font Style** and **Size** menus. *Clicking* on **OK** dismisses the dialog with selections kept. *Clicking* on **Cancel** or on ☒ dismisses the dialog but selections are lost.

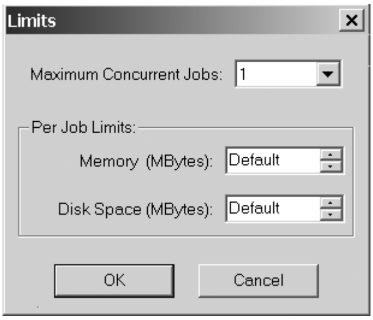
Monitor



Job	Path	Status	CPU Time	Wall Clock
D:\Life Chemicals\LifeStock\StockTrimmed170.spartan	C:\DOC...	Confanal	00:43:53.60	00:46:31.36

This provides a listing of all executing/queued jobs and their status. To see accumulated output for an executing job, *click* on its name. To kill a job, *click* on its name, and then select **Kill Selected** from the **Edit** menu at the top of the dialog. To start a queued job (irrespective of the imposed queue limits; see below), *click* on its name and then select **Start Selected** from the **Edit** menu.

Job limits are set using **Limits** under the **Options**[*] menu.



Maximum Concurrent Jobs: 1

Memory (MBytes): Default

Disk Space (MBytes): Default

Maximum Concurrent Jobs designates the maximum number of jobs that can be run at one time and **Memory** and **Disk Space** maximum amounts of memory and disk for a job. The dialog is dismissed with changes instituted by *clicking* on **OK**. *Clicking* on **Cancel** or on ☒ dismisses the dialog but changes are lost.

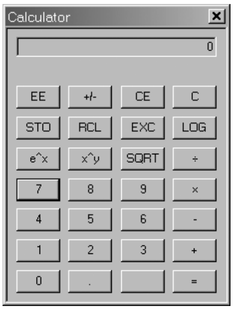
The **Monitor** may be removed either by selecting **Exit** from the **File** menu or by *clicking* on ☒ at the top of the dialog.

---

[*] Located in the **Preferences** dialog under **Jobs** for Macintosh version. While the monitor lists jobs running or queried to run on remote compute servers, cumulative output for these jobs is not available in the monitor.

Calculator

Selection brings up a **Calculator** (**NAM**).



This functions the same way as a normal pocket calculator. The **Calculator** is removed by *clicking* on ☒.

Model Kit

If *checked*, this signifies that a model kit (organic, inorganic, peptide, nucleotide or substituent) is to remain on screen. Does not apply to ChemDraw.

File Toolbar, Geometry Toolbar, Build Toolbar, Search Toolbar

If *checked*, this provides display of toolbars that access functions contained in the **File**, **Build**, **Geometry** and **Search** menus, respectively.

Cascade, Tile

Arranges open windows in a cascade or as tiles on top of ***Spartan***'s main window (**NAM**).

Arrange Icons

Arranges icons at bottom of ***Spartan***'s main window (**NAM**).

Chapter 19

The Help Menu

This chapter describes help.

Help

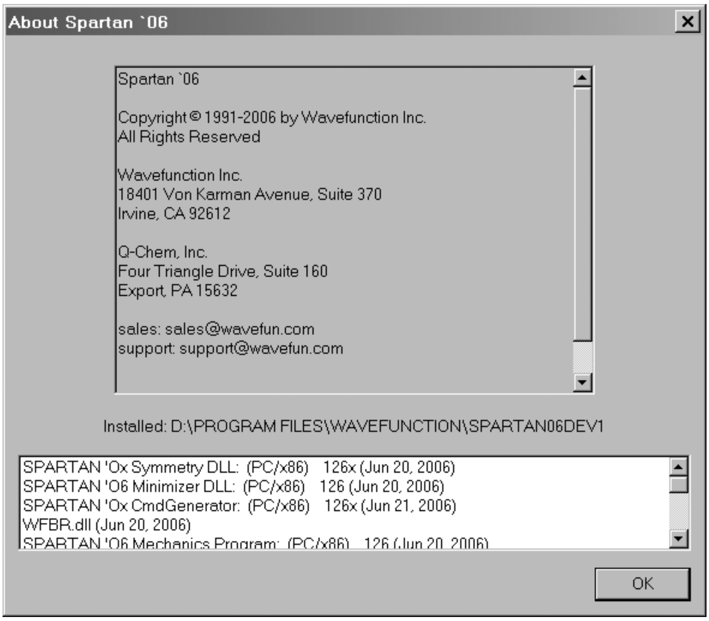
This provides information relating to application of computational methods available in ***Spartan***, as well as technical details regarding the program's operation.

A number of topics are dealt with under **Help**; including Mouse/Keyboard Functions Quick Reference, General Operating Features, Units of Measure, Differences between Spartan'04 and '06, Selecting a (Theoretical) Model, Relative Computational Times, Memory Usage, Calculation Options, and a number of FAQ documents related to computational questions.

The ***Spartan*** Tutorial and User's Guide (this document) is also available (as a PDF file) under **Help**. Help files are HTML documents and require that Internet Explorer is installed to access them.

About...*

Provides information about the user's release of ***Spartan***.



Spartan `06

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Wavefunction Inc.
18401 Von Karman Avenue, Suite 370
Irvine, CA 92612

Q-Chem, Inc.
Four Triangle Drive, Suite 160
Export, PA 15632

sales: sales@wavefun.com
support: support@wavefun.com

Installed: D:\PROGRAM FILES\WAVEFUNCTION\SPARTAN06DEV1

```
SPARTAN 'Ox Symmetry DLL:  (PC/x86)   126x (Jun 20, 2006)
SPARTAN 'O6 Minimizer DLL:  (PC/x86)   126 (Jun 20, 2006)
SPARTAN 'Ox CmdGenerator:  (PC/x86)   126x (Jun 21, 2006)
WFBR.dll (Jun 20, 2006)
SPARTAN 'O6 Mechanics Program:  (PC/x86)   126 (Jun 20, 2006)
```

---

* About is located under the **Spartan 06** menu on the Macintosh version.

Appendix A

Capabilities and Limitations

Essential Edition of *Spartan'06* for Windows and Macintosh

Spartan'06 for Windows and Macintosh are available in two versions: a full version, referred to as ***Spartan'06***, and a lower-cost version, referred to as the Essential Edition. The latter shares the same graphical user interface as the full version, except that it lacks the ability to assign chemical function descriptors and to display UV/visible and NMR spectra. The essential edition also does not support quantum chemical calculations beyond the Hartree-Fock level, does not provide for calculation of UV/visible or NMR spectra and does not support either conformer library generation or similarity analysis.

Only the full version of the Linux implementation of ***Spartan'06*** is available.

Molecular Mechanics Models[1]

The molecular mechanics module provides for the calculation of equilibrium geometries, strain energies and vibrational frequencies, as well as for conformational searching. SYBYL (Tripos, Inc.) and MMFF (Merck Pharmaceuticals) force fields are available. Strain energies from the latter may be corrected for the effects of aqueous solvent (MMFFaq). Structures are unaffected. There are no atom limits for molecular mechanics calculations.

Molecular mechanics parameters are read from a set of files: SYBYL.spp (SYBYL parameters) and MMFF94.spp (MMFF parameters). New parameters may be added or existing parameters modified by accessing these files.

Semi-Empirical Models[1]

The semi-empirical module provides for calculation of heats of formation, wavefunctions, equilibrium and transition-state geometries and vibrational frequencies, as well as for conformational searching.* MNDO, AM1, RM1 and PM3 models are supported. MNDO/d replaces MNDO for second-row (and heavier) main-group elements, and PM3 parameterizations for transition metals are available.** MNDO has been parameterized for H, He, Li-F, Al-Cl, Ca, Zn, Ge, Br, Cd, Sn, I, Hg and Pb; AM1 for H, B-F, Al-Cl, Zn, Ge, Br, Sn and I; RM1 for H, C–F, P, S, Cl, Br and I; PM3 for H-Ne, Mg-Ar, Ca, Ti-Br, Zr, Mo-Pd, Cd-I, Hf-Pt and Hg-Bi and Gd.

Preset limits for semi-empirical calculations are enumerated below.

maximum number of atoms (any type)	300

Hartree-Fock Models[1-3]

The Hartree-Fock module provides for calculation of energies and wavefunctions, equilibrium and transition-state geometries and vibrational frequencies, as well as for conformational searching.* Both closed-shell and open-shell (either ROHF or UHF) calculations are supported with minimal (STO-3G), split-valence (3-21G) and polarization (6-31G*, 6-311G*, cc-pVDZ[4], cc-pVTZ[4] and cc-pVQZ[4]) basis sets supplemented by additional polarization and/or diffuse functions. Dual-basis set techniques are supported for energy calculations (only). Also available are pseudopotentials for calculations on molecules incorporating heavy atoms.[4]

Preset limits for Hartree-Fock calculations are enumerated below.

maximum number of atoms	200
maximum number of basis functions	2000

---

* Except generation of conformer libraries.

** Parameters for all available transition metals except Zn, Cd and Hg include d-type orbitals in the basis set.

Density Functional Models[1,2,4]

The density functional module provides for calculation of energies and wavefunctions, equilibrium and transition-state geometries and vibrational frequencies, as well as for conformational searching.* The module supports local density calculations and BP, BLYP, EDF1, B3LYP density functional calculations. The same basis sets and pseudopotentials supported for Hartree-Fock calculations are available, although use of the minimal STO-3G and split-valence 3-21G basis sets is strongly discouraged. Dual basis set techniques are supported for energy calculations (only).

Preset limits for density functional calculations are enumerated below.

maximum number of atoms	200
maximum number of basis functions	2000

Møller-Plesset Models[1,2,4]

The Møller-Plesset module provides for calculation of energies and wavefunctions and equilibrium and transition-state geometries as well as for conformational searching* using either the MP2 or RI-MP2 models. Vibrational frequencies are also available from both models, but these are not performed analytically, but rather involve numerical differentiation of analytical gradients. The same basis sets and pseudopotentials supported for Hartree-Fock calculations are available, although use of the minimal STO-3G and split-valence 3-21G basis sets is strongly discouraged. Dual basis set techniques are supported for energy calculations (only).

Preset limits for MP2 and RI-MP2 calculations are enumerated below.

maximum number of atoms	200
maximum number of basis functions	2000

Localized MP2 and RI-MP2 are also supported. MP3 and MP4 calculations are supported under **Advanced Correlated Models**.

---

* Except generation of conformer libraries.

Advanced Correlated Models[1,2,4]

The advanced correlated module provides for calculation of energies (only) using the MP3, MP4, CCSD, CCSD(T), CCSD(2), OD, OD(T), QCISD, QCISD(T), QCCD and QCCD(2) correlated models. The same basis sets and pseudopotentials supported for Hartree-Fock calculations are also available, although use of the minimal STO-3G and split-valence 3-21G basis sets is strongly discouraged. Dual basis set techniques are not supported for any of these techniques.

Depending on basis set, practical considerations limit application of these techniques to molecules comprising 10-20 heavy (non-hydrogen) atoms, although program limits are set much larger.

Thermochemical Recipes

The G2, G3 and G3(MP2) recipes are available for heat of formation calculations. Practical considerations limit application of the first two recipes to molecules comprising less than 10 heavy atoms and the G3(MP2) recipe to molecules comprising less than 15 heavy atoms, although program limits are set much larger.

A new recipe, termed T1, has been developed to closely reproduce G3(MP2) heats of formation. It is based on G3(MP2), but replaces the large basis set MP2 calculation by a dual basis set RI-MP2 calculation, eliminates both the QCISD(T) calculation and the vibrational frequency calculation (needed to obtain zero-point energy and to correct the energy for finite temperature) and introduces an empirical correction based on the atom counts and Mulliken bond orders. T1 makes us of an HF/6-31G* geometry, instead of the MP2/6-31G* geometry in G3(MP2).

T1 is limited to closed-shell uncharged molecules comprising H, C, N, O, F, S, Cl only, and that can be properly described in terms of a conventional valence structure. Calculations in the range of 30-50 heavy atoms are practical. As a result, T1 requires 2-3 orders of magnitude less computation time than G3(MP2).

Excited-State Models

Two classes of models are available for calculations of excited states: configuration interaction (CI) models and time dependent density functional (TDDFT) models. The former comprises two models: CIS (configuration interaction singles) and CISD (configuration interaction singles with doubles correction), while the latter supports the local density model as well as BP, BLYP, EDF1 and B3LYP density functional models. At the present time, only the CIS model is available for geometry optimization and frequency calculations, all other models being restricted to single-point energy calculations. The same basis sets and pseudopotentials supported for ground-state calculations are available. Dual basis set techniques are not supported.

Preset limits for excited-state calculations are enumerated below.

maximum number of atoms	200
maximum number of basis functions	2000

Properties and Spectra

The properties module (that is automatically called from the molecular mechanics module or one of the quantum chemical modules) provides for text output printing, population analyses (Mulliken, natural bond orbital and based on fits to electrostatic potentials), evaluation of thermodynamic quantities (enthalpy, entropy and free energy), and calculation of the dipole moment. Aqueous solvation energies, may be estimated using the SM5.4 model of Cramer and Truhlar[5] (available for H, C-F, S-Cl, Br and I), and added to gas-phase total energies obtained at other levels of calculation.

The properties module is also responsible for calculating quantities related to infrared/Raman spectra (vibrational frequencies and infrared/Raman intensities), UV/visible spectra (excited state transition energies) and NMR spectra (chemical shifts). IR spectra calculations may be carried out with molecular mechanics models, semi-empirical models, Hartree-Fock models, density functional models and MP2 and RI-MP2 models. UV/visible spectra calculations are limited to Hartree-Fock models (CIS for excited states) and density functional models TDDFT for excited states and NMR spectra calculations to Hartree-Fock and density functional models.

Graphics

The graphics module provides for data preparation associated with the display as surfaces, property maps and slices of molecular orbitals, electron densities, spin densities, electrostatic potentials and local ionization potentials. Accessible and inaccessible regions may be distinguished for electron density surfaces and all property maps based on electron density surfaces.

Similarity Analysis

The similarity analysis code evaluates and quantifies the extent to which molecules are similar based either on selected atomic centers or on selected chemical function descriptors. In addition, it quantifies the degree of fit of a molecule into a chemical environment (a pharmacophore). Similarity analyses are carried out between one or more molecules or pharmacophores in a document (the template) and one or more molecules or pharmacophores in one or more documents (the library). Molecules in the library (only) may either correspond to single conformers or to collections of diverse conformers.

---

1. For a general discussion and assessment of the techniques and methods available in ***Spartan***, see: W.J. Hehre, ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***, Wavefunction, Inc., Irvine, CA 2003.
2. For a review of the quantum chemical methods utilized in ***Spartan*** (except for semi-empirical methods) with emphasis on recent developments, see: Y. Shao, L.F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S.T. Brown, A.T.B. Gilbert, L.V. Slipchenko, S.V. Levchenko, D.P. O'Neill, R.A. DiStasio Jr., R.C. Lochan, T. Wang, G.J.O. Beran, N.A. Besley, J.M. Herbert, C.Y. Lin, T. Van Voorhis, S.H. Chien, A. Sodt, R.P. Steele, V.A. Rassolov, P.E. Maslen, P.P. Korambath, R.D. Adamson, B. Austin, J. Baker, E.F.C. Byrd, H. Dachsel, R.J. Doerksen, A. Dreuw, B.D. Dunietz, A.D. Dutoi, T.R. Furlani, S.R. Gwaltney, A. Heyden, S. Hirata, C-P. Hsu, G. Kedziora, R.Z. Khalliulin, P. Klunzinger, A.M. Lee, M.S. Lee, W.Z. Liang, I. Lotan, N. Nair, B. Peters, E.I. Proynov, P.A. Pieniazek, Y.M. Rhee, J. Ritchie, E. Rosta, C.D. Sherrill, A.C. Simmonett, J.E. Subotnik, H.L. Woodcock III, W. Zhang, A.T. Bell, A.K. Chakraborty, D.M. Chipman, F.J. Keil, A.Warshel, W.J. Hehre, H.F. Schaefer, J. Kong, A.I. Krylov, P.M.W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.,* **8**, 3172 (2006).
3. For an older account see: W.J. Hehre, L. Radom, P.v.R. Schleyer and J.A. Pople, ***Ab Initio* Molecular Orbital Theory**, Wiley, New York, 1986.
4. Not available in essential edition.
5. C.C. Chambers, G.D. Hawkins, C.J. Cramer and D.G. Truhlar, *J. Phys. Chem.*, **100**, 16385 (1996).

Appendix B

Menus

File

New	Brings up a model kit for molecule building
Open...	Opens (imports) a molecule
Close	Closes a molecule
Save	Saves (exports) a molecule
Save As...	Saves a molecule under a user-specified name
New Molecule	Adds a molecule to an existing list; brings up a model kit for molecule building
Delete Molecule	Deletes a molecule (or molecules) from a list
Append Molecule(s)...	Appends molecules to an existing list
Print...	Prints on-screen display
Print Setup...	Setup for printing
Exit	Exits ***Spartan***

Edit

Undo	Undoes previous operations
Cut	Moves the current molecule or contents of the selection box to the clipboard
Copy	Copies the current molecule or contents of the selection box to the clipboard
Paste	Pastes contents of the clipboard to the screen
Find...	Locates a text string in the output dialog or an on-screen molecular fragment
Find Next	Locates next occurrence of a text string or molecular fragment
Center	Centers the molecule on screen
Clear	Clears the screen (build mode only)

Model

Wire	Displays structure as wire-frame model
Ball and Wire	Displays structure as ball-and-wire model
Tube	Displays structure as tube model
Ball and Spoke	Displays structure as ball-and-spoke model
Space Filling	Displays structure as space-filling model
Line	Displays structure as a line drawing
Hide	Hides structure model from view
Global Model	Applies model type and labels of current molecule to all molecules in the list
Coupled	Couples motions of all molecules in the list
Hydrogens	Toggles hydrogens “on” and “off”
Labels	Toggles labels “on” and “off”
Ribbons	Toggles ribbons “on” and “off”
Hydrogen Bonds	Toggles hydrogen bonds “on” and “off”
CFD’s	Toggles chemical function descriptors (hydrophobes, hydrogen bond donors/ acceptors, positive/negative centers) “on” and “off”
Configure...	Labels atoms, bonds, etc., provides information about polypeptides/polynucleotides residues and designates ribbon displays

Geometry

Measure Distance	Displays and/or sets bond distance
Measure Angle	Displays and/or sets bond angle
Measure Dihedral	Displays and/or sets dihedral angle
Freeze Center	Freezes selected atomic positions
Set Torsions	Selects bond rings for conformational searching
Set Similarity Centers	Identifies atoms /CFD’s for similarity analyses
Constrain Distance	Constrains bond distance
Constrain Angle	Constrains bond angle
Constrain Dihedral	Constrains dihedral angle

Define Point	Defines a point as a geometric mean of a set of atoms
Define Plane	Defines a plane made by three atoms
Define CFD	Defines the location of a CFD
Align	Aligns molecules in a document according to selected atoms, structure, or CFD's

Build

View	Removes the model kit
Add Fragment	Adds atomic fragment, functional group, ring, ligand, custom fragment or substituent library
Delete	Deletes atoms, bonds, points, planes, etc.
Make Bond	Makes bonds between free valences or atoms
Break Bond	Breaks a bond
Minimize	Performs molecular mechanics energy minimization

Setup

Calculations...	Sets up molecular mechanics and quantum chemical calculations and similarity analyses
Surfaces	Sets up generation of and displays graphical surfaces
Submit	Submits job to the execution queue

Display

Output	Displays text output
Properties	Displays molecule, bond and atom properties as well as information about geometrical constraints, graphical surfaces, plots and statistical analyses
Surfaces	Sets up generation of and displays graphical surfaces (same as entry in **Setup** menu)
Spectra	Displays IR, NMR and/or UV/visible spectra and animates vibrational modes
Spreadsheet	Displays spreadsheet

Plots...	Creates plots from the data in the spreadsheet
Similarities	Displays results of similarity analyses

Search

Databases	Performs substructure search on Cambridge Structural Database (CSD), Spartan Molecular Database (SMD) and Spartan Reaction Database (SRD) and provides on-line access to Protein Data Bank (PDB)
Ligands	Extracts ligands and pharmacophores based on protein-ligand binding from PDB files
Transition States	Provides transition state guess based on reaction database or, lacking a database entry, based on linear synchronous transit
Tautomers	Identifies tautomers

Options

Preferences...	Sets various run-time preferences
Colors	Sets screen and model colors
Fonts...	Sets fonts for labels and plot displays
Monitor	Monitors and allows for killing executing jobs as well as control job queue
Calculator	Pocket calculator
Model Kit	Keeps a model kit on screen
File, Build, Geometry, Search Toolbar	Toggles toolbars “on” and “off”
Cascade	Arranges open windows in a cascade
Tile	Arranges open windows as tiles
Arrange Icons	Arranges icons at bottom of screen

Help

Help	Provides information about using computational methods in ***Spartan’06***
About...	Provides program version information

Appendix C

Commonly-Used Program Options

This appendix describes a number of commonly-used program options. These are specified using keywords input into the **Options** box in the **Calculations** dialog (**Setup** menu). Keywords are case insensitive. An equals sign (=) separates a keyword from its integer, real or character string value. Keywords may either be single words or expressions. **Keyword=N** indicates an integer argument, **keyword=C** indicates a character argument, and **keyword=F** indicates a floating point argument. Real values can optionally include an **eNN** or **e-NN** (floating point power of ten). Default values for keywords are indicated in **bold**, and alternative values in *italics*.

Conformational Search

keyword	value	description
SearchMethod	**C**	conformational searching method employed; overrides default choice which depends on complexity of system may be overridden with one of the following: *Systematic* use systematic method *MonteCarlo* use Monte-Carlo method *Sparse* use systematic method but randomly eliminate conformers to stay within set conformer limits. Used in conformer library generation.
MaxEnergy	**F**	sets the maximum energy (in kJ/mol) at which a conformer will be kept to (minimum energy + F), where minimum energy is the energy of the lowest energy conformer encountered at that point in the search; default is **40** kJ/mol

StartTemperature	**F**	sets initial temperature (in K) for a Monte Carlo search (only) to F; high temperatures will result in the molecule further exploring global space, while low temperatures will result in the molecule further exploring local space; default is **5000**K

Similarity Analysis

keyword	value	description
SingleEnantiomer	–	Limits similarity analysis to the enantiomer actually in specified library documents. The default is to consider both enantiomers
QuitSimilarity	**N**	Quit similarity analysis involving a conformer list (in the graphical user interface) and/or one or more conformer libraries when N good matches have been identified; default is **1**
QuitCriterion	**F**	R^2 criterion for a good match; default is **0.9**

Geometry Optimization

keyword	value	description
GeometryCycle	**N**	set maximum number of equilibrium and transition-state geometry optimization cycles to N; default is **number of independent variables +20** for equilibrium geometry optimization and **3x number of independent variables** for transition-state geometry optimization
GradientTolerance	**F**	set convergence criterion in equilibrium and transition-state) geometry optimization for the maximum gradient component (in hartrees/bohr) to F; default is **4.5 x 10^{-4}**
DistanceTolerance	**F**	set convergence criterion in equilibrium and transition-state geometry optimization for the maximum change in a bond length (in Å) to F; default is **1.8 x 10^{-3}**
Hess	**C**	Choose Hessian (matrix of second derivatives) for start of geometry (transition-state geometry) optimization (in the absence of a Hessian from a previous calculation, the default is **MMFF**

molecular mechanics for geometry optimization and **PM3** semi-empirical for transition-state geometry optimization; may be overridden with one of the following:

unit	unit matrix
MMFF	MMFF molecular mechanics
AM1	AM1 semi-empirical
STO-3G	STO-3G Hartree-Fock
3-21G	3-21G Hartree-Fock
*6-31G**	6-31G* Hartree-Fock

Molecular Mechanics Calculations

keyword	description
MMFF94s	Use MMFF94s method insted of MMFF94. The only significant change is to make nitrogens attached to aromatic rings planar (as in aniline)

Quantum Chemical Calculations

keyword	value	description
Diis	**N**	switch on diis all the time in SCF procedure. N is the size of the iterative subspace; it should be an integer between 2 and 10; default is **5**
NoDiis		turn off diis SCF convergence accelerator
ScfCycle	**N**	set maximum number of SCF iterations to N; default is **50**
Guess	**C**	choose initial wavefunction guess; in the absence of a guess from a previous calculation, the default is either **sad** or **PM3** depending on the calculation type, and may be overridden with one of the following: *core* — diagonalize the core Hamiltonian *sad* — superposition of atomic densities *PM3* — PM3 semi-empirical
Scf	**C**	SCF procedure; default is **restricted** for closed-shell systems and **unrestricted** for open-shell systems, either of which may be specified for both closed and open-shell systems

SmallBasis	**C**	specifies the small basis set to be used in dual basis set calculations. The large basis set is that indicated in the menu.
Core	**C**	use of frozen core approximation in Møller-Plesset and advanced correlated calculations; default is **frozen** which may be changed to *thawed*
ScfTolerance	**C**	control of all tolerances in SCF procedure and to affect the precision of the algorithm; default is **normal** which may be changed to *high* or *veryhigh*
	F	set SCF energy convergence criterion (in hartrees) to F; default is **1.0 x 10^{-6}**
BigGrid	–	uses very large grid in density functional calculations
Mix	–	specifies that α and β HOMO's in the guess wavefunction should be constructed according to: $\text{HOMO}_\alpha = \frac{\text{HOMO + LUMO}}{\sqrt{2}}$ $\text{HOMO}_\beta = \frac{\text{HOMO - LUMO}}{\sqrt{2}}$ useful for generating a guess wavefunction for singlet diradical
Fast HF	**C**	**on** forces use of fast Hartree-Fock techniques that keep integrals in memory (1GB of memory allows calculation with approximately 160 basis functions), while **off** does not invoke fast Hartree-Fock techniques under any conditions (these techniques are normally automatically invoked for Hartree-Fock calculations on small systems but may result in an increase in geometry optimization cycles)
Direct	–	uses fast Hartree-Fock routines where applicable, but does not keep integrals in memory (this is the default for the essential edition of ***Spartan'06***, but is not normally employed for the full edition)

In addition to the above, any method and/or basis set supported in ***Spartan*** (and not included explicitly in the menus) may be typed into the options box. For example, typing **EDF2 6-311G(2df,2pd)** will result in density functional calculation using the EDF2 functional and the 6-311G(2df,2pd) basis set.

Semi-Empirical Calculations

keyword	value	description
NoAmideFix	–	turns "off" molecular mechanics amide correction in PM3 calculations
hh	**C**	turns "on" and "off" hydrogen-hydrogen repulsion term in PM3 calculations; default is **on** only where transition metals are involved and **off** otherwise
Polarizability	–	calculates and prints polarizabilities and hyperpolarizabilities

Property and Spectra Calculations

keyword	value	description
NBO	**C**	specify details of NBO population analysis; default is **normal** which may be overridden for *ionic* and *3C* (three center) systems
NoElCharge	–	turns "off" calculation of electrostatic charges
ElCharge	**N**	adjusts size of grid used to calculate charge from electrostatic potential; default is **1** point/atomic unit
Temperature	**F**	temperature (in K) used in calculation of thermodynamic properties; default is **298**°K
Pressure	**F**	pressure (in atm) used in calculation of thermodynamic properties; default is **1** atm
Moments	–	calculates and prints principal moments of inertia
NoSolvent	–	turns "off" calculation of aqueous solvation energy using SM5.4 model
NoAreaVolume	–	turns "off" calculation of surface area and volume
MaxPropWeight	**N**	sets limit of molecular weight for electrostatic charge, solvent and area/volume calculations; default is **500** amu

Polarizability	**F**	calculates and prints either static (F not specified) or frequency dependent (frequency F in cm^{-1}) polarizabilities and hyperpolarizabilities
FreqScale	**F**	scales calculated vibrational frequencies by F; default is **1**
NumericalFreq	–	uses numerical differentiation (of analytical gradients) for frequency calculation
UVstates	**N**	specifies number of states to be examined in UV/visible spectra calculation; default is **5**
IRCSteps	**N**	maximum number of steps allowed in constructing IRC; default is **40**
IRCStepSize	**N**	maximum step size (in mass-weighted atomic units x 100) for IRC; default is **150**

Miscellaneous and Printing

keyword	**value**	**description**
3DPlot	–	treat dynamic constraints independently (rather than in concert). This allows data for 3D (XYZ) plot to be collected. Two dynamic constraints only.
Execute	**C**	either skip execution (**skip**) or force execution regardless of history (**force**)
PrintVibCoords	–	print coordinates corresponding to normal mode vibrational frequencies
PrintCoords	–	prints Cartesian coordinates
PrintLev	**C**	print level; default is **normal** which may be changed to *verbose*

Appendix D

Units

Geometries

Cartesian coordinates are given in Ångstroms (Å), but are also available in atomic units (au).

Bond distances are given in Å but are also available in au. Bond angles and dihedral angles are given in degrees (°).

Surface areas, accessible surface areas and polar surface areas are given in Å^2 and volumes in Å^3, but are also available in au^2 (au^3).

1 Å = 0.1 nm=1.889762 au

Energies, Heats of Formation and Strain Energies, Enthalpies and Gibbs Energies and Entropies

Total energies from Hartree-Fock calculations are given in au, but are also available in kcal/mol, kJ/mol and electron volts (eV).

Experimental heats of formation as well as those from semi-empirical calculations and from thermochemical recipes are given in kJ/mol, but are also available in au, kcal/mol and eV.

Strain energies from molecular mechanics calculations are given in kJ/mol, but are also available in au, kcal/mol and eV.

Energies, heats of formation and strain energies corrected empirically for the effects of aqueous media are given in the same units as the corresponding gas-phase quantities.

Enthalpies and Gibbs Energies are given in kJ/mol. Entropies are given in kJ/mol•degree.

Orbital Energies

Orbital energies are given in eV, but are also available in kcal/mol, kJ/mol and au.

Energy Conversions

	au	kcal/mol	kJ/mol	eV
1 au	-	627.5	2625	27.21
1 kcal/mol	1.593 (-3)	-	4.184	4.337 (-2)
1 kJ/mol	3.809 (-4)	2.390 (-1)	-	1.036 (-2)
1 eV	3.675 (-2)	23.06	96.49	-

a) exponent follows in parenthesis, e.g., 1.593 (-3) = 1.593 x 10^{-3}

Electron Densities, Spin Densities, Dipole Moments, Charges, Electrostatic Potentials and Local Ionization Potentials

Electron densities and spin densities are given in electrons/au^3.

Dipole moments are given in debyes.

Atomic charges are given in electrons.

Electrostatic potentials are given in kJ/mol.

Local ionization potentials are given in eV.

Vibrational Frequencies

Vibrational frequencies are given in wavenumbers (cm^{-1}).

Chemical Shifts

Chemical shifts are given in parts-per-million (ppm) relative to appropriate standards: hydrogen, tetramethylsilane; carbon, tetramethylsilane; nitrogen, nitromethane; fluorine, fluorotrichloromethane; silicon, tetramethylsilane, phosphorous, phosphoric acid.

UV/visible Spectra

λ_{max} is given in wavenumbers (cm^{-1}).

Appendix E

Citation

The proper citation for ***Spartan'06*** is as follows:

Spartan'06
Wavefunction, Inc.
Irvine, CA

Except for molecular mechanics and semi-empirical models, the calculation methods used in ***Spartan*** have been documented in: Y. Shao, L.F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S.T. Brown, A.T.B. Gilbert, L.V. Slipchenko, S.V. Levchenko, D.P. O'Neill, R.A. DiStasio Jr., R.C. Lochan, T. Wang, G.J.O. Beran, N.A. Besley, J.M. Herbert, C.Y. Lin, T. Van Voorhis, S.H. Chien, A. Sodt, R.P. Steele, V.A. Rassolov, P.E. Maslen, P.P. Korambath, R.D. Adamson, B. Austin, J. Baker, E.F.C. Byrd, H. Dachsel, R.J. Doerksen, A. Dreuw, B.D. Dunietz, A.D. Dutoi, T.R. Furlani, S.R. Gwaltney, A. Heyden, S. Hirata, C-P. Hsu, G. Kedziora, R.Z. Khalliulin, P. Klunzinger, A.M. Lee, M.S. Lee, W.Z. Liang, I. Lotan, N. Nair, B. Peters, E.I. Proynov, P.A. Pieniazek, Y.M. Rhee, J. Ritchie, E. Rosta, C.D. Sherrill, A.C. Simmonett, J.E. Subotnik, H.L. Woodcock III, W. Zhang, A.T. Bell, A.K. Chakraborty, D.M. Chipman, F.J. Keil, A.Warshel, W.J. Hehre, H.F. Schaefer, J. Kong, A.I. Krylov, P.M.W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.,* **8**, 3172 (2006).

A discussion and assessment of commonly-used calculation methods is found in: W.J. Hehre, ***A Guide to Molecular Mechanics and Quantum Chemical Calculations***, Wavefunction, Inc., Irvine, CA, 2003.

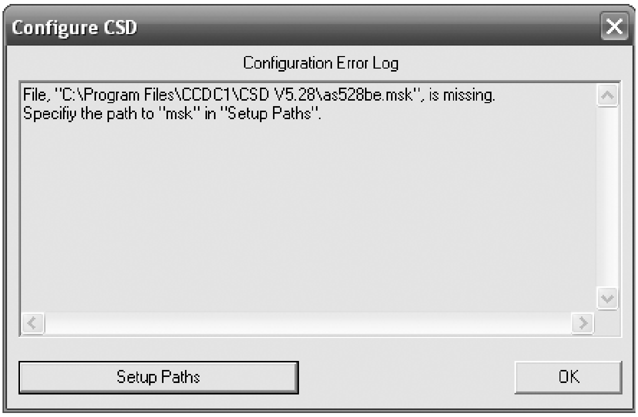
Appendix F

Installing the Cambridge Structural Database

Access to the Cambridge Structural Database (CSD)[*] from ***Spartan*** should be automatic, following successful installation of the ConQuest program (supplied with CSD) according to the detailed instructions provided. If access is denied, the following steps need to be taken:

Windows:

(i) *Click* on the square box immediately to the left of the **Retrieve** button at the bottom of the **CSD** dialog. This brings up the **Configure CSD** dialog,

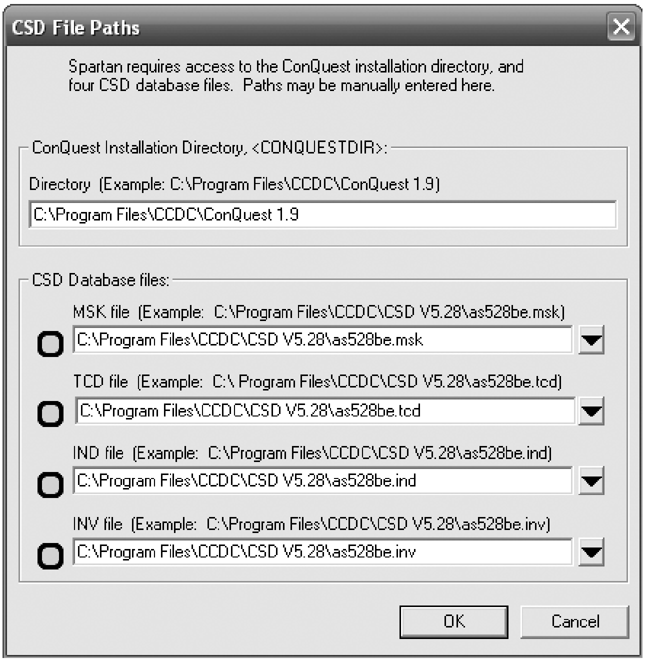


```
File, "C:\Program Files\CCDC1\CSD V5.28\as528be.msk", is missing.
Specifiy the path to "msk" in "Setup Paths".
```

This will list any files which are missing. *Click* on **Setup Paths** at the bottom of the dialog to bring up the **CSD File Paths** dialog,

---

[*] **NAM**.



Spartan requires access to the ConQuest installation directory, and four CSD database files. Paths may be manually entered here.

ConQuest Installation Directory, <CONQUESTDIR>:

Directory (Example: C:\Program Files\CCDC\ConQuest 1.9)

C:\Program Files\CCDC\ConQuest 1.9

CSD Database files:

MSK file (Example: C:\Program Files\CCDC\CSD V5.28\as528be.msk)

○ C:\Program Files\CCDC\CSD V5.28\as528be.msk

TCD file (Example: C:\ Program Files\CCDC\CSD V5.28\as528be.tcd)

○ C:\Program Files\CCDC\CSD V5.28\as528be.tcd

IND file (Example: C:\Program Files\CCDC\CSD V5.28\as528be.ind)

○ C:\Program Files\CCDC\CSD V5.28\as528be.ind

INV file (Example: C:\Program Files\CCDC\CSD V5.28\as528be.inv)

○ C:\Program Files\CCDC\CSD V5.28\as528be.inv

This dialog may show one or more red lights.

(ii) Make certain that the path to ConQuest is correctly specified. The most common error will be that the version number is not current. (At the time of writing, the current version is 1.9.) You can get the current version number from your installation of ConQuest.

(iii) Given the proper version number for ConQuest, update the file names in the boxes below **MSK file**, **TCD file**, **IND file** and **INV file**. You can get the current file names from your installation of ConQuest. As you enter the current file names, the red lights turn to green lights. When all lights are green, *click* on **OK** to dismiss the **CSD File Paths** dialog and then *click* on **OK** to dismiss the **Configure CSD** dialog.

Linux:

(i) **CSD HOME** must be defined in order for ***Spartan*** to locate the CSD program.

(ii) Please refer to **Chapter 9** of “Cambridge Structural Database System Release and Installation Notes” for instructions on setting up **CSD HOME**.

Appendix G

Constructing Custom Databases

Custom collections may be added to both SMD and SRD. These may either include the geometry, energy (heat of formation, strain energy), HOMO and LUMO energies, dipole moment, atomic charges, chemical shifts and vibrational frequencies obtained from quantum chemical calculations, or (for SMD only) conformer libraries generated from molecular mechanics calculations. Entries for SRD (transition states) need to derive from ***Spartan's*** transition state guessing facility (**Transition States** under the **Search** menu; **Chapter 17**) in order that they include the original set of reaction arrows.

Creation of a new collection follows by saving all molecules (or lists of molecules) to be included as Spartan Entry (***.spentry***) files (**Save As** under the **File** menu with **Save as type** set to **Spartan Entry**) in a single directory. The path to the directory must be entered into the **Paths Preferences** dialog under **Preferences...** in the **Options** menu (**Chapter 18**).

If a name has been provided for a particular molecule, it will be used to identify the molecule. Otherwise, a default label will be attached. Name specification is done as a **Label** either in the **Molecule Properties** dialog (see **Properties** under the **Display** menu in **Chapter 16**) or in the spreadsheet (see **Spreadsheet** under the **Display** menu in **Chapter 16**).

Appendix H

Pharmacophore Input

The following file format is used for input of a pharmacophore (illustrated for a pharmacophore with four hydrophobes and one positive ionizable center) :

```
Blank line
Blank line
Blank line
ENDCART
BEGINCFD
HPHOBE|RING_AROM   8.050 -4.180 -0.400 0 2.000 1.000 1
HPHOBE|RING_AROM   9.630 -0.640 -3.590 1 2.000 1.000 1
HPHOBE|RING_AROM  10.280 -0.380  3.200 2 2.000 1.000 1
HPHOBE|RING_AROM   8.130 -2.300  4.330 3 2.000 1.000 1
POS               14.370 -1.700  0.280 4 3.000 1.000 1
ENDCFD
```

The lines between BEGINCFD and ENDCFD define the individual pharmacophore elements (one line/element):

type1|type2… (| separates types for multiple definitions), Cartesian (X,Y,Z) coordinates (in Angstroms), unique number, radius of element (in Angstroms), weight of element in fit, use the element in fit (1) or ignore the element (5)

The following element types are available:

HPHOBE	hydrophobe
RING_AROM	aromatic ring
POS	positive ionizable center
NEG	negative ionizable center
HBA_CENTER	hydrogen bond acceptor
HBD_CENTER	hydrogen bond donor
EXCL_VOL	excluded volume

Appendix I

Installing a Network HASP

Spartan'06 requires a hardware license key which is normally installed on each machine. However, a network hardware key can be obtained from Wavefunction and installed on a server. This allows ***Spartan'06*** to be run on a specified number of client machines on the network. A one-time installation is required.*

On the Server:

1. The License Manager software must be installed. To do so, please run the **lmsetup.exe** file.
   a. (Recommended). The latest release of this file can be obtained by visiting the following link at the Aladdin Web Site:

      http://www.aladdin.com/support/hasp/enduser.asp#lm

   b. The **lmsetup.exe** file may also be obtained directly from a subdirectory in the ***Spartan*** folder if you install the program directly onto your server . . . if you opt to install the program on your server, run through the installation procedure guided via the installation wizard. Upon completion, **lmsetup.exe** can be found in the following subdirectory:

      SPARTAN'06** : C:\...\Wavefunction\Spartan06Vxxx\Network\SERVERS\

2. It is suggested that you choose to configure the program to run as a 'service' during the installation procedure. When the program is finished installing, restart the server and verify that the NetHASP License Manager has loaded the necessary protocols for your network.

---

* The network HASP license management option requires a Windows machine to act as the license manager, client machines may be either Windows or Macintosh (**NAL**).

** ***Spartan*** has multiple Windows release versions, the pathname depends on which version you are running (Spartan'06 v.1.1.2 program directory = Spartan06V112) – Each contains the Network and SERVERS folders. Your server must be running Windows 2000 or higher.

3. If you are running a Firewall, open port 475. (Used by default, but also configurable).

For additional server options, you can also configure an NHSRV.ini file. Such options include specifying which client machines can access Spartan by IP range.

On Each Client Computer:

1. Install software locally on the network clients that will access the NetHASP through the network. Follow the installation procedure as guided by the installation wizard.

If the client machine is located on a different subnet than the server, you will need to add a network configuration file (nethasp.ini) to one or more directories as described below. Several variations of the file can be downloaded from the Aladdin website or you can use the template that is installed with Spartan:

http://www.aladdin.com/support/hasp/enduser.asp#ini

2. ***Spartan***: The template nethasp.ini can be found in:

C:\...\Wavefunction\Spartan06Vxxx\Network\

Locate the NETHASP.ini file and open with a text editor (ex. Notepad). The line that requires modification is the ";;NHSERVER_ADDR = <Addr1>, <Addr2>". Delete the two semicolons (;) and delete the <Addr1>, <Addr2>. Insert the IP address of your server on the right of the =. If you have more than one NETHASP installed, subsequent server IP addresses may be entered by placing a comma after the first address, followed by a space. After these modifications are completed, save the file.

Next, right Click on this nethasp.ini file and select 'Copy'. Move up one level to the ***Spartan*** folder. Right click on the background and select 'Paste'. Open both the P2 and P4 folder and also right click and 'Paste' the NETHASP.ini file in these folders as well.

Need additional help? Visit the Windows or Macintosh FAQs, www.wavefun.com, support section.

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Note: Items in **bold type** refer to entries in ***Spartan*** menus.

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