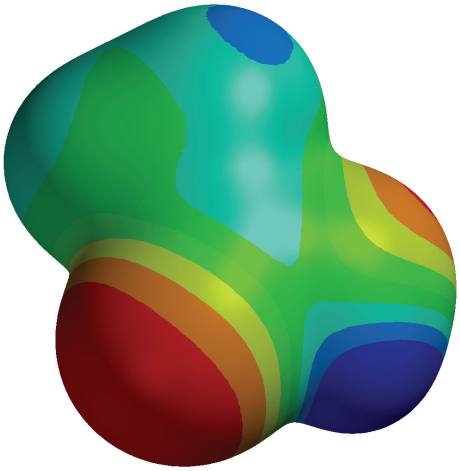
SpartanModel
An Electronic Model Kit



Organic Chemistry
Problems by Topic

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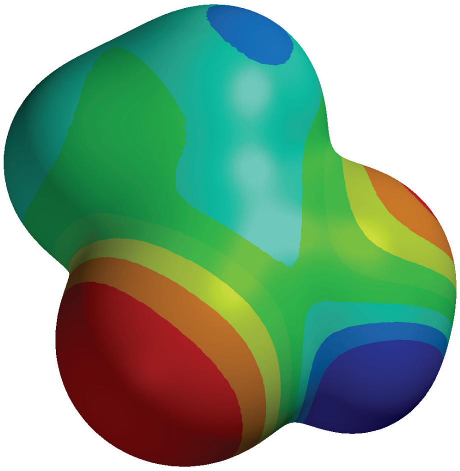

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Section I

INTRODUCTION

SpartanModel is a virtual model kit, designed to provide students of organic chemistry information about molecular structure, stability and properties. In the simplest of terms, ***SpartanModel*** is the 21st century equivalent of "plastic models" used by students of previous generations. Both provide the means to move from the two-dimensional drawings of molecules found in most modern textbooks to accurate three-dimensional portrayals. However, ***SpartanModel*** offers a number of significant advantages over plastic models.

The first advantage is that ***SpartanModel*** overcomes the fact that a plastic model kit contains only a limited number of "parts", perhaps ten or twenty "carbon atoms" and a much smaller number of nitrogen and oxygen atoms. Therefore, only relatively small molecules can be constructed. More importantly, a shortage of parts means that a molecule needs to be disassembled before another molecule can be assembled. This makes it impossible, or in the best circumstances, unnecessarily difficult, to compare the structures of different molecules. ***SpartanModel*** is unbounded, and molecules with dozens or even hundreds of atoms can be accommodated. Comparisons between different molecules can easily be made.

A related shortcoming of plastic model kits is that they are able to show off just a single aspect of molecular structure, most commonly, the connections (bonds) between atoms. Plastic models that depict overall size and shape are available, but need to be purchased and used separately. On the other hand, models made with ***SpartanModel*** may be portrayed either to emphasize bonding or to convey information about a molecule's overall size and shape. A further disadvantage is that plastic models "show" but do not "tell" us about important aspects of molecular structure, for example, about the volume that a molecule requires or its surface area. ***SpartanModel*** provides both a visual image as well as numerical values for these quantities. Of even greater practical value, ***SpartanModel*** assigns and displays R/S chirality, both for simple molecules where the rules are relatively easy to apply as well as for complex molecules where even an "expert" would be challenged.

Neither ***SpartanModel*** nor a plastic model kit is able to build proteins. However, ***SpartanModel*** connects seamlessly to the on-line ***Protein Data***

Bank[1] (PDB), providing access to ~60,000 experimental protein crystal structures. A PDB entry is automatically retrieved given its identifier, and displayed as a "ribbon model" (eliminating atomic details so as to emphasize the backbone structure). The model may be manipulated enabling detailed visual inspection.

The second advantage is that the structures obtained by ***SpartanModel*** are not based on the fixed dimensions of the "parts" as they are with plastic models, but rather result from application of quantum mechanics. This means that ***SpartanModel*** is actually a predictive tool, not merely one following empirical rules. It can be used to explore chemistry.

The third advantage is that the information provide by ***SpartanModel*** is not restricted to molecular structure as it is with plastic models. Energies, atomic charges and dipole moments, molecular orbitals and orbital energies and electrostatic potential maps may be obtained for any molecule. In addition, heats of formation and infrared spectra for approximately 6000 molecules obtained from high-quality quantum chemical calculations (beyond those provided in ***SpartanModel***) are available from a database included with and easily accessed from ***SpartanModel***. The availability of energies (as well as selected heats of formation) allows the most stable isomer to be identified and to say whether a reaction is *exothermic* or *endothermic*. Calculated energies may also be employed to assign the lowest-energy conformation of a molecule and to examine the likelihood that other conformers will be present. The infrared database provides realistic spectra and allows association of individual features in the spectrum with the motions of specific groups of atoms.

In short, plastic models are severely restricted, in terms of the complexity of what can be built, the accuracy of the presentations and in what information they are able to provide.

Some may argue that plastic models are "tried and tested", and that an electronic model kit is "unfamiliar" or "intimidating". We suspect that the vast majority of students will have the opposite perspective. After all, today's students have grown up with computers and expect to use them during their college education. In the final analysis, the choice is not between plastic and computer-based models, but whether or not models have something to offer in a chemist's education. We think that they do.

Section II

Getting Started with *SpartanModel*

A series of ***tutorials*** are supplied with ***SpartanModel*** and are directly accessible under **Tutorials** in the **Welcome** screen. These are intended to provide a "hands-on" start with the program, and cover molecule building and manipulation, examination of energies and molecular properties, display of molecular orbitals and electrostatic potential map, access to ***SpartanModel***'s databases, and to the Protein Data Bank. Starting with the **Basic Operations** tutorial, the entire set of tutorials may easily be completed in the span of one hour and we strongly recommend this as the starting point.

A set of ~140 ***problems***, accessible under **Problems** in the **Welcome** screen, address the wide range of topics found in organic chemistry textbooks. The collection is indexed according to topic, for example, aromatic compounds, but will also been keyed by chapter number and topic to the current editions of several widely-used texts.

Most of the problems are made up of text (html) files only, opening up a "blank screen" in ***SpartanModel***. However, some of the problems include materials that cannot be generated with ***SpartanModel*** and have been prepared using ***Spartan***. These include materials that involve reaction transition states and reaction energy profiles. These files have been marked "read only" and while the models may be examined and manipulated and measurements taken, they may not be altered.

The instructor is free to make additional tutorials and problems using ***Spartan***, and to add these to the existing collections.

Technical Overview of *SpartanModel*

SpartanModel may be viewed in terms of its components: a molecule builder including a molecular mechanics based scheme for preliminary structure refinement, a "real-time" quantum chemical "engine" and two databases.

SpartanModel's builder uses atomic fragments (for example, sp, sp^2 and sp^3 carbon fragments), functional groups (for example, amide and nitro groups) and rings (for example, cyclohexane and benzene). Some molecules can be made in just one or two steps ("mouse clicks"), while most others require fewer than ten steps. For example, fewer than 20 steps are required to build the steroid androsterone, the most complicated molecule provided in a tutorial that accompanies ***SpartanModel***. Once constructed, molecules can be displayed as to depict bonding (as with most types of plastic models) or overall size and shape (so-called space-filling or CPK models). Associated with the builder is a simple "molecular mechanics" procedure to provide a refined geometry as well as measurement tools for bond distances and angles, volumes, surface areas and polar surface areas (of space-filling models) and for assignment of R/S chirality.

The quantum chemical engine provided in ***SpartanModel*** may be used to obtain the geometries and properties of the vast majority of molecules encountered in elementary organic chemistry. The desire for open-endedness (any "reasonable size" molecule may be calculated) together with practical concerns, requires use of a very simple quantum chemical model. The procedure used in ***SpartanModel*** involves two quantum chemical steps and is preceded by a molecular mechanics[2] step to ensure a reasonable starting geometry. The first quantum chemical step is calculation of geometry using the PM3[3] semi-empirical model and the second step is calculation of the energy and wavefunction at this geometry using the Hartree-Fock 3-21G[4] model. The resulting wavefunction is used for calculation of the dipole moment and atomic charges and (if requested) graphical displays of the molecular orbitals and electrostatic potential map. PM3 geometry calculations and 3-21G energy calculations for molecules comprising up to 30-40 heavy (non-hydrogen) atoms are likely to require less than one minute on a present day Windows or Macintosh computer.

The quantum chemical calculations in ***SpartanModel*** properly account for geometry and provide a sound basis for graphical displays of molecular orbitals and electrostatic potential maps. They also provide a qualitatively accurate account of the energies of most types of chemical reactions as well as conformational energy differences. Heats of formation for ~6000 molecules obtained from the T1[5] thermochemical recipe and included in a database can be used to supplement calculated energies where higher accuracy may be necessary. T1 has been shown to reproduce experimental heats of formation with an rms error of ~8 kJ/mol.

The second database contains infrared spectra for ~6000 molecules obtained from the EDF2[6]/6-31G* density functional model, adjusted to account for known systematic errors and for finite temperature. The resulting spectra are visually and quantitatively very similar to observed infrared spectra. Vibrational motions associated with individual lines in the spectrum may be "animated". For example, it is now easy to "see" that the strong peak in the infrared spectrum of a carbonyl compound in the vicinity of 1700 cm^{-1} is due to a stretching motion of the CO double bond.

References:

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2. T.A. Halgren, *J. Computational Chem.*, **17**, 490 (1996).
3. J.J.P. Stewart, *J. Computational Chem.*, **10**, 209 (1989).
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5. W.S. Ohlinger, P.E. Klunzinger, B.J. Deppmeier, W.J. Hehre, *J. Phys. Chem. A.*, **113** 10, 2165 (2009).
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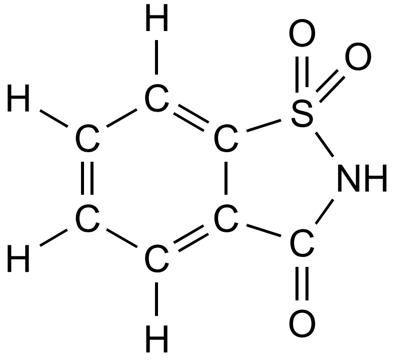
Section III

Organic Chemistry Problems

1. Structure and Bonding

1. Structure of Saccharin. The "language" that chemists use to convey molecular structures often relies on a broad base of knowledge about what is "reasonable" and what is not. For example, taken at face value a drawing of the artificial sweetener saccharin would seem to imply that all atoms reside in a single plane, that is, the molecule is planar. An experienced chemist would know that it is not correct. Molecular models can help to make the connection between two-dimensional drawings and three dimensional structures, especially in the beginning when students are just starting to acquire this knowledge



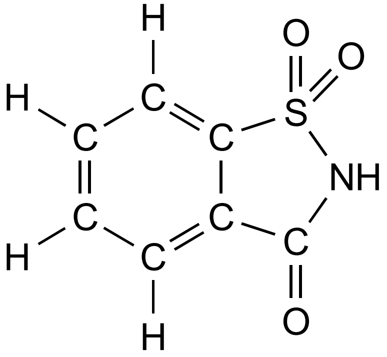
Build saccharin and obtain its structure. You will see that the two oxygen atoms bonded to sulfur rise above and below the plane made by all the other atoms. The molecule has a plane of symmetry (the two out-of-plane oxygen atoms are equivalent), but it is not planar.

2. Dipole Moment of Saccharin. The direction of the dipole moment in a diatomic molecule such as hydrogen fluoride, +−H─F→ (→ is at the negative end of the dipole) follows from the fact that fluorine is more electronegative than hydrogen. This may easily be generalized to a molecule like fluoromethane. The fact that fluorine is at the negative end of the dipole would lead us to conclude that it is also more electronegative than a methyl group. The situation becomes complicated where the molecule contains two or more different polar bonds. For example, saccharin contains polar bonds between carbon and nitrogen, oxygen and sulfur as well as a polar NH bond and two polar sulfur-oxygen bonds. The dipole moment for saccharin results from a combination of all of these.

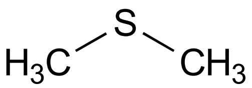
Build saccharin and display the dipole moment vector. Assuming that the nitrogen is at the negative end of the NH bond dipole and O is at the negative end of the C=O bond dipole, is sulfur or oxygen at the negative end of the S=O bond dipoles? Which appears to be larger, the C=O bond dipole or the pair of S=O bond dipoles? Explain your reasoning.

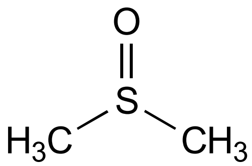
3. Electrostatic Potential Maps and the Charge Distributions in Molecules. The dipole moment of a molecule provides a measure of its overall polarity. Much more detail about the charge distribution in a molecule may be obtained from an electrostatic potential map. The electrostatic potential measures the extent to which a point positive charge (an electrophile) is either attracted to or repelled by a molecule. A negative potential corresponds to attraction and is likely to occur where electrons are in excess, whereas a positive potential corresponds to repulsion and is likely to occur where there is a deficiency of electrons. An electrostatic potential encodes the value of the potential onto the molecular "surface", defined as a "skin" that encloses a large fraction of the total number of electrons. Such a surface is much like a space-filling model in that both are intended to convey overall molecular size and shape. By convention, the surface is colored red in regions of negative potential and blue in regions of positive potential, with colors in between (orange, yellow, green and cyan) designating regions with intermediate values of the potential. For a neutral molecule, ***SpartanModel*** uses the color green to designate regions on the surface that are close to electrically neutral.

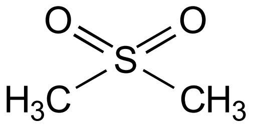
First, examine the electrostatic potential map for saccharin. Which atoms are negative and which are positive? Is there a correlation between electrostatic potential and atomic electronegativity?



Next, compare maps for dimethyl sulfide (left), dimethyl sulfoxide (middle) and dimethyl sulfone (right).



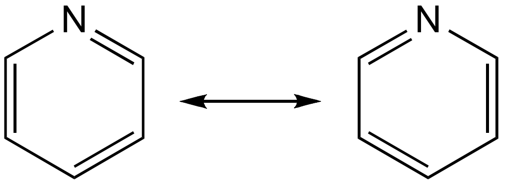




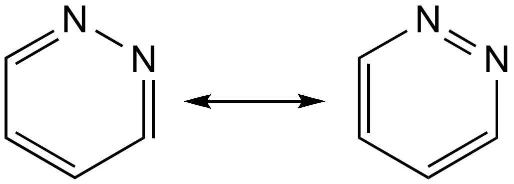
Which molecule shows the greatest variation in charge? Which shows the least variation? Next, compare maps for the corresponding di-(*tert*-butyl) compounds. Compared to the methyl compounds, do these show lesser or greater variations in charge distribution? Assume that the greater the variation in charge, the more likely the compound will be to dissolve in a polar solvent. Propose an order of solubility for the three dimethyl compounds, the three di-(*tert*-butyl) compounds, and each of the dimethyl compounds relative to its di-(*tert*-butyl) analogue.

Note that it is essential to use the same scale in comparing electrostatic potential maps for different molecules. ***SpartanModel*** enforces a single scale for all neutral molecules, from -200 kJ/mol (red) to +200 kJ/mol (blue). All anions are presented on a second fixed scale from -800 kJ/mol (red) to 0 (green) and all cations are presented on a third fixed scale from 0 (green) to +800 kJ/mol (blue).

4. Pyridine and Pyrazine. The heterocycles pyridine and pyrazine are each represented by a pair of Lewis structures.



pyridine



pyrazine

While the two structures are the same for pyridine, they are different for pyrazine. Calculate geometries for both pyridine and pyrazine. Using the geometry of pyridine as a reference, would you conclude that the two Lewis structures for pyrazine are equally important? If not, which structure should be given more weight?

5. Carbon Monoxide. While carbon monoxide is not usually thought of as an "organic reagent", it is by far the most common small molecule bound to metals in organometallic compounds. Here the carbon acts as a σ electron donor, something that might seem surprising given that oxygen is the more electronegative element.

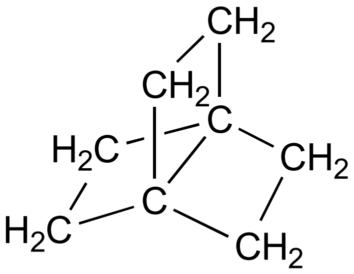
The dipole moment of formaldehyde, $H_2C=O$, is typical of a compound incorporating a CO double bond. What is its magnitude? Is the direction of the dipole moment consistent with the relative electronegativities of carbon and oxygen? Is the direction of the dipole moment in carbon monoxide the same as that of formaldehyde? Is the magnitude similar? Provide an explanation for any significant differences. It might help to compare electrostatic potential maps for the two molecules.

6. Molecular Orbitals and Molecular Symmetry. The distribution of electrons in a molecule reflects the symmetry of the molecule. For example, the electron distribution in water reflects the fact that the two hydrogen atoms are the same. The electron distribution follows from the ***square*** of the molecular orbitals, rather than from the molecular orbitals themselves. This means that only the magnitude of a molecular orbital and not its sign needs to reflect the symmetry of a molecule. While the overall sign of a molecular orbital is unimportant, changes in sign are informative. Continuity of sign over nearby atoms generally indicates favorable bonding interactions involving these atoms, whereas a change in sign between atoms that are close generally indicates unfavorable antibonding interactions.

One after the other, examine the four valence molecular orbitals of water. For each, indicate whether the hydrogen atoms are involved or are not involved in the orbital. If they are involved, indicate whether the orbital has the same or opposite sign for the two hydrogen atoms.

Repeat your analysis for ethylene where both carbon atoms are equivalent and all four hydrogen atoms are equivalent.

7. Propellane. Two of the carbons in [2.2.2]propellane are planar (or close to planar) just as are the carbons involved in the double bond in an alkene.



Are the “planar carbons” really planar (measure CCC bond angles)? Is the bond connecting these two carbons a “normal” or slightly extended single bond (<1.6Å), or is it significantly longer? Compare the electrostatic potential map for [2.2.2]propellane with that of 2,3-dimethyl-2-butene. Is the potential in the vicinity of the planar carbon as negative as that in the alkene?

2. Polar and Non-Polar Molecules

1. Hydronium. The proton in water is usually depicted as H_3O^+ or hydronium ion. This is not an adequate description. The positive charge will disperse through hydrogen bonding between the hydrogen atoms of hydronium and oxygen atoms on surrounding water molecules and *vice versa*, forming a first ***solvation shell***. Additional water molecules will in turn hydrogen bond to those that make up the initial shell, further dispersing the charge.

How many water molecules make up the first solvation shell for hydronium cation? Compare electrostatic potential maps for hydronium cation and hydronium cation surrounded by this number of water molecules. What evidence do you see that the positive charge is dispersed? Double or triple the number of water molecules around hydronium cation and obtain another electrostatic potential map. Is there evidence for further dispersal of charge? Elaborate.

Starting with hydronium cation, select sp^3 oxygen from the palette of atomic fragments and *click* anywhere on screen, move the cursor to a blank area of the screen and *double click*. Repeat to add a second, third, … water molecule Rotate the graphic every few molecules to provide a three-dimensional starting structure.

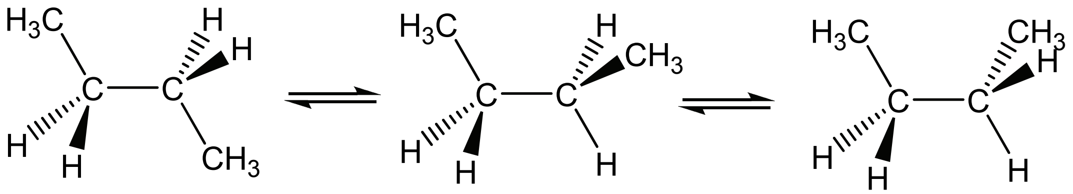
2. Weak vs. Strong Acids. Ethanol is a very weak acid, acetic acid of a moderately strong acid and sulfuric and nitric acids are very strong acids. Compare electrostatic potential maps for these molecules. Focus your attention on the acidic hydrogen. Do the maps reveal the known ordering of acid strengths in these compounds? Use electrostatic potential maps to try to find compounds that are stronger acids than nitric or sulfuric acids.

3. Changing Structure Changes Acid Strength. What effect does changing the structure of a molecule have on its acid strength? Compare electrostatic potential maps for acetic acid (CH_3CO_2H), pivalic acid (Me_3CCO_2H) and trifluoroacetic acid (CF_3CO_2H). Focus on the carboxylic acid hydrogen. Which is the strongest acid? Which is the weakest acid? Relative to a methyl group, do you conclude that a *tert*-butyl group acts to donate or accept electrons? Relative to a methyl group, does the trifluoromethyl group donate or accept electrons? Elaborate.

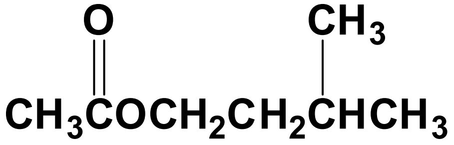
4. Steric Effects and the Conformations of Alkanes. The fact that the *anti* conformer of *n*-butane is favored over the *gauche* conformer is given as evidence that alkyl groups in close contact will repel each other. Is it reasonable to expect that the larger the alkyl group, the larger will be the repulsion and the greater the preference for the "least crowded" conformer?

Calculate the difference in energy between *anti* and *gauche* conformers of *n*-butane and 2,2-dimethylpentane. Is the *anti* conformer of *n*-butane favored over the *gauche* conformer? Is the conformational preference that you find in 2,2-dimethylpentane larger (in favor of the *anti* conformer) larger than that for *n*-butane? If so, provide an explanation.

5. Flexible Molecules. While there are important lessons to be learned from examining the best conformation of a molecule like *n*-butane where there is only a single rotatable bond, most "real" molecules have several flexible bonds and may exhibit large numbers of conformers. A good "rule of thumb" is that each σ bond between non-hydrogen atoms that does not involve a symmetrical group (such as a methyl or *tert*-butyl group) multiplies the number of conformers by three. Thus, a molecule with one such bond has as many as three conformers and a molecule with two bonds has as many as nine conformers. The total number of unique conformers may be fewer, especially for very small molecules. For example, the rotation about the central bond in *n*-butane leads to three conformers, but two of them are identical.

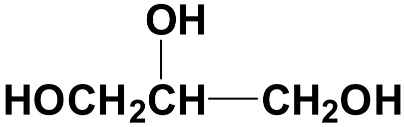


Estimate the number of conformers available to 3-methylbutyl acetate, to 2,3-dihydroxypropanol and to vitamin E.



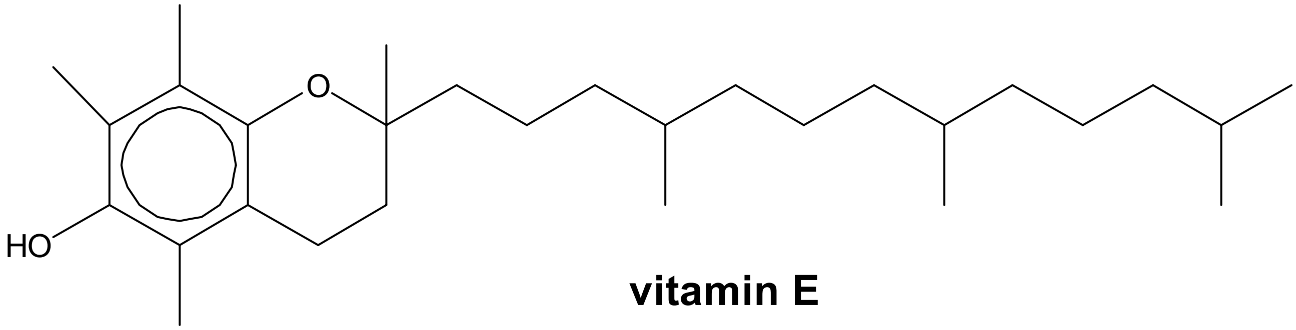
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3$

3-methylbutyl acetate



$HOCH_2\overset{OH}{\overset{|}{C}}H-CH_2OH$

2,3-dihydroxypropenol



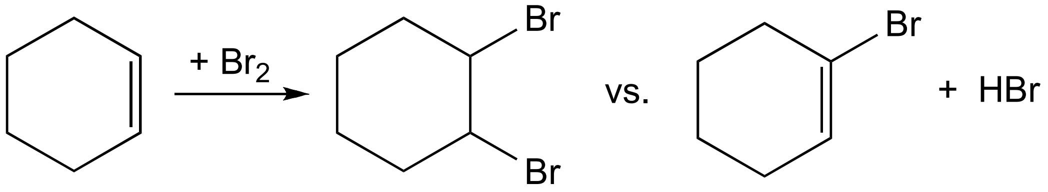
vitamin E

6. Exothermic and Endothermic Reaction. Two parts contribute to the Gibbs energy (ΔG) of a reaction, the enthalpy or heat (ΔH) and the entropy (ΔS).

$$\Delta G = \Delta H - T\Delta S$$

T is the temperature in K. Enthalpy is typically the more important in determining whether a reaction is favorable or unfavorable. Where a molecule might undergo two or more different reactions, differences in the enthalpies of reaction are normally a good indicator of which will occur.

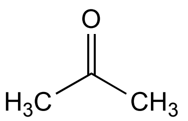
A good example is provided by the two pathways that may be followed in the reaction of cyclohexene with bromine. On the one hand is ***addition*** leading to *trans*-1,2-dibromocyclohexane and on the other is ***substitution*** leading to 1-bromocyclohexene and hydrogen bromide.



Calculate energies for reactants and for both sets of products (or obtain them by using ***SpartanModel*** to access the database of estimated heats of formation). Are both reactions *exothermic*? Which reaction is favored? Would you expect the difference in Gibbs energy between the two reactions to be smaller or greater than the difference in enthalpy? Elaborate.

7. Using Electrostatic Potential Maps to Classify Organic Solvents. Most molecules will dissolve in either aqueous or "organic" solvents, but not both. Of course, not all organic solvents are the same, but span a wide range from non-polar molecules such as hexane, to polar molecules that lack hydrogen-bond donors such as acetone, to polar molecules with hydrogen bond donors such as ethanol. Electrostatic potential maps can help to quantify the character of a particular solvent.

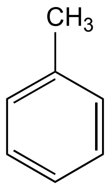
Obtain electrostatic potential maps for water and hexane to serve as a "baseline". Assume that values of the potential between -100 and 100 kJ/mol correspond to non-polar regions while those where the potential lies outside this range correspond to polar regions. For each molecule, estimate what fraction of the total surface is non-polar. Repeat your calculations for a series of common organic solvents, among them, acetone, ethanol, toluene, tetrahydrofuran (THF), and dimethylformamide (DMF). Add a few other solvents of your choice. For each, estimate the fraction of the surface that is non polar. Rank all solvents according to polarity.



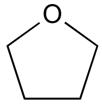
acetone

CH_3-OH

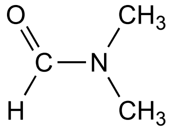
ethanol



toluene



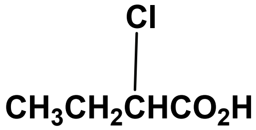
tetrahydrofuran



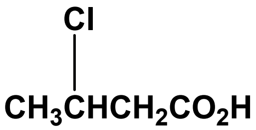
dimethylformamide

8. Ordering Acidities with Electrostatic Potential Maps. Use electrostatic potential maps to order the acidities for each of the following sets of compounds.

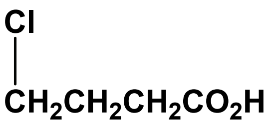
a.



$CH_3CH_2\overset{Cl}{C}HCO_2H$

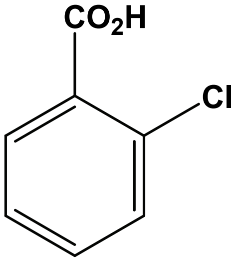


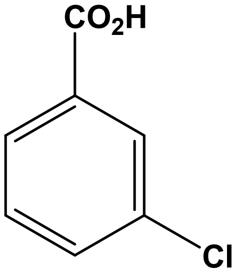
$CH_3\overset{Cl}{C}HCH_2CO_2H$

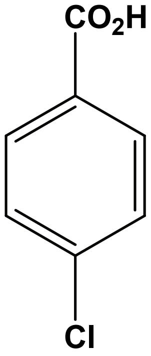


$\overset{Cl}{C}H_2CH_2CH_2CO_2H$

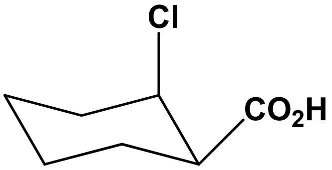
b.

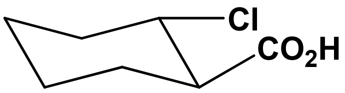






c.





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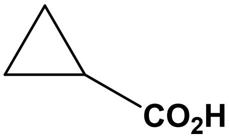
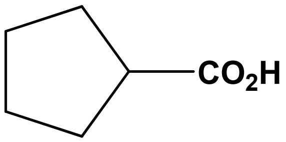
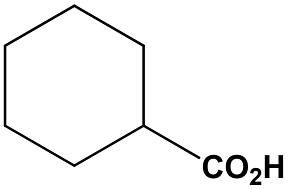






9. Dipole Moments and Atomic Charges in Diatomic Molecules. The charge on an atom in a molecule, Q_A, is not something that can actually be measured. However, the charge on an atom in a diatomic molecule may be related to the dipole moment for that molecule, which can be measured.

Q_A = dipole moment (debyes)/ 4.8 R_{AB}

R_{AB} is the AB bond distance.

One after another, obtain dipole moments and AB bond lengths for hydrogen fluoride, hydrogen chloride, hydrogen bromide and hydrogen iodide.

Calculate atomic charges. Do these follow the electronegativities of the halogens?

10. Miscible and Immiscible Liquids. Some liquids are “miscible” (mix in any proportion) while others are “immiscible”. While ***SpartanModel*** does not allow you to observe “real” liquids or mixtures of liquids, you can judge whether two molecules are likely to be miscible by looking at what happens when you add a molecule to a small cluster (“droplet”) of a different molecule. What happens when you add an ammonia molecule to a droplet of water? What happens when you add a molecule of methane to a water droplet?

Build a droplet 40-50 water molecules, and minimize its geometry ***using molecular mechanics***.

Select sp^3 oxygen O- from the palette of atomic fragments and *click* anywhere on screen. Then move the cursor to a blank area of the screen and *double click*. A second water molecule appears. Repeat the process until you have a “droplet” of 45-50 water molecules (a count is provided at the bottom of the screen). Rotate the graphic every few molecules to provide a three-dimensional starting structure for the droplet. *Click* on E (or select **Minimize** from the **Build** menu). The calculation may take one or two minutes. To replace a (centrally located) water molecule with an ammonia or methane) molecule, select sp^3 nitrogen N (icon) or sp^3 carbon C- from the palette and *double click* on the oxygen atom (not free valence). *Click* on E.

When it is done, examine the resulting structure. How many hydrogen bonds stem from water molecules near the center of the droplet?

Replace one of the water molecules at the center of the water droplet by an ammonia molecule. Is the number of hydrogen bonds associated with the ammonia molecule the same as that with the water molecule it replaced? What does your result suggest about the miscibility of water and ammonia?

Finally, replace the ammonia molecule with a molecule of methane. Examine the resulting structure with regard to hydrogen bonding. Does it suggest that methane and water are likely to be miscible? Switch to a space-filling model. Describe what you observe. Is it consistent with whatever changes occur to hydrogen bonding?

3. Alkanes and Cycloalkanes

1. Charge Distribution in Cycloalkanes. Cyclopropane is a highly-reactive molecule whereas cyclopentane and cyclohexane are largely inert. Is this due entirely to strain (thermodynamics) or is cyclopropane also unusually reactive (kinetics). Compare the electrostatic potential map for cyclopropane with those of cyclopentane and cyclohexane. Are the hydrogen atoms in cyclopropane more electron deficient than those in the larger cycloalkanes, suggesting that it is likely to be more acidic? Are the carbon-carbon bonds in cyclopropane more electron rich than those in the larger cycloalkanes, suggesting increased reactivity toward electrophiles? Obtain an electrostatic potential map for propene. Does this appear to be a closer match to the map for cyclopropane than the maps for the larger cycloalkanes? Elaborate.

2. Bond Lengths in Small-Ring Cycloalkanes. One might suspect that the carbon-carbon bond distances in cyclopropane are longer than those in an “unstained” cycloalkane such as cyclohexane? Afterall, this would seem to be an “obvious” way to ease the strain. The same argument suggests that carbon-carbon bond lengths in cyclobutane should be in between those in cyclopropane and in cyclohexane. Obtain equilibrium geometries for cyclopropane, cyclobutane and cyclohexane. What is the actual ordering of carbon-carbon bond lengths in the three cycloalkanes? If this differs from your expectations, try to provide a rationale.

3. Stereoisomers of Disubstituted Cyclopropanes. *cis* and *trans* stereoisomers exist for 1,2-disubstituted cyclopropanes for the same reason that *cis* and *trans* stereoisomers exist for 1,2-disubstituted ethylenes. In both situations, interconversion requires breaking a carbon-carbon bond, something that is difficult and not likely to be observed under normal conditions. As *trans* cyclopropanes are likely to be less crowded than the corresponding *cis* structures, is it reasonable to anticipate that they will the more stable (lower in energy), just as *trans* alkenes are more stable than *cis* alkenes. What is not obvious is whether the *cis-trans* energy differences in disubstituted cyclopropanes will be smaller, larger or about the same as the difference for the corresponding disubstituted alkenes?

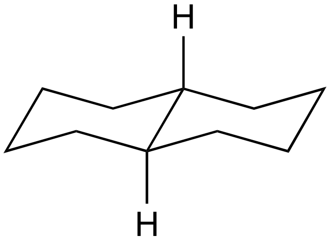
Obtain energies for *cis* and *trans* stereoisomers of *1,2*-dimethylcyclopropane and *cis* and *trans* stereoisomers of 2-butene. Alternatively, obtain heats of formation from the database accessible from ***SpartanModel***. Is the *trans* stereoisomer favored for both *1,2*-dimethylcyclopropane and 2-butene? Calculate *cis*-*trans* energy differences. Is the preference noted for the cycloalkane smaller, larger or comparable to that noted for the alkene? Rationalize your result.

4. Axially-Substituted Cyclohexanes. The usual explanation given for the observation that substituents on cyclohexane prefer *equatorial* over *axial* positions is that this minimizes non-bonded (steric) interactions. While the energy from a quantum chemical calculation may not be broken down into different components, the geometry can reveal atoms that have moved closer than the sum of their van der Waals radii. For non-bonded HH interactions the distance is 2.4Å (twice the van der Waals radius for hydrogen). Non-bonded HH contacts that are only slightly less than 2.4Å would be expected to lead only to a modest increase in energy, while those that are 2.3Å or less would be expected to have greater effect.

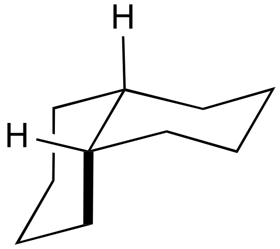
Obtain structures for both *equatorial* and *axial* methylcyclohexane. How many HH contacts are shorter than 2.3Å for the *equatorial* conformer? How many short contacts exist for the *axial* conformer? Is the conformer with the fewer number of short HH contacts also the lower energy conformer?

Repeat your analysis for the two conformers of *cis*-1,3-dimethylcyclohexane. You need to consider non-bonded contacts between hydrogen atoms on the two methyl groups in addition to those involving one methyl hydrogen and one *axial* ring hydrogen. How many HH contacts are shorter than 2.3Å for the *diequatorial* conformer? How many short contacts exist for the *diaxial* conformer? Is the conformer with the fewer number of short HH contacts also the lower energy conformer? Compare the conformer energy difference for *cis*-1,3-dimethylcyclohexane with that for methylcyclohexane. Does it parallel the difference in the number of short HH contacts between conformers? Elaborate.

5. Cis and trans-decalin. The four carbon-carbon bonds involved with “fusing” the two rings are all *equatorial* in *trans*-decalin, but one of the four is *axial* in *cis*-decalin. This provides the rationale why the *trans* form is the more stable.



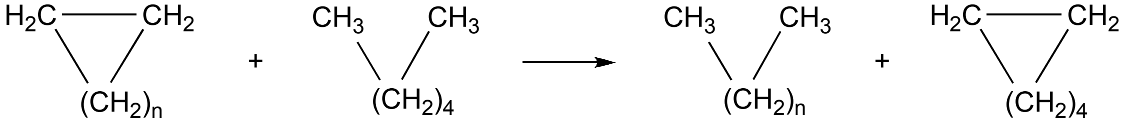
trans-decalin



cis-decalin

Calculate energies for both decalin isomers. Which isomers is preferred and by how much? Is the direction of the preference the same as for *cis* and *trans* isomers of 1,2-dimethylcyclohexane? Is the magnitude of the preference similar? If it is significantly different, suggest a reason why. What happens to the preference when you substitute methyl groups for hydrogen atoms at both the carbons involved in the ring junction? Rationalize your result.

6. Strain Energies of Small-Ring Cycloalkanes. Cyclopropane is a highly strained molecule whereas cyclohexane is not. Is the strain energy of cyclobutane closer to that of cyclopropane or cyclohexane? Is the strain energy of cyclopentane intermediate between those of cyclobutane and cyclohexane? Is cycloheptane more strained than cyclohexane? To assess the strain in cyclopropane, cyclobutane, cyclopentane and cycloheptane relative to that in cyclohexane, calculate energies of reactants and products for the reaction shown below where n = 1, 2, 3 and 5. Alternatively, use heats of formation from the database accessible from ***SpartanModel***.



4. Properties of Haloalkanes

1. Carbon-Fluorine Bond Lengths in Fluoromethanes. Do the lengths of bonds between sp^3 carbon and attached atoms or functional groups vary significantly with the number of groups? Experimental carbon-carbon bond lengths for ethane (1.531Å), propane (1.526Å), 2-methylpropane (1.541Å) and 3,3-dimethylpropane (1.540Å) show only slight variation. Is this always the case? Obtain carbon-fluorine bond lengths in fluoromethanes, CF_nH_{4-n} (n=1-4). Do they increase or decrease significantly with increasing number of fluorines, or are they relatively constant? If you find that bond lengths change significantly, offer an explanation as to why.

Repeat your calculations and analysis for the chloromethanes, CCl_nH_{4-n} (n=1-4). Point out any significant differences with the results for fluoromethanes. For which, if either, set of compounds is the change in bond lengths with increasing substitution most similar to what is observed for alkanes?

2. Bond Stengths in Fluoromethanes. Carbon-fluorine bond distances change significantly with increased number of fluorine atoms attached to carbon. Are these changes are mirrored by changes in carbon-fluorine bond strengths? One measure is provided by comparing the energies of the three reactions below.

$$CF_4 + CH_4 \longrightarrow CF_3H + CH_3F$$

$$CF_3H + CH_4 \longrightarrow CH_2F_2 + CH_3F$$

$$CH_2F_2 + CH_4 \longrightarrow 2CH_3F$$

Calculate energies for all reactants and products for (alternatively use heats of formation from the database accessible from ***SpartanModel***), and evaluate reaction energies. Is replacement of a CF bond in carbon tetrafluoride by a CH bond more or less difficult than replacement in fluoroform (CF_3H)? Is replacement of a CF bond in fluoroform more or less difficult than replacement in methylene fluoride (CF_2H_2)? Is there a relationship between CF bond lengths and bond energies? Elaborate.

Repeat your calculations and analysis for the chloromethanes, CCl_nH_{4-n} (n=1-4). Point out any significant differences with the results for fluoromethanes. Are any differences in bond energy changes between fluoromethanes and chloromethanes reflected in differences in bond length changes?

5. Reactions of Alkanes

1. tert-Butyl Radical. *tert*-Butyl radical may be formed from *tert*-butyl iodide either by heating or by exposuring the compound to light.

$$Me_3C-I \longrightarrow Me_3C^{\bullet} + I^{\bullet}$$

What kind of environment does *tert*-butyl radical present? To decide, compare the electrostatic potential map for *tert*-butyl radical with that of 2-methylpropene. Which is more electron rich, the radical or the alkene? Compare the electrostatic maps methyl and *tert*-butyl radicals. Do the methyl groups act to increase or decrease electron count at the radical center? Is this what you expect based on comparisons of electrostatic potential maps for the analogous alkenes, ethylene and 2-methylpropene? Elaborate.

2. Tetramethylbutane. The central carbon-carbon bond in 2,2,3,3-tetramethylethane (tetramethylbutane) is known to be significantly weaker than the CC bond in ethane. One explanation is that bond cleavage relieves the crowding of the methyl groups. Another is that is *tert*-butyl radical (the product of bond dissociation of tetramethylbutane) is much more stable than the methyl radical (the product of dissociation of ethane). To find out which explanation is correct or if both contribute, calculate energies for the following four reactions. (Do not to start with a symmetrical staggered structure for tetramethylbutane.)

$$\mathrm{Me_3C{-}CMe_3 + 2H_3C^{\bullet} \longrightarrow 2Me_3C^{\bullet} + H_3C{-}CH_3}$$

$$\mathrm{Me_3C{-}CMe_3 + H_2 \longrightarrow 2Me_3CH}$$

$$\mathrm{H_3C{-}CH_3 + H_2 \longrightarrow 2CH_4}$$

$$\mathrm{Me_3CH + H_3C^{\bullet} \longrightarrow Me_3C^{\bullet} + CH_4}$$

The first reaction directly compares carbon-carbon bond energies of tetramethylbutane and ethane. The next two reactions provide the energies of hydrogenation of tetramethylbutane and ethane (both giving rise to uncrowded products). The last reaction compares bond energies of these (uncrowded) products (providing a measure of the relative stabilities of the methyl and *tert*-butyl radicals).

Is the bond energy in tetramethylbutane less than that in ethane? If it is, by how much? Is there evidence for crowding in the geometry of tetramethylbutane? Is the central carbon-carbon bond similar in length to the bond in ethane? Are all single bonds staggered? Does the difference between the hydrogenation energies of tetramethylbutane and ethane partially or fully account for the difference in bond energies? Does the difference in difficulty of formation of *tert*-butyl and methyl radicals partially or fully account for the difference in bond energies?

6. Stereochemistry

1. Properties of Enantiomers and Diastereomers. Molecules that are mirror images but that are not superimposable mirror images are referred to as ***enantiomers***. This distinguishes them from molecules that are superimposable mirror images, which are identical. Are the properties of enantiomers the same or different?

1-chloro-1-fluoroethane is a molecule with a single chiral center. Its mirror image is not superimposable. Build either the R or S enantiomer, calculate its geometry and record the carbon-carbon bond length, binding energy, dipole moment and atomic charges. Next, build the other enantiomer, calculate its geometry and record the same quantities. Are the properties of the two enantiomers the same or are they different?

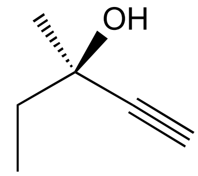
SpartanModel provides an easy way to make the enantiomer of a molecule. Inside the builder, *double click* on any atom while holding down on the both the **Shift** and **Ctrl** (**Control**) keys.

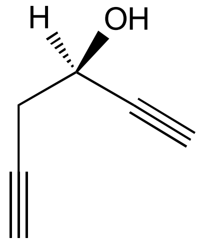
The situation is more complicated where there are two chiral centers in a molecule. For example, *trans*-1,2-dichloro-1-fluorocyclopropane has two chiral centers, ***both of which*** are either R or S. Simultaneous inversion of both centers leads to the enantiomer. Build one of the enantiomers of *trans*-1,2-dichloro-1-fluorocyclopropane, calculate its geometry and record the three carbon-carbon bond lengths, binding energy, dipole moment and atomic charges. Next, build the other enantiomer, obtain its geometry and record the same quantities. Are they the same or are they different?

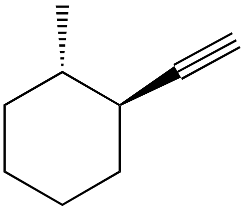
Inversion of only one of the two centers leads to a ***diastereomer***. Are the properties of diastereomers the same or different? To see, invert only one of the two chiral centers in *trans*-1,2-dichloro-1-fluorocyclopropane. Without doing any calculations, can you tell if the original molecule and its diastereomer are likely to have the same properties? Elaborate. Test your thinking by obtaining the geometry of the new structure and comparing its properties to those obtained previously.

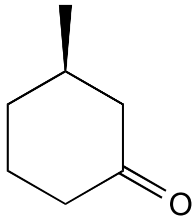
To “invert” a single chiral center**,** *double click* on the appropriate atom while holding down on only the **Ctrl** (**Control**) key.

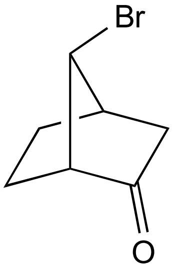
2. Assigning R/S Chirality. The procedure for assigning R/S chirality “by hand” is easily applied to acyclic molecules as well as molecules with simple rings. Provide R/S assignments for all chiral centers in each of the compounds shown below, and then check your results using ***SpartanModel***.

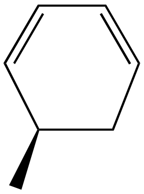




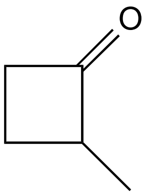
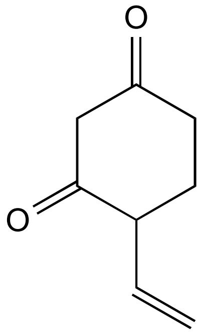


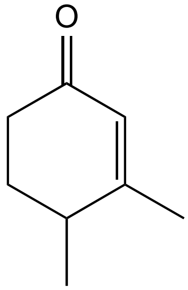
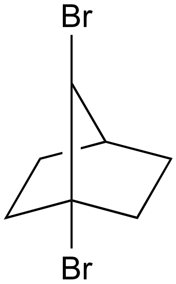




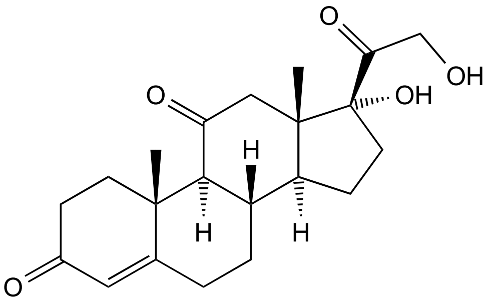


Provide drawings including stereochemical markers for the specified enantiomer of each of the following molecules. When you are done use ***SpartanModel*** to check your assignments.

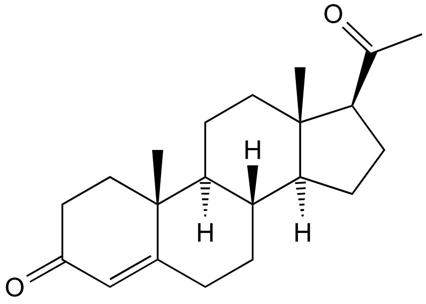
R enantiomer of  R enantiomer of 

S enantiomer of  S enantiomer of 

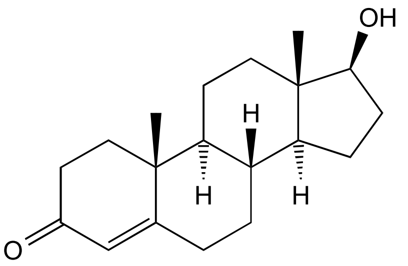
Correctly assigning chirality in complex molecules, in particular, molecules with "fused rings" can be much more problematic. Identify and assign the chiral centers in the four well-known steroids sketched below. When you are done, check you results with ***SpartanModel***.



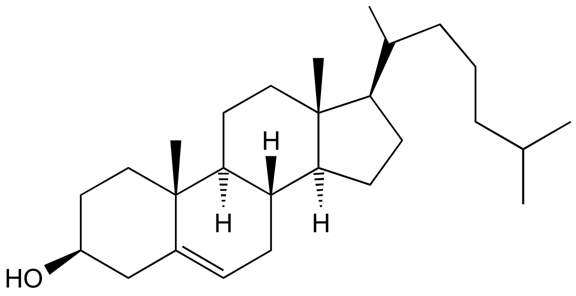
Cortisone



Progesterone

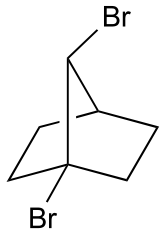


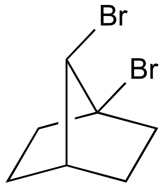
Testosterone

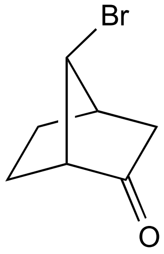


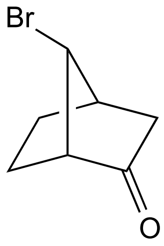
Cholesterol

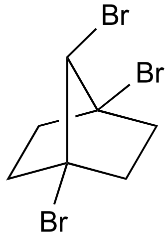
3. Stereochemical Relationships. Are the two molecules in each of the following pairs, the same, enantiomers or diastereomers? Use ***SpartanModel*** to help you decide.

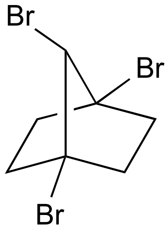




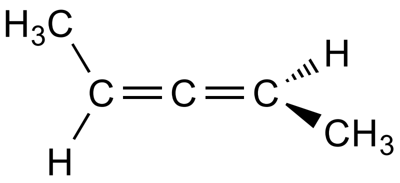








4. Chiral Molecules Without Chiral Centers? A chiral molecule is a molecule which is not superimposable on its mirror image. Does such a molecule need to incorporate a chiral (R/S) center? Construct 2,3-pentadiene along with its mirror image. Are the two molecules superimposable? If not, do they contain one or more R/S centers? Calculate energies, dipole moments and atomic charges for the two molecules. Are they the same? Do the molecules fit the definition of enantiomers?



7. Alcohols

1. Boiling Points of Alcohols and Ethers. To gain insight why the boiling point of ethanol (79°C) is much higher than that of dimethyl ether (-23°C), build clusters of 15-20 molecules for both molecules. Use molecular mechanics.

The cluster geometries that you have obtained are assumed to be representative of the enormous number of possible structures. A more quantitative approach to calculate the properties of clusters (and ultimately liquids) is to average over all possible geometries. Obtaining the geometry for even a single cluster structure is difficult and beyond the practical range of the quantum chemical model available in ***SpartanModel***. Molecular mechanics presents the only viable alternative.

What is the maximum number of hydrogen bonds involving a single molecule of ethanol? What is the maximum number of hydrogen bonds involving a single molecule of dimethyl ether? Provide a plausible explanation for the difference in boiling points between the two molecules.

2. Sulfur Analogues of Alcohols and Ethers. The dipole moment for a molecule may be thought of as a vector sum of the dipole moments of its component bonds. Each bond dipole is proportional to the product of the difference in charge on the two atoms and the distance between them. Oxygen is more electronegative than sulfur, which suggests that OH and OC bond dipoles will be larger than the corresponding SH and CS bond dipoles. However, an OH bond is shorter than a SH bond (and a CO bond shorter that a CS bond), which leads to the opposite conclusion. Are dipole moments of thiols and sulfides typically larger or smaller than those of the corresponding alcohols and ethers?

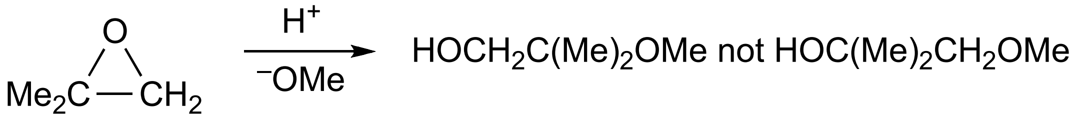
Obtain equilibrium geometries and atomic charges for methanol and methanethiol and for dimethyl ether and dimethyl sulfide. Is the OH bond distance in the alcohol shorter than the SH distance in the thiol? Is the average of the CO bond distances in the alcohol and ether shorter than the average of the CS bond distances in the sulfide? Is the charge separation in an OH bond larger than that in an SH bond? Is the average charge separation in a CO bond larger than that in a CS bond (count the charges on the three hydrogen atoms)? Are the dipole moments in the oxygen compounds larger, smaller or about the same as those in their sulfur analogs?

3. 18-Crown-6. A crown ether is a ring made up of sp^3 carbon and oxygen atoms, for example, 18-crown-6 is made up of six repeating $–OCH_2CH_2-$ units. 18-crown-6 and molecules like it provide an electron-rich environment and may be able to "tie up" the cation in a salt, thereby releasing the anion to "do chemistry". Strong binding requires not only that the "host" (the crown ether) presents a suitably hospitable (negative) environment for the "guest" (the positive ion), but also that the guest fits comfortably inside the host.

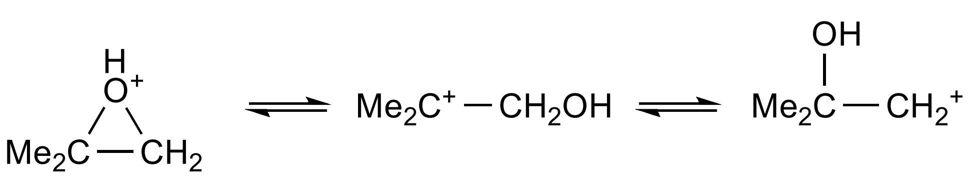
18-crown-6 and a few of its complexes with alkakli metal cations appear on screen. Measure the distance between oxygen atoms at opposite sides of the ring in "free" 18-crown-6 (top left of the screen). Compare this to the corresponding distances in 18-crown-6 complexes of lithium (top right), sodium (bottom left) and potassium (bottom right) cations. (The complexes are initially shown as space-filling models in order to give you an idea of fit. You can display them as ball-and spoke models to better see the relationship between the host and the different guests and to make distance measurements.) Which alkai metal ion requires the smallest change to the structure of free 18-crown-6 in order to be accommodated? Which cation requires the greatest change?

8. Ethers

1. Acid Catalyzed Ring Opening of Epoxides. Protonation of oxacyclopropanes (epoxides) followed by addition of base, leads to ring opening. Where the expoxide is unsymmetrically-substituted, a single product usually results. For example, protonation of 2,2-dimethyloxacyclopropane followed by addition of methoxide anion (from methanol) leads only to 2-methoxy-2-methyl-1-propanol. 1-methoxy-2-methyl-2-propanol is not detected.



The usual explanation is that the species resulting from protonation at oxygen is in equilibrium with two alternative structures in which the positive charge is on carbon. This suggests that there are three different structures for the protonated epoxide, and that the structure in which the positive charge resides on the tertiary carbon as opposed to either the primary carbon or the oxygen is the most stable.



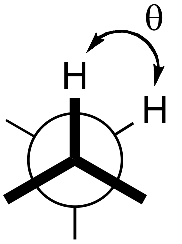
Is the oxygen-protonated structure resulting from initial protonation a stable species or does it collapse to one of the other structures? Are both carbocation structures stable, or does the primary carbocation collapse to the tertiary carbocation? To tell, attempt to calculate geometries for all three ions starting each in a geometry that closely resembles its presumed structure. Are all three ions stable? If they are, calculate the amounts that each would be present in an equilibrium mixture at room temperature. Are two of the three ions stable? If yes, then identify the more stable ion and calculate the amount of the less stable ion present in an equilibrium mixture. If only one ion is stable, identify it.

2. Acid Catalyzed Ring Opening of Larger-Ring Oxacycloalkanes. As described in the previous problem, protonation of oxacyclopropanes results in opening the three-member ring and, in the case of an unsymmetrically-substituted reactant, leads exclusively to the product derived from the more stable of the two possible carbocations. Is ring opening in oxacyclopropanes driven primarily by relief of strain?

Attempt to obtain geometries for the initial (oxygen) protonated forms of 2,2-dimethyloxacyclobutane, 2,2-dimethyloxacyclopentane and 2,2-dimethyloxacyclohexane and for the carbocations that can result from ring opening of each. Analyze your results in the same way you did for 2,2-oxacyclopropane (see previous problem) and answer the same questions. What do you conclude about the importance of ring strain?

9. NMR Spectroscopy

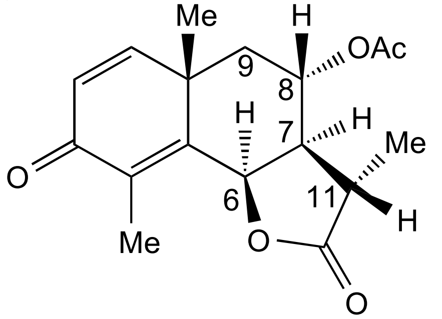
1. The Karplus Equation. The coupling constant, J, between protons on adjacent carbons (vicinal protons) varies with dihedral angle, θ, may be described by the Karplus equation. This says that J is largest when the CH bonds are *anti* ($\theta=180^o$) and smallest when they are perpendicular ($\theta=90^o$)



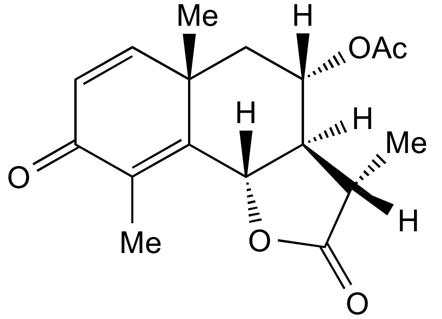
$$J = (7 - \cos\theta + 5\cos 2\theta)\ \text{Hz}$$

Because of their dependence on dihedral angle, vicinal coupling constants may be used to assign the three-dimensional structure of molecules and to distinguish between closely related structures.

Use calculated geometries together with the Karplus equation to decide which molecule, artemisin acetate and its isomer 6-epiartmisin acetate, more closely fits the set of vicinal coupling constants: $J_{6,7}$=5.7, $J_{7,8}$=10.5, $J_{7,11}$=0 and $J_{8,9axial}$ =10.5.

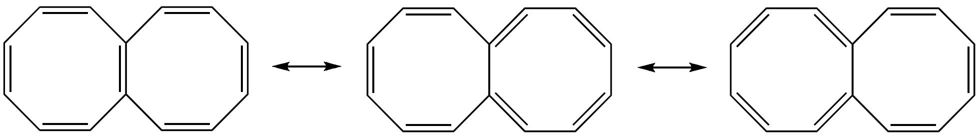


artmisin acetate



6-epiartmisin acetate

2. Octalene. Three Lewis structures may be drawn for octalene, the first of which is unique and the second and third of which are equivalent.

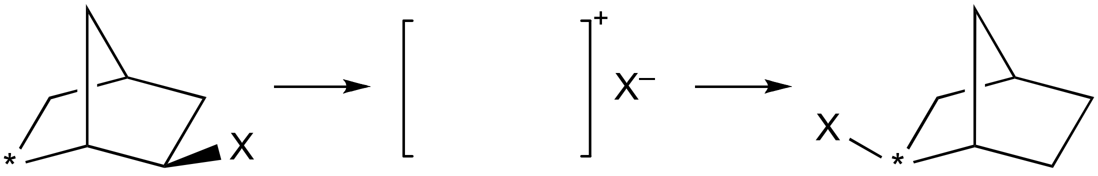


Calculate the geometry of octalene starting both from the unique Lewis structure and from one of the pair of equivalent Lewis structures. Are the final geometries that result the same or do you find two different structures?

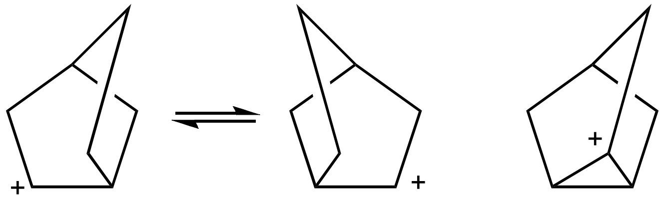
The experimental ^{13}C NMR spectrum of octalene depends on the temperature. At room temperature, seven lines are observed, but 14 lines are seen at -150°C. How many lines in the ^{13}C spectrum would be expected if octalene were properly represented by the unique Lewis structure alone? How many lines would be expected if octalene were it properly represented solely by a combination of the two equivalent Lewis structures?

Interpret the NMR data in view of your results for the geometry of octalene, and if needed redraw the diagram shown above.

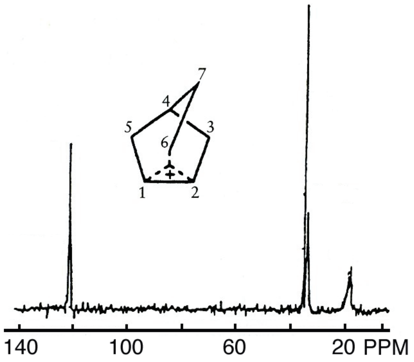
3. 2-Norbornyl Cation. 2-Norbornyl cation ranks among the most studied and controversial molecules in 20th century organic chemistry. Literally hundreds of papers found their way into the literature, and prompted a lively and sometimes vitriolic debate between two future Nobel laureates on what became known as the “non-classical ion problem”. The observation that led to the debate was that C_2 and C_6 positions in norbornane substituted in the 2 position by a good (anionic) leaving group scrambled.



This could be accommodated either by invoking a rapid equilibration between two "classical" cations in which the "positively charged" carbon is tricoordinate, or insisting that there was only a single "non-classical" cation incorporating a pentacoordinate carbon.



Reliable quantum chemical calculations for molecules as large as 2-norbornyl cation were not practical at the time of the debate, but pretend for the moment that the issue is not resolved. The calculated structure of 2-norbornyl cation appears on screen. Does it incorporate a distinct tricoordinate cation center such as that found in *tert*-butyl cation? Are all CC distances consistent with single bonds (1.45-1.55Å) or some unusually short or usually long? Labels attached to carbon atoms are calculated ^{13}C NMR chemical shifts. Are these consistent with the experimental low temperature carbon spectrum provided below? If they are, assign the lines in the experimental spectrum. Does 2-norbornyl best described as a classical or non-classical ion?



10. Alkenes/IR Spectroscopy

1. Crowded Alkenes. A carbon involved in the double bond of an alkene is expected to exhibit a trigonal planar geometry. Any significant deviations from planarity or from idealized 120^o bond angles could be taken as evidence of strain. Measure both C-C and C=C bond lengths and CCC bond angle in propene, a "strain free". Compare these to the analogous lengths and angles in 2-methylpropene, *cis* and *trans* isomers of 2-butene, 3,3-dimethyl-1-butene and *cis* and *trans* isomers of 2,2,5,5-tetramethyl-3-hexene. For which molecules are the changes in bond lengths and angles relatively modest (<0.01Å and 2^o, respectively)? For which molecules are they largest? Which molecules appear to be the most strained?

2. Dipole Moments in Alkenes. The dipole moment is a measure of the overall distribution of charge in a molecule. The dipole moment for a diatomic molecule, A-B, is proportional to the product of the charge on A (or on B) and the AB bond distance. While generalization to a polyatomic molecule is conceptually straightforward (perform a vector sum over all the atoms taking into account the charge on each atom), it is complicated because electrons cannot be treated as point charges.

Dipole moments for alkenes are generally <1 debye, while dipole moments for molecules incorporating oxygen or nitrogen atoms are typically in the range of 1-4 debyes. Even though alkene dipole moments are small, they are able to provide insight into the transfer of charge from one part of an alkene to another. For example, dipole moments may be employed to test the "conventional wisdom" that double bonds are more "electron rich" than single bonds.

Obtain dipole moments for ethylene, propene and 2-methylpropene, and for each display the dipole moment vector. Rationalize the magnitude of the dipole moment of ethylene. Is the methyl group in propene at the positive or negative end of the dipole vector? Is your result what you expect? Elaborate. Could the magnitude of the dipole moment in 2-methylpropene have been accurately guessed from the dipole moment in propene? (Hint: you need to do a vector addition of the individual bond dipole moments.)

Obtain dipole moments in cyclopropene, cyclobutene, cyclopentene and cyclohexene, and for each display the dipole moment vector. Is the direction of the dipole moment in all of these molecules consistent with your previous results for propene and 2-methylpropene? Point out any exceptions and (if there are any) attempt to provide a reason why.

3. Electron-Rich and Electron-Poor Alkenes. Groups attached to a double bond will either act to add or remove π electrons, knowledge of which is important as electron-rich and electron-poor double bonds may exhibit entirely different chemistry. Electostatic potential maps provide a simple indicator of the effect on the π system of a directly-bonded substituent.

Compare electrostatic potential maps for 2,3-dimethyl-2-butene (tetramethylethylene), tetrafluoroethylene and tetrachloroethylene with that for ethylene (the "standard"). For which is the electrostatic potential above and below the double bond most negative? For which is it most positive. Relative to hydrogen, classify methyl, fluoro and chloro groups as π-electron-donating or π-electron-withdrawing substituents.

Using the electrostatic potential as a measure, see if you can identify a tetrasubstituted ethylene (all substituents the same) that is more electron rich than the best of the compounds above. Repeat the exercise to find a compound that is more electron poor than the best previously noted.

4. Heats of Formation. The heat of formation of a molecule is the enthalpy of a hypothetical reaction that converts a molecule into the most stable "single element" products, solid graphite in the case of carbon and gaseous hydrogen molecule in the case of hydrogen. For example, the products for all isomers of formula C_4H_8 are four carbon atoms (in graphite) and four molecules of hydrogen gas. Heats of formation, where available, provide a direct means to judge the stabilities of isomeric molecules. However, due to the destructive nature of the experiment required to determine the heat ("burning" the molecule), experimental data are quite limited.

SpartanModel does not actually calculate heats of formation, although it can calculate the energy for any reaction for which reactants and products are well defined ***molecules***. In the case of alkenes, the carbon standard (graphite) is not a well-defined molecule. The alternatives are either to choose another reaction or to access a database of values that have been obtained from quantum chemical calculations and empirically corrected as to refer to well defined standards. This problem takes the latter approach.

Use the database attached to ***SpartanModel*** to obtain heats of formation for 1-butene, *cis* and *trans*-2-butene and 2-methylpropene as well as the remaining C_4H_8 isomer, cyclobutane. Order the five molecules from most stable (most negative or least positive heat of formation) to least stable.

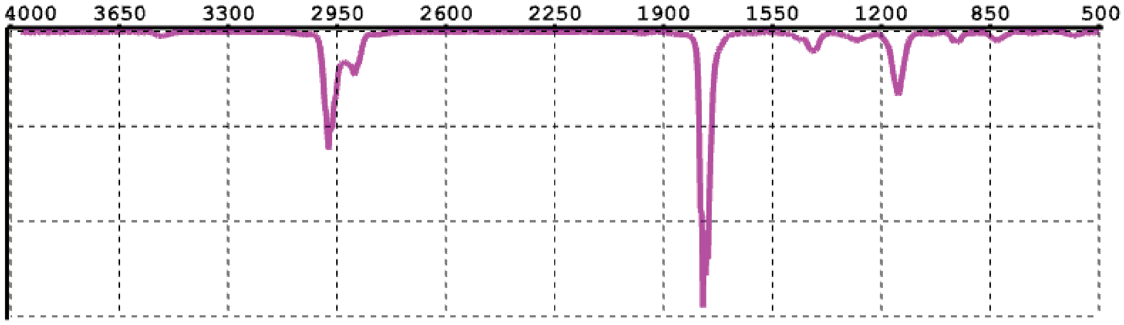
In a similar manner, order the isomers of formula C_5H_{10} according to their heats of formation. Is the most stable C_5H_{10} isomer analogous in structure to the most stable C_4H_8 isomer?

5. Molecular Orbitals of Ethylene. While the π molecular orbital (π bond) of ethylene is well known to all students of chemistry, the molecular orbitals that make up the underlying σ bonds are much less familiar. The molecular orbitals of ethylene are simple enough as to allow connections to be made with the bonds in a Lewis structure, revealing both similarities and differences.

One after another and starting from the HOMO and going down in energy, display the six valence molecular orbitals of ethylene. Classify each as σ or π and as bonding, antibonding or non-bonding with respect to the CC bond and each of the four CH bonds. (It might help to switch to a mesh or transparent display.) Is there a relationship between the energy of the molecular orbital and the number of bonding interactions? Elaborate.

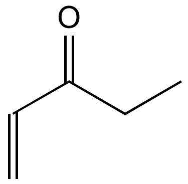
Note that the five in-plane molecular orbitals do not correspond one-to-one with the five localized σ bonds in the Lewis structure of ethylene. Rather, the molecular orbitals are spread out throughout the molecule, and each molecular orbital involves all six atoms. Such a “delocalized” representation is necessary to satisfy the requirement that (the square of) each molecular orbital must exhibit the symmetry of the molecule. In the case of ethylene, this means that each molecular orbital must reveal that the two carbon atoms are equivalent and that the four hydrogen atoms are equivalent.

6. Using Infrared Spectra to Identify Molecules. The measured infrared spectrum of a molecule of formula C_5H_8O is shown below.

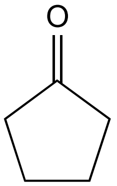


SpartanModel does not actually calculate infrared spectra as the quantum chemical model that it employs is too simple to expect reliable results. Rather, it accesses a database of values that have been obtained from more sophisticated and more reliable calculations. Furthermore, the calculated infrared spectra have been empirically corrected to take account both of known systematic errors and of finite temperature.

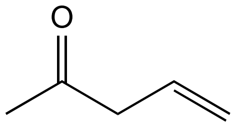
One after another, obtain infrared spectra for the following C_5H_8O isomers. Identify the isomer that best fits the experimental spectrum.



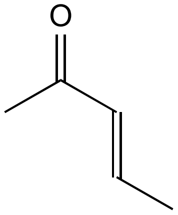
1-penten-3-one



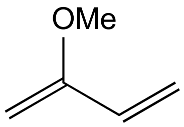
cyclopentanone



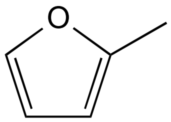
methyl allyl ketone



trans-3-penten-2-one



2-methoxy-1,3-butadiene



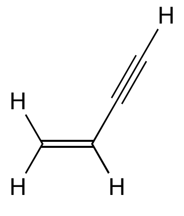
2-methylfuran

7. trans **Cycloalkenes.** *Trans* alkenes are generally slightly favored over the corresponding *cis* isomers. For example, the experimental heat of formation of *trans*-2-butene is 4 kJ/mol lower than that of *cis*-2-butene. On the other hand, *trans* cycloalkenes are strongly disfavored relative to their *cis* isomers. The smallest system for which reliable experimental thermochemical data are available is cyclooctene. Here, the *trans* isomer is 43 kJ/mol less stable than the *cis i*somer.

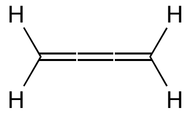
Establish the relative stabilities of *cis* and *trans* isomers of cycloheptene, cyclooctene, cyclononene and cyclodecene both from energies calculated with the simple quantum chemical model available in ***SpartanModel***, and from the database of heats of formation accessible from ***SpartanModel***. The former approach is likely to provide less accurate results but can be applied to any molecule, whereas the latter is much more limited in coverage but can be expected to provide accurate data. For each approach, answer the following questions.

Is the *cis-trans* difference obtained for cyclooctene in accord with the experimental value (43 kJ/mol)? Is the *cis-trans* difference for cycloheptene about the same as that for cyclooctene or is it significantly larger (in favor of the *cis* isomer) or significantly smaller. Are there significant differences in the structures *cis* and *trans* cycloheptene, in particular, in the vicinity of the double bond? Are the *cis-trans* differences for the larger cycloalkanes cyclononene and cyclodecene comparable to that for cyclooctene or are they significantly smaller or larger. Finally, use your results to predict *cis-trans* differences of both smaller larger cycloalkenes.

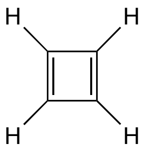
8. Identifying Short Lived Molecules with Infrared Spectroscopy. Highly-reactive molecules may sometimes be "captured" in a solid matrix of argon (or another rare gas) at very low temperature. In this environment, infrared spectroscopy usually provides the best means of characterization. Use the infrared database accessible from ***SpartanModel*** to identify which C_4H_4 isomer is consistent with strong absorptions at 215, 854, 1608, 2994 and 3080 cm^{-1}. Consider but-1-yne-3-ene, butatriene, cyclobutadiene, tetrahedrane and methylenecyclopropene as candidates.



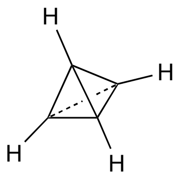
but-1-yne-3-ene



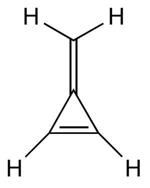
butatriene



cyclobutadiene

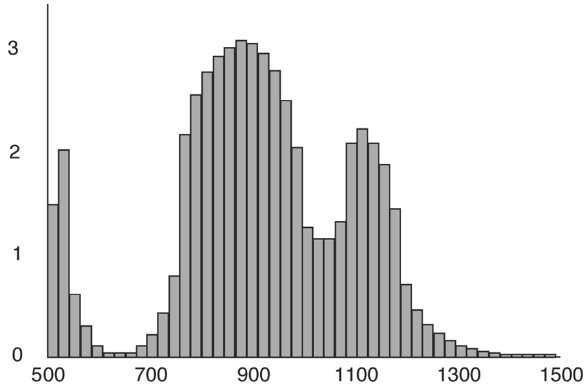


tetrahedrane

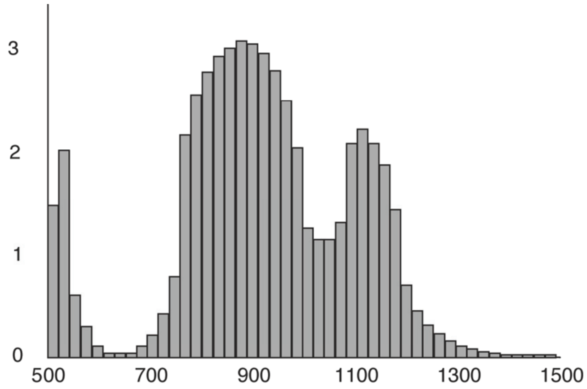


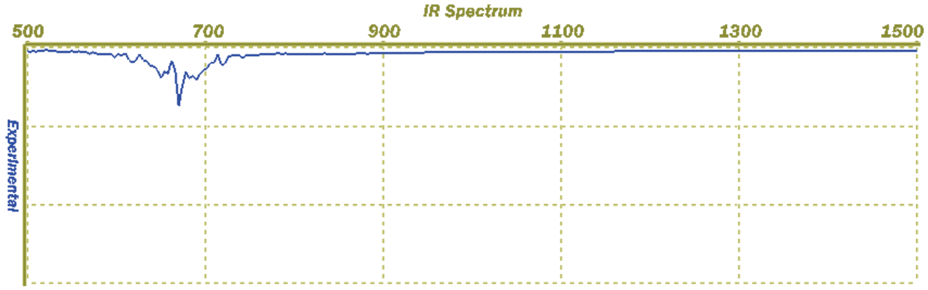
methylenecyclopropene

9. Greenhouse Gases. In order to dissipate the energy that falls on it due to the sun, the earth "radiates" as a so-called "blackbody" into the universe. The "theoretical curve" is a smooth distribution peaking around 900 cm^{-1} and decaying to nearly zero around 1500 cm^{-1}. This is in the infrared, meaning that some of the radiation will be intercepted by molecules in the earth's gaseous atmosphere. This in turn means that the earth is actually warmer than it would be were it not to have an atmosphere. This warming is known as the ***greenhouse effect***, to make the analogy between the earth's atmosphere and the glass of a greenhouse. Both allow energy in and both impede its release. The actual distribution of radiated energy as measured from outside the earth's atmosphere in the range of 500-1500 cm^{-1} is given below. The overall profile matches that for a blackbody, but the curve is peppered with holes.



Neither nitrogen nor oxygen, which together comprise 99% of the earth's atmosphere absorbs in the infrared and causes the "holes". However, several "minor" atmospheric components, carbon dioxide most important among them, absorb in the infrared and contribute directly to greenhouse warming. Its infrared spectrum shows a strong absorption in the region centering 670 cm^{-1}, the location of the most conspicuous hole in the blackbody radiation profile.

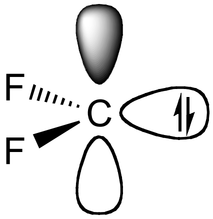




Identify three of the top 10 chemicals manufactured worldwide. For each, examine the infrared spectrum (available from the database supplied with ***SpartanModel***), and comment whether or not you would expect it to be a significant greenhouse gas.

11. Reactions of Alkenes

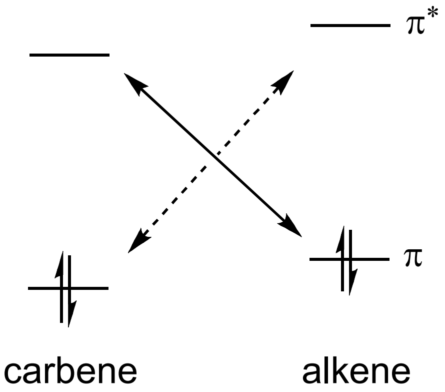
1. Carbenes. Difluorocarbene, :CF_2, dichlorocarbene, :CCl_2, and other carbenes, possess both a non-bonded electron pair in the plane of the molecule and a low energy unfilled orbital perpendicular to the plane.



difluorocarbene

Carbenes that are described in this way are referred to as ***singlet carbenes***. This means that all electrons are paired. Other carbenes, including the parent compound methylene, have two unpaired electrons, one in the plane of the molecule and the other in an orbital perpendicular to the plane. They are referred to as ***triplet carbenes***. We consider only singlet carbenes.

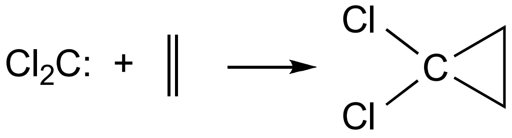
The fact that carbenes behave as electrophiles and add to alkenes suggests that the energy gap between the empty orbital and the π orbital of the double bond is smaller than the corresponding gap between the carbene lone pair and the double bond π* orbital.



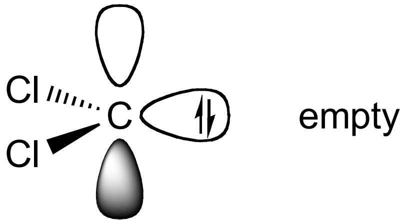
Display the HOMO and LUMO of difluorocarbene. Is the HOMO properly described as an in-plane lone pair? Elaborate. Describe the LUMO. Is it a σ orbital or is it a π orbital, that is, does it lie in the plane of the molecule or is it perpendicular to the plane? Record the energies of the two orbitals. Obtain HOMO and LUMO energies for cyclohexene. Calculate energy gaps between the HOMO of cyclohexene and the LUMO of difluorocarbene and between the LUMO of cyclohexene and the HOMO of difluorocarbene. Which is smaller? Is your result consistent with the observed chemical behavior of singlet carbenes? Elaborate.

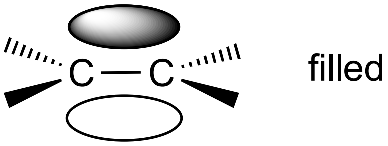
Repeat your calculations and analysis using dichlorocarbene.

2. Carbenes Add to Double Bonds. The HOMO of a carbene corresponds to a lone pair in the plane of the molecule. This presents an interesting dilemma in that carbenes readily add to alkenes to yield cyclopropanes. For example, dichlorocarbene adds to ethylene to yield 1,1-dichlorocyclopropane.



The problem is than the approach that leads to a product with the "correct" geometry pushes the lone pair of the carbene directly into the π bond of the alkene. A more favorable approach would be to push the unoccupied p orbital on carbon (the LUMO) onto the π bond. However, this leads to a product with the "incorrect" geometry. What actually happens?





A transition state for the reaction of dichlorocarbene and ethylene is provided on screen. Is it as an "early" or "late" transition state? One "clue" follows from the carbon-carbon bond distance in the transition state. Is it closer to a double bond (as in the reactant) or a single bond (as in the product)? A second clue may be found in the orientation of the reactants. Does the lone pair on dichlorocarbene point toward the π bond?

3. Diazomethane. Diazomethane is commonly employed as a precursor to methylene.

$$H_2C^{-}-N^{+}\equiv N \longleftrightarrow H_2C=N^{+}=N^{-} \longrightarrow :CH_2 + N_2$$

Is diazomethane better described in terms of a Lewis structure with the negative charge on carbon or on nitrogen, or is the proper description somewhere in between? One way to decide is to see if the geometry of diazomethane is more consistent with that of methylamine, which incorporates a CN single bond, and nitrogen molecule, which incorporates an NN triple bond, or with methyleneimine ($H_2C=NH$), which incorporates a CN double bond, and *trans*-diimide (HN=NH), which incorporates a NN double bond.

To build diazomethane, attach a sp^3 carbon anion fragment to an sp^3 nitrogen cation fragment. Attach sp^3 nitrogen to nitrogen and make two bonds between the nitrogen atoms.

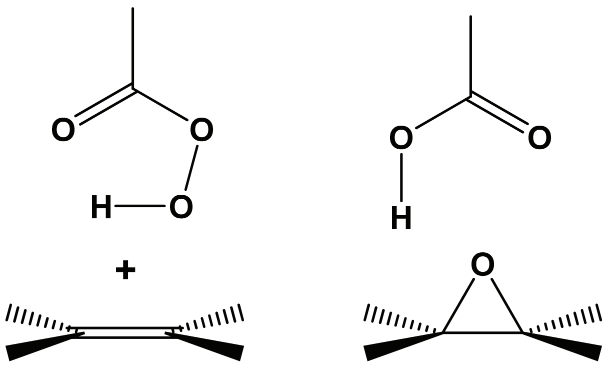
Atomic charges may also be used to distinguish between the two Lewis structures. Both require that the nitrogen at the center is positively charged. Is this actually the case? Is the methylene group negatively charged as suggested by the first Lewis structure, or is the terminal nitrogen negatively charged as suggested by the second Lewis structure?

Which, if either, Lewis structure provides a better model for diazomethane? Are your results based on geometry comparisons consistent or at odds with your results based on atomic charges?

Repeat your analysis with hydrogen azide, a molecule that has the same number of electrons as diazomethane (the two molecules are isoelectronic).

$$HN^{-}-N^{+}\equiv N \longleftrightarrow HN=N^{+}=N^{-}$$

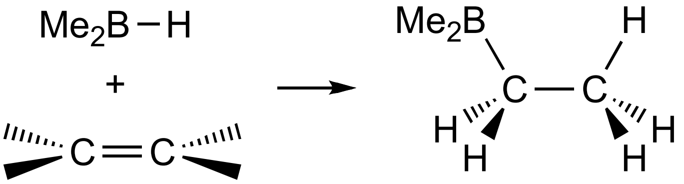
4. Epoxidation of a Double Bond. Peroxycarboxylic acids such as MCPBA (*meta*-chloroperoxybenzoic acid) react with double bonds leading to oxacyclopropanes (epoxides).



A transition state for the reaction of peroxyacetic acid and ethylene is provided on screen along with the corresponding equilibrium structures of the reactants (peroxyacetic acid and ethylene) and products (acetic acid and oxacyclopropane). Refer to the these structures to answer the following questions.

Which bond in peroxyacetic acid, OO or OH, has lengthened more (on a percentage basis) in moving to the transition state? Rationalize your observation in terms of what you know about the relative strengths of OO and OH bonds. Is the CC bond in the transition state closer to that in the reactant (ethylene) or that in the product (oxacyclopropane)? Are the CO single and double bonds in the transition state closer to those in the reactant (peroxyacetic acid) or those in the product (acetic acid)? Based on changes in these three bonds, would you conclude that the transition state is better characterized as “early” or “late”. Elaborate. Does your result suggest that the reaction is likely to be *exothermic* or *endothermic*? Elaborate.

5. Hydroboration. Hydroboration involves the addition of a BH bond to a carbon-carbon double bond. The initially formed alkylborane is not typically isolated but rather oxidized to an alcohol.



A transition state for the reaction of dimethylborane and ethylene is provided on screen along with the corresponding equilibrium structures of the reactants (dimethylborane and ethylene) and product (dimethylethylborane). Is the length of carbon-carbon bond in the transition state closer to that in the reactant (a double bond) or the product (a single bond)? Has the hydrogen migrated more or less that halfway? (Look at the percentage change in BH and CH distances from those in the dimethylborane and in the product, respectively.) Is the transition state better characterized as “early” or “late”? Elaborate. Does your result suggest that the reaction is likely to be *exothermic* or *endothermic*? Elaborate.

12. Alkynes

1. Atomic Hybrids and Carbon-Carbon Bond Lengths. The fact that the CH bonds in ethane are slightly longer than those in ethylene, which in turn are slightly longer than the CH bonds in acetylene, is usually explained in terms of the different atomic hybrids from which they are made. The CH bonds in ethane involve sp^3 hybrids (one part 2s to three parts 2p), while those the in ethylene involve sp^2 hybrids (one part 2s to two parts 2p) and those in acetylene involve sp hybrids (one part 2s to one part 2p). As 2p orbitals extend further from carbon than the 2s orbital, CH bonds should therefore increase in length with increasing p content.

Obtain equilibrium geometries for ethane, ethylene and acetylene. Verify the known ordering of CH bond lengths. Calculate and record the percentage increase in CH bond length from acetylene to ethylene and from ethylene to ethane. Obtain equilibrium geometries for propane, propene and propyne and record the length of the CC single bond in each. Is the percentage change in CC bond length from propyne to propene comparable to the percentage change in CH bond length from acetylene to ethylene? Is the percentage change in CC bond length from propene to propane comparable to the percentage change in CH bond length from ethylene to ethane?

Are changes in CC single bond lengths with changes in hybridization at carbon additive? Obtain equilibrium geometries for *n*-butane, 1-butene, 1-butyne, 1,3-butadiene, but-1-yne-3-ene and 1,3-butadiyne. Is the change in the central CC bond length from 1-butene to 1,3-butadiene more or less than twice than that from *n*-butane to 1-butene? Is the corresponding change from 1-butyne to 1,3-butadiyne more or less than twice than that from *n*-butane to 1-butyne? Is the change in CC single bond length from *n*-butane to but-1-yne-3-ene anticipated by the sum of the changes from *n*-butane to 1-butene and from *n*-butane to 1-butyne?

2. Cycloalkynes. Incorporation of a carbon-carbon triple bond into a small ring is problematic due to the requirement of a linear (or nearly linear) geometry. What is the smallest cycloalkyne for which this can reasonably be accomplished? To find out, obtain geometries for cycloalkynes starting from cycloheptyne and measure the pair of C≡C–C bond angles. End when you identify a compound where both angles are greater than 170°.

3. Dipole Moments in Alkynes. Alkynes, like alkenes, typically have very small dipole moments. Is the magnitude of the dipole moment in propyne similar to that in propene or is it significantly smaller or larger? Is the direction of the moment (the dipole moment vector) the same in propyne and propene? Is the the methyl group in propyne at the positive or negative end of the dipole moment vector?

4. Electrophilic Reactivity: Alkenes vs. Alkynes. The π bonds of both alkenes and alkynes are susceptible to attack by electrophiles. Is the triple bond more or less susceptible than a double bond? One possible way to answer the question is to compare the energy of the highest-occupied molecular orbital (the HOMO) of an alkene with that of the corresponding alkyne. The higher the energy, the more the π bond will be susceptible to electrophilic attack.

First examine HOMO energies for ethylene and acetylene. Which is higher? Which should be susceptible to electrophilic attack? Repeat your analysis for propyne and propene and then for 3,3-dimethylpropyne and 3,3-dimethylpropene. Is the conclusion the same for all three pairs of molecules? If it is, would you conclude that alkenes or alkynes are generally more or less reactive toward electrophiles?

An alternative measure of electrophilic reactivity is provided by the electrostatic potential. The more negative the potential at the π bond, the more the π bond will be susceptible to electrophilic attack. Compare electrostatic potential maps for the three pairs of molecules. Does this approach yield the same results as comparison of HOMO energies?

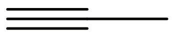
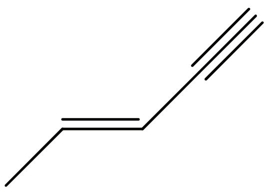
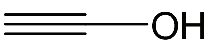
5. Triple Bond vs. Two Double Bonds. Is the total π-bond energy of the triple bond in acetylene more or less than twice the π-bond energy of ethylene? An obvious way to address the question is to ask if disproportionation of two molecules of ethylene into one molecule of ethane and one molecule of acetylene is *exothermic* or *endothermic*.

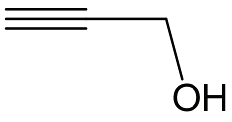
$$2\ H_2C{=}CH_2 \longrightarrow H_3C{-}CH_3 + HC{\equiv}CH$$

Calculate the energy for the ethylene disproportionation reaction. You can either use the quantum chemical model available in ***SpartanModel*** or (for more accurate results) access the database of estimated heats of formation from ***SpartanModel***. What does your result suggest about the relative energies of double and triple bonds? What have you assumed in order to reach this conclusion?

Repeat your analysis starting from *trans*-2-butene instead of ethylene. Is the result qualitatively the same?

6. Deprotonation of Alkynes. What anion results from deprotonation of each of the following alkynes and alkynols? Are any of the alternative (higher-energy) anions likely to be seen at room temperature? (Assume a minimum abundance of 5% in order to be detected.)



You can build the anion resulting from deprotonation at the alkyne carbon by first connecting sp^3 carbon >C- and sp^3 anionic carbon $>C^-$ fragments and then making two additional bonds between them. This leaves the original sp^3 carbon with one remaining free valence.

13. Dienes, Higher Polyenes and UV Spectroscopy

1. Butadiene. 1,3-butadiene, $H_2C=C-C=CH_2$, exists as a mixture of two "conformational isomers" or conformers. The two double bonds are *trans* in the lower-energy conformer, and *cis* or nearly *cis* in the higher-energy conformer.

Obtain the energies of both "*cis"* and *trans* conformers of 1,3-butadiene.

The procedure for structure finding incorporated into ***SpartanModel*** will not "jump out" of an energy well. This means that structures and energies for different conformers may be found by starting with different structures. Furthermore, with the quantum-chemical model (but not with the molecular mechanics model), the procedure will not "break symmetry". For example, a planar molecule will remain planar even if the planar geometry is an energy maximum rather than an energy minimum. For this reason, it is important to start "*cis*" 1,3-butadiene in a non-planar geometry.

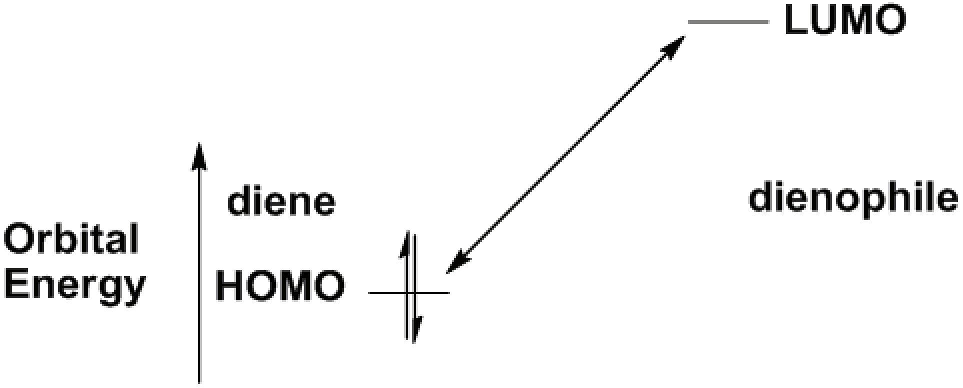
Which conformer is lower in energy? What is the difference in energies between the two conformers? Are your results in line with the experimental data which shows that the *trans* conformer is ~12 kJ/mol more stable than the *cis* (or nearly *cis*) conformer? Is the *cis* conformer planar or has it distorted from planarity? If the latter, what is the difference in energies of the planar and non-planar cis conformers? (You can obtain the energy of the planar *cis* conformer, by starting from a planar geometry.)

Repeat your calculations for *cis* and *trans* conformers of 2,3-dimethyl-1,3-butadiene. Is the preferred conformer the same as it is in 1,3-butadiene? If not, provide a rationale as to why it is not.

Repeat your calculations for cis and *trans* conformers of 2,2,3,4,5,5-hexamethyl-2,4-hexadiene. Is this molecule qualitatively similar to the previous two or are their significant differences?

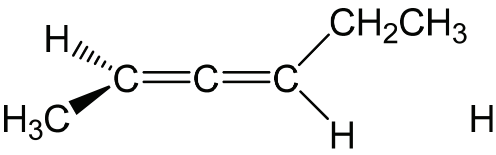
2. Diels-Alder Dienes. Butadiene vs. Cyclopentadiene. Cyclopentadiene is known to be a much more reactive Diels-Alder diene than 1,3-butadiene. One plausible explanation for this is that the two double bonds in cyclopentadiene are already in the *cis* conformation required for the reaction to occur, whereas the lowest-energy form of 1,3-butadiene is instead the *trans* conformer (see previous problem). Could another reason be that cyclopentadiene is inherently more electron rich than 1,3-butadiene?

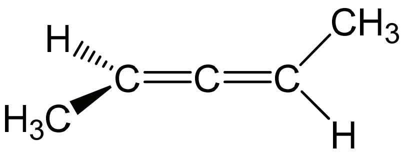
There are at least two ways to test such an hypothesis using molecular modeling. The first involves comparing HOMO energies of the two dienes. Since the key interaction driving the reaction is that between the HOMO of the diene and the LUMO of the dienophile, the higher the HOMO energy, the smaller the HOMO-LUMO gap and the stronger the interaction. Obtain HOMO energies of cyclopentadiene and the (nearly) *cis* conformer of 1,3-butadiene. For which is the HOMO energy smaller? Which diene would be expected to be more reactive?



The second way is to compare the value of the electrostatic potential on the face of the diene. The more negative the electrostatic potential, the more electron rich the diene and the more likely the diene is to interact with an electron-deficient dienophile. Compare electrostatic potential maps for cyclopentadiene and (nearly) *cis*-1,3-butadiene. For which is the value of the electrostatic potential on the diene face larger? Which diene would be expected to be more reactive? Is your result consistent with that provided by comparison of HOMO energies?

3. Isomeric Dienes. In addition to 1,3-pentadiene and 1,4-pentadiene, there are two additional C_5H_8 isomers that incorporate two carbon-carbon double bonds. They are 1,2-pentadiene and 2,3-pentadiene.

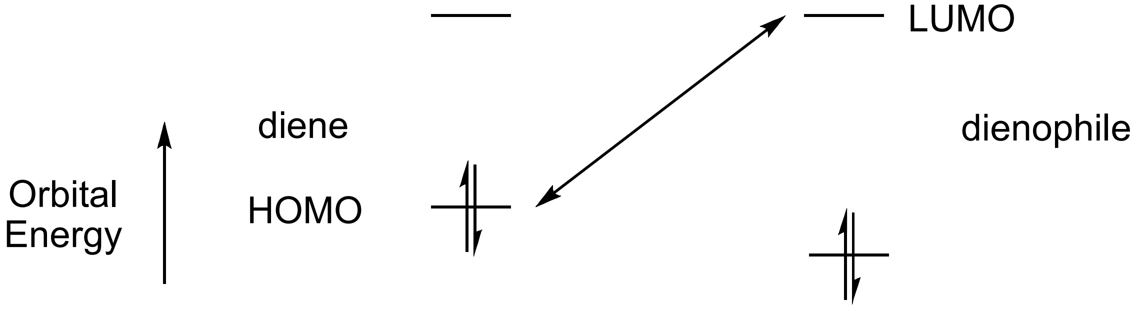




Which of the four dienes is most stable and which is least stable? Provide a rationale for the preference. You can either use the quantum chemical model available in ***SpartanModel*** to obtain energies or access the database of estimated heats of formation accessible from ***SpartanModel***.

Identify other isomers of formula C_5H_8. Are any lower in energy than the best of the dienes?

4. Dienophiles in Diels-Alder Reactions. The rates of Diels-Alder reactions are known to increase with the extent to which the dienophiles are electron deficient. Thus, tetracyanoethylene is a better (more reactive) dienophile than acrylonitrile which in turn is a better dienophile than ethylene. The usual explanation is that the more electron withdrawing groups attached to the double bond serve to reduce the energy of the lowest-unoccupied molecular orbital (a π* orbital), and therefore reduce the HOMO-LUMO gap.

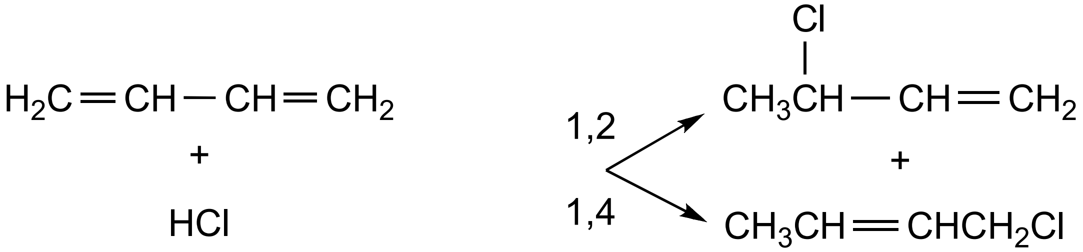


One after another, obtain geometries for ethylene, acrylonitrile, *trans*-1,2-dicyanoethylene, tricyanoethylene and tetracyanoethylene. For each, display the LUMO and (using the scale on the left of the ***SpartanModel*** screen) record its energy. Is the trend in the LUMO energy consistent with the observed trend in rates of Diels-Alder reactions?

Compare electrostatic potential maps for ethylene, acrylonitrile, *trans*-1,2-dicyanoethylene, tricyanoethylene and tetracyanoethylene, focusing on the region above and below the carbon-carbon double bond. Does there appear to be a direct correlation between the potential and LUMO energy? Elaborate.

5. Allene. The Lewis structure of allene depicts a molecule with two double bonds to the central carbon. Examine the occupied molecular orbitals of allene, and identify the two orbitals that correspond to the two π bonds in the Lewis structure. Do they have the same energy? Is each localized only on two carbons (as in ethylene) or are there contributions from the remaining carbon? Are there contributions from other atoms?

6. 1,2 vs. 1,4 Addition. Hydrochloric acid adds to conjugated dienes in the same way as it adds to alkenes. Here, however, there is the possibility that products will arise from both 1,2 addition (as in alkenes) as well as from 1,4-addition (unique to conjugated dienes).

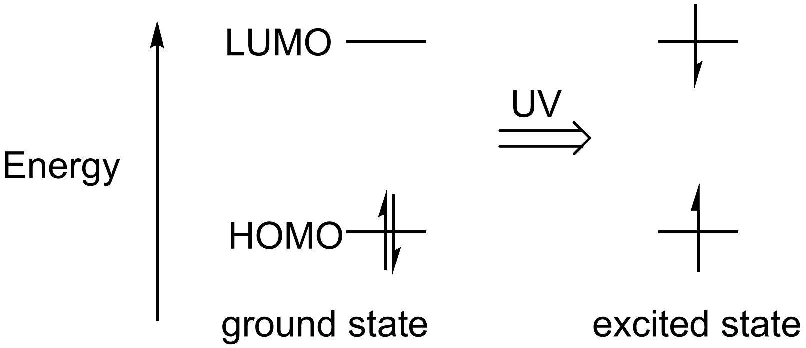


Examine the energies of all products that might arise from addition of HCl to 2-methyl-1,3-butadiene (isoprene). What is the thermodynamic product of addition? Are any alternative products likely to make up >5% of the total at normal temperatures?

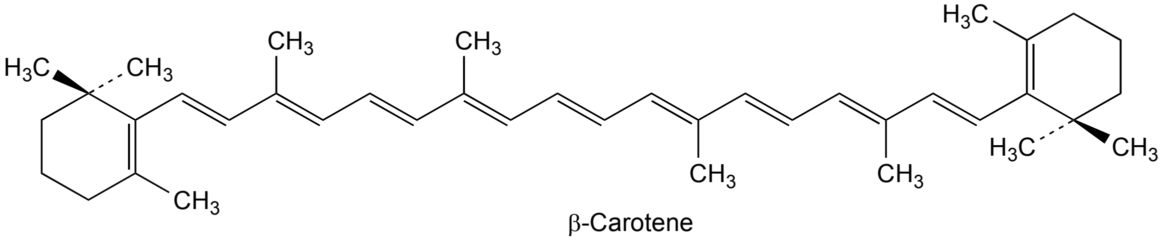
The most plausible meachanism for HCl addition involves protonation of the diene, followed by rearrangement of whatever cation that is first formed to the most stable cation. This cation in turn reacts with chloride anion to give the observed product. Examine the energies of all cations that could arise both from initial protonation of isoprene or from rearrangement. Identify the most stable cation and the product that would result. Is this the same product as anticipated from the thermodynamic stabilities of the neutral products?

7. UV/Visible Spectra of Conjugated Alkenes. UV/visible spectra arise due to transitions between the ground (electronic) state and various excited states. A simple way to model the absorption maximum in a UV/visible spectrum (λ_{max}) is to relate it to the energy gap between the highest-occupied and lowest-unoccupied molecular orbitals, the so-called HOMO-LUMO gap.

The lower the gap, the lower the energy of transition, and the more the absorption shifts from the UV toward the visible.

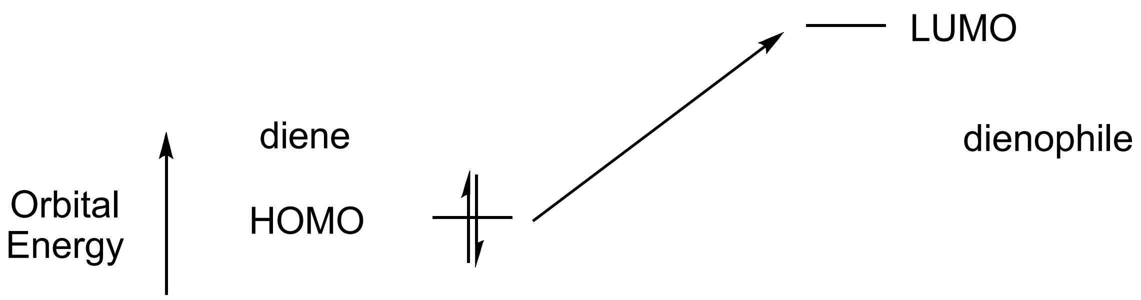


λ_{max} values for ethylene, 1,3-butadiene, 1,3,5-hexatriene *β*-carotene are 165, 217, 253 and 452 nm. These data suggest a relationship between chain length and the energy of transition. Does this also suggest that increase in chain length leads to a decrease in HOMO-LUMO gap? To decide, calculate the HOMO-LUMO gap for the first three molecules as well as that for a longer chain polyene to simulate *β*-carotene (six to ten double bonds should be sufficient).



β-Carotene

8. Electron Transfer in Diels-Alder Reactions. I. The most common and synthetically-useful Diels-Alder reactions are between electron-rich dienes such as cyclopentadiene and electron-deficient dienophiles such as acrylonitrile. The usual interpretation is that the transition state for the reaction is stabilized through interaction of a high-energy diene HOMO and a low-energy dienophile LUMO. It might be expected, therefore, that the electron distribution in the transition state would reflect a transfer of electrons from diene to the dienophile.

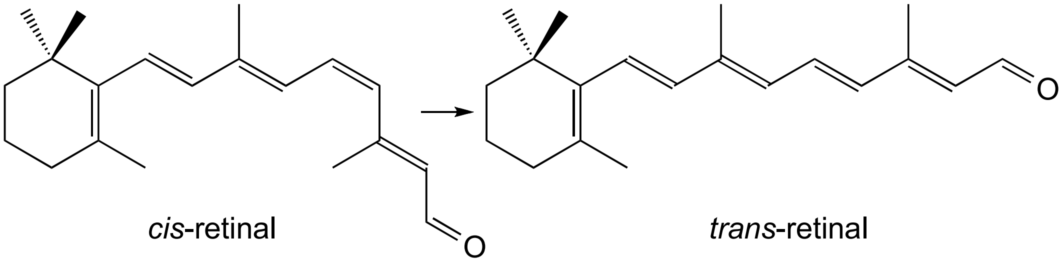


Provided on screen are electrostatic potential maps for cyclopentadiene (left), acrylonitrile (middle) and the Diels-Alder transition state (right). Does the potential in that region of the transition state that comes from cyclopentadiene show evidence of electron depletion? Does the potential in that region of the transition state that comes from the acrylonitrile show evidence of electron gain? Do you conclude that significant electron transfer has occurred in the transition state?

9. Electron Transfer in Diels-Alder Reactions. II. The rates of Diels-Alder reactions increase with increasing electron deficiency of the carbon-carbon double bond in the dienophile. Thus, tetracyanoethylene reacts faster than *cis*-1,2-dicyanoethylene which in turn reacts (much) faster than ethylene. Does this order reflect the extent of charge transfer in the transition state?

Provided on screen are electrostatic potential maps for transition states of Diels-Alder reactions involving cyclopentadiene and ethylene (left), *cis*-1,2-dicyanoethylene (middle) and tetracyanoethylene (right). Is charge transfer in the expected direction? Elaborate. Which of the three transition states shows the most charge transfer and which shows the least? Is the transition state that shows the greatest amount of electron transfer that for the fastest Diels-Alder reaction?

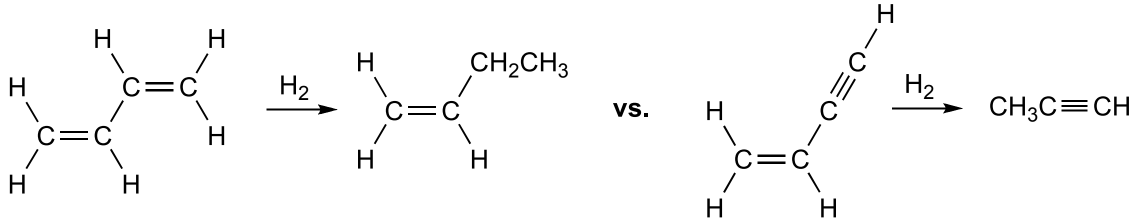
10. Retinal. Isomerization of *cis*-retinal to *trans*-retinal is the key step in the processing of visual information.



cis-retinal   *trans*-retinal

Is the *cis-trans* isomerization *exothermic* or *endothermic*? Speculate on the reason for the direction.

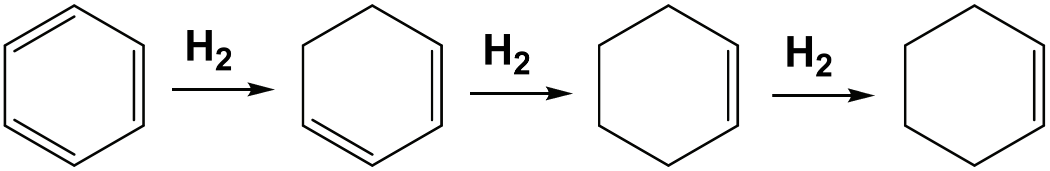
11. Mixed Conjugated Compounds. Is the benefit of conjugation greater for two double bonds or for adjacent double and triple bonds? Use either calculated energies or heats of formation from the database accessible from ***SpartanModel*** to compare the first step in the hydrogenation of 1,3-butadiene with that of hydrogenation of the ***double bond*** in but-1-yne-3-ene.



Which reaction is more *exothermic*? What does this say about the conjugation energies of two double bonds vs. a double bond and a triple bond?

14. Aromaticity

1. Aromatic Stabilization in Benzene. One way to "measure" the aromatic stabilization of benzene is to compare the energy of adding H_2 (leading to 1,3-cyclohexadiene) with the energy of adding hydrogen to 1,3-cyclohexadiene (leading to cyclohexene), or the energy of adding hydrogen to cyclohexene (leading to cyclohexane).



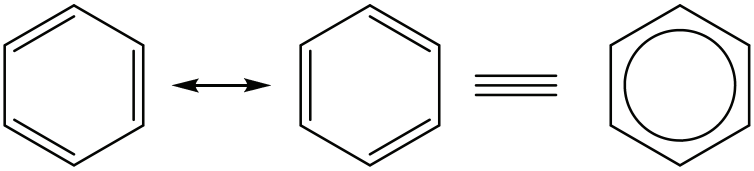
The three steps are similar insofar as each trades a CC π bond and an HH bond for two CH bonds. Normally such a trade would be expected to be energetically favorable (leading to an *exothermic* reaction) as σ bonds are stronger than π bonds. However, the first hydrogenation step presumably results in loss of the aromaticity of benzene, whereas there is nothing to lose in the second and third steps. This suggests that the difference in reaction energy between the first and second (or third) steps should reflect the aromatic stabilization of benzene.

Use either calculated energies or heats of heats of formation from the database associated with ***SpartanModel*** to calculate energies (heats) for all the hydrogenation steps starting from benzene and leading finally to cyclohexane. What is the difference in reaction energy between the first and second steps in the overall hydrogenation reaction? Is this similar to the difference between the first and third steps? What is your estimate of the aromatic stabilization of benzene?

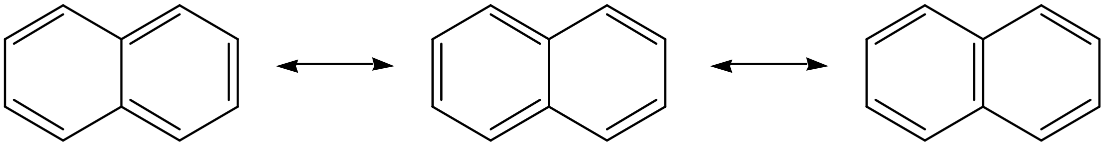
3. Are Cyclobutadiene and Cyclooctatetraene Antiaromatic? The Hückel "4n+ 2" rule, which "predicts" the unusual stability of benzene, would also seem to suggest that molecules with 4n π electrons such as cyclobutadiene (C_4H_4) and cyclooctatetraene (C_8H_8) should be unusually unstable. Use either calculated energies or heats of formation from the database accessible from ***SpartanModel*** to calculate energies (heats) for hydrogenation of cyclobutadiene to cyclobutene and then from cyclobutene to cyclobutane. Is the second step *exothermic* as expected? If so, is the heat of reaction similar to those for the corresponding steps in the hydrogenation of benzene (see previous problem)? Is the first step also *exothermic* (opposite to the direction of the first step in the hydrogenation of benzene)? If so, is it more *exothermic* than the second step (cyclobutene to cyclobutane)? Provide an estimate for the "antiaromaticity" of cyclobutadiene.

Repeat your analysis for cyclooctatetraene, by comparing the energy of the first hydrogenation step (from cyclooctatetraene to cyclooctatriene) with that on one of the subsequent steps. Do you conclude that cyclooctatetraene is antiaromatic? Elaborate. Can you point to any other evidence to support your conclusion?

4. Naphthalene. Some molecules cannot be adequately represented in terms of a single Lewis structure, and a combination of two or more structures are needed. These fall into two categories. The first is where the individual Lewis structures show different but equivalent arrangements of bonds and are, therefore, weighted equally. For example, equal weighting of the two Lewis structures for benzene leads us to conclude that the six carbon-carbon bonds are identical and midway in length between normal single and double bonds. This is in accord with observation.

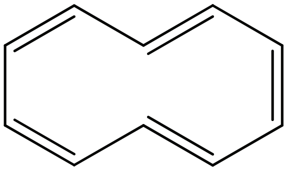


The second is where the Lewis structures are not all the same. For example, two of the three Lewis structures that can be written for naphthalene are the same but the third is different.



Assigning equal weights to all three Lewis structures, this suggests that four of the bonds in naphthalene should be shorter than the remaining seven bonds. Is the calculated structure for naphthalene in accord? If it is not, which Lewis structure (or pair of Lewis structures) makes the greater contribution?

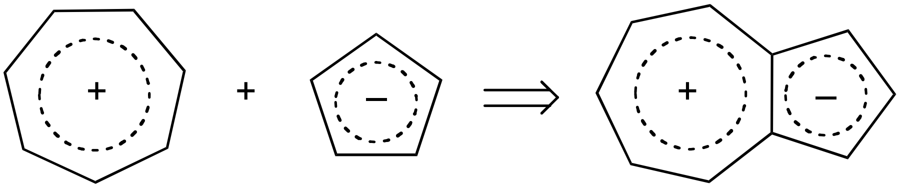
5. "Open" Naphthalene. (1Z,3E,5Z,7E,9Z)-cyclodeca-1,3,5,7,9-pentaene contains 10π electrons in a ring and might be expected to be aromatic as is naphthalene.



(1Z, 3E, 5Z, 7E, 9Z)-cyclodeca-1,3,5,7,9-pentane

Examine the geometry of the molecule. Is it planar? Are all carbon-carbon bonds of similar length midway between single and double bonds, or are there localized single and double bonds? Would you expect (1Z,3E,5Z,7E,9Z)-cyclodeca-1,3,5,7,9-pentaene to be aromatic?

6. Azulene. Azulene, an isomer of naphthalene, is often represented as the fusion of two aromatic ions, each with 6π electrons, the seven-member ring cycloheptatrienyl (tropylium) cation and the five-member ring cyclopentadienyl anion.



If this picture is at all realistic, then the "cycloheptatrienyl side" of azulene should be positively charged while the "cyclopentadienyl side" should be negatively charged. A suitable "neutral" reference compound is naphthalene (a more stable $C_{10}H_8$ compound).

Obtain an electrostatic potential map for azulene.

> You can build azulene by first constructing a seven-member ring comprising three double bonds and a carbocation center and then using one of the double bonds as part of the five-member ring (adding a double bond and a carbanion center). The two charges cancel leaving you with an uncharged molecule.

Do you see evidence of charge separation in azulene? Is it in the expected direction? If there is charge separation, what effect, if any, would you expect it to have on its energy of azulene relative to naphthalene (where there is no charge separation)? Elaborate.

7. Charge Distributions in Substituted Benzenes. Both the magnitude and direction of the dipole moment provide good indicators of the overall charge distribution in a molecule, for example, in a substituted benzene. Dipole moment directions can classify a substituent as either an electron donor or electron acceptor. Unfortunately, such quantities are difficult to measure and in practice experimental data are limited to a small number of simple molecules. On the other hand, dipole moment magnitudes ("dipole moments") are easily measured and are available for large numbers of molecules. Quantum chemical methods provide easy access to both quantities.

Obtain the dipole moment of ethylbenzene. Based on the direction of the dipole moment vector, do you conclude that the ethyl group is acting as an electron donor or as an acceptor relative to benzene? Is this the same behavior noted for an ethyl group attached to ethylene? Examine the dipole moment vector for the *gauche* conformer of 1-butene to decide.

Next, obtain dipole moments for styrene and phenylacetylene. Is the direction of electron transfer between substituent and benzene ring the same as noted for ethylbenzene? Is the direction of the dipole moment vector the same in the two molecules? Do you conclude that the vinyl group donates or accepts electrons from the benzene ring? Do you conclude that the ethynyl group donates or accepts electrons from the benzene ring?

Does the benzene ring appear to play a constant role (either as electron donor or acceptor) with regard to groups that are attached?

8. Benzenium Cations. Benzenium cations result from addition of a positively-charged electrophile onto a substituted benzene, and there is strong evidence that they are intermediates in electrophilic aromatic substitution. The simplest benzenium ion is that resulting from protonation of benzene. It is a commonly seen in mass spectra and simple derivatives have been crystallized and structurally characterized using X-ray diffraction.

Draw the Lewis structure (or sequence of Lewis structures) that represent protonated benzene. Where is the positive charge? Obtain an electrostatic potential map for the ion. Does this show a distribution of charge that is consistent with that suggested by the Lewis structure(s)? Where would electron donor substituents be most effective in stabilizing the positive charge?

9. "Localized" Benzene. The common picture of benzene as a pair of equivalent Lewis structures each with localized single and double bonds is easily misinterpreted by first-time students of organic chemistry as an equilibrium between two stable structures. Of course, there is only a single structure for benzene, in which all six carbon-carbon bonds are intermediate in length between single and double bonds. However, it may be possible to make a substituted benzene that exhibits significant bond localization.

One reasonable approach involves attaching bulky substituents on adjacent carbons thus forcing extension of one bond. Obtain the geometry of 1,2-

di(*tert*-butyl)benzene. Is the bond connecting the carbons with the two bulky substituents longer than normal? Does the molecule show evidence of bond localization?

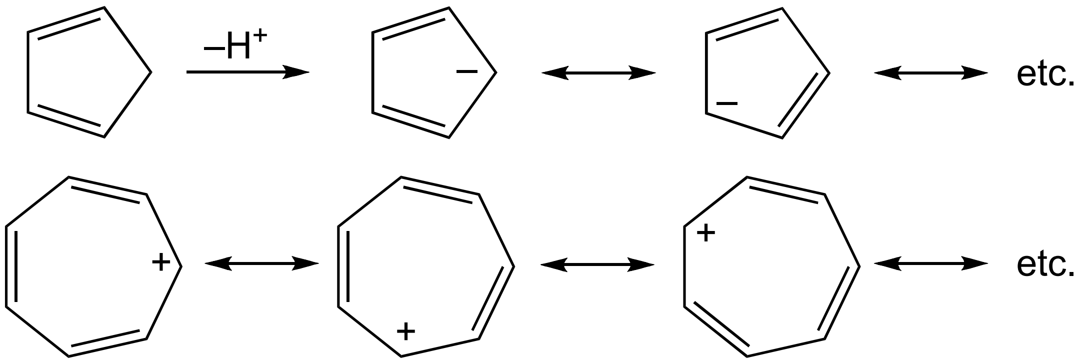
Another possibility is to try to shorten one of the ring bonds by fusing it to a small ring. Benzocyclobutene (benzene fused to cyclobutadiene) is a good candidate. Obtain its geometry. Is the bond that is common to the two rings shorter than normal? Does the molecule show evidence of bond localization?

Feel free to further explore these two directions for better candidates or to suggest yet another approach to building localized benzene.

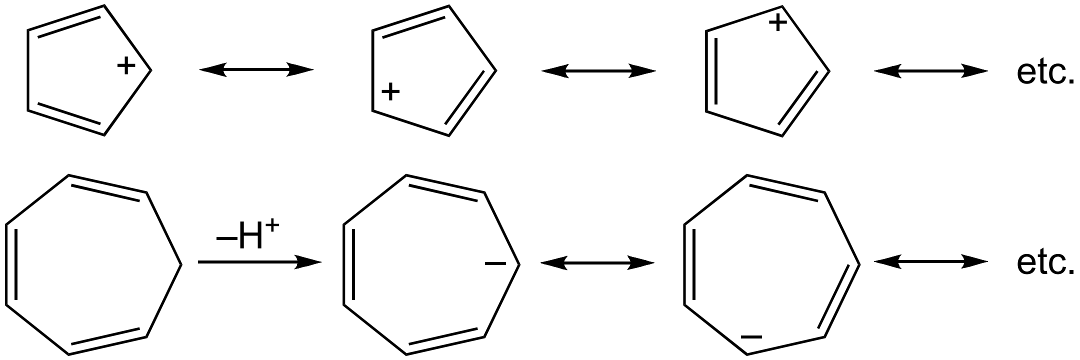
10. Buckmeister Fullerene "Buckyball". Buckmeister fullerene, more commonly known as or buckyball or C_{60}, is a fascinating molecule on several grounds. For one, it is a form of elementary carbon, distinct from the other two known forms (graphite and diamond). In fact, C_{60} is just one of several ball-shaped molecules that have come to light in the past two decades. Second, buckyball has been shown to be able to encapsulate a number of atoms and small molecules which are then unable to diffuse out. The obvious question is how the molecules get inside. The answer is that they don't "get in". Rather, buckyball needs to be formed from around them.

While the size of the cavity (and by inference the maximum size of a molecule that can be encapsulated) can be estimated using the known geometry of buckyball and the van der Waals radius of carbon, there is no way to assess the environment presented to a molecule held inside the cavity. However, this can be accomplished using an electrostatic potential map.

11. Multiple Lewis Structures and Stability. Is the fact that several Lewis structures may be needed to provide adequate description of bonding necessarily mean that the molecule is unusually stable? Certainly, cyclopentadienyl anion and cycloheptatrienyl cation, the descriptions of which require two and three Lewis structures, respectively, are unusually stable.



Are cyclopentadienyl cation and cycloheptatrienyl anion, which also require two and three Lewis structures to portray, respectively, also especially stable?



Examine the geometries for the two cations and the two anions. Are the four molecules planar? (Be certain to start with non-planar geometries in order to allow for this result.) If not, which are non planar? Are all carbon-carbon bonds of equal length or are there distinct single and double bonds? If not, which show localized bonding? Calculate energies for the following pair of reactions.

$$C_5H_6 + C_7H_7^+ \longrightarrow C_5H_5^+ + C_7H_8$$

$$C_5H_6 + C_7H_7^- \longrightarrow C_5H_5^- + C_7H_8$$

The first compares the energy required to remove hydride anion from cyclopentadiene and cycloheptatriene, and the second the energy of protonation of cyclopentadiene and cycloheptatriene. What do your data tell you about the relative stabilities of the two anions and of the two cations?

Are these results consistent with the calculated geometries for the ions? Elaborate.

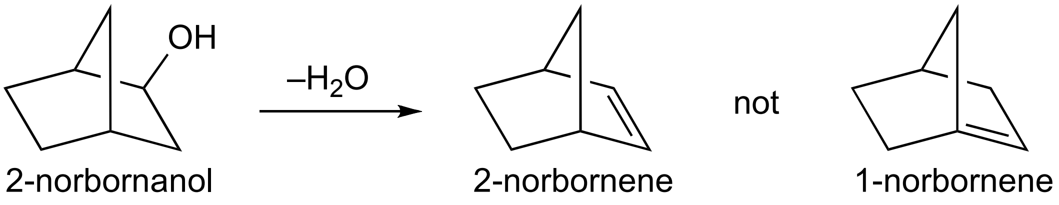
Use your experience to guess which molecule, 7-bromo-1,3,5-cycloheptatriene or 5-bromo-1,3-cyclopentadiene, would be expected to dissociate into ions when dissolved in water. Elaborate.

The map for provided on screen has been sliced in half to allow the electrostatic potential for not only the outside but also the inside of buckyball to be seen. Is the environment electron rich, electron poor or neutral? Is the "inside" environment significantly different from the "outside" environment? Would cations, anions or neutral atoms and molecules be best accommodated inside of buckyball? Would you expect buckyball to be soluble in non-polar or polar solvents?

12. Are All Diels-Alder Reactions Exothermic? Diels–Alder reactions in which two π bonds are destroyed and two σ bonds are created would be expected to be highly *exothermic*. Thus, according to the Hammond Postulate, the transition states for Diels-Alder reactions should closely resemble reactants. Are there exceptions to this generalization?

Calculate the energy for Diels-Alder reaction of cyclopentadiene and maleic anhydride. Is the reaction *exothermic* as expected? If so, is the *exothermicity* of the reaction roughly twice the difference of "average" carbon-carbon σ and π bond energies? Next, calculate the energy for the analogous Diels-Alder reaction of cyclopentadiene and phthalic anhydride. Is this reaction

13. *Dehydrogenation of 2-Norbornanol.* Elimination of water from 2-norbornanol leads to 2-norbornene rather than to 1-norbornene.



Calculate energies for both isomers of norbornene. Is the observed product of dehydrogenation also the thermodynamic product? Is it likely that the other product will be observed at room temperature? (Assume that it would need to comprise at least 5% of the total mixture in order to be detected.)

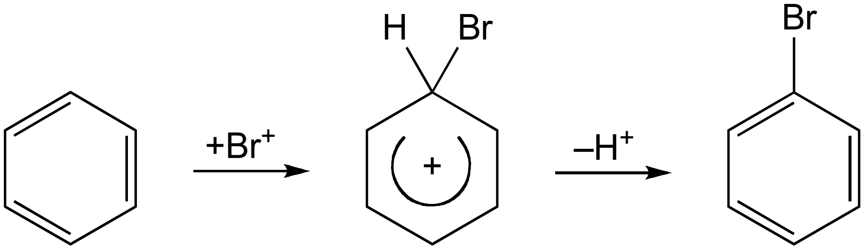
Compare geometries for the two isomers and point any differences that might contribute to the instability of the higher-energy product.
exothermic? If it is not, provide and explanation as to why.

15. Regiochemistry in Electrophilic Aromatic Substitution

1. Electrostatic Potential Maps Anticipate Electrophilic Reactivity. An electrostatic potential map measures the extent to which a point positive charge (an electrophile) interacts with the accessible surface of a molecule. Visual comparison of potential maps provides a simple means to judge electrophilic reactivities of related compounds.

Compare electrostatic potential maps for benzene, toluene, N,N-dimethylaniline, anisole and nitrobenzene. Relative to benzene, which groups would you expect to facilitate electrophilic substitution? Which groups would you expect to retard it? Try to identify a "new" substituent that is likely to be even more effective in promoting electrophilic substitution than the best from the above list. Similarly, try to identify a substituent that is likely to be even more effective in retarding the reaction. Consider only uncharged substituents.

2. Intermediates in Electrophilic Bromination of Benzene. Reaction of bromine with benzene leads to bromobenzene (the substitution product), presumably via a charged "benzenium ion" intermediate.

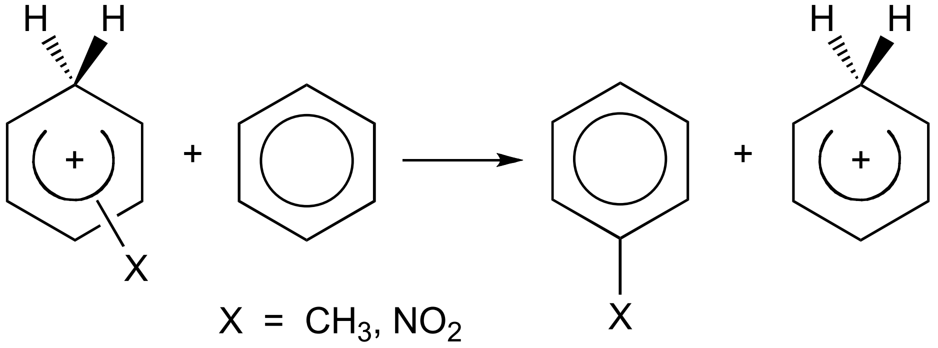


bromobenzenium ion

Examine the geometry of the intermediate ion. Are the carbon-carbon bonds made from sp^2 carbons all roughly the same length or are single and double bonds clearly distinguishable? Examine atomic charges. Which carbons are most positively charges (use the sum of the charge on carbon and its attached hydrogen)? Display an electrostatic potential map. Does this provide a similar account of the charge distribution in the intermediate?

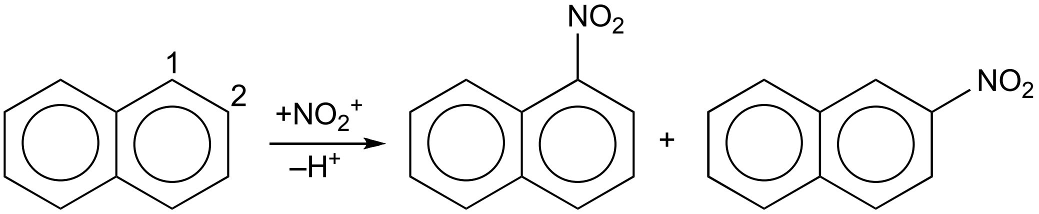
3. Activating and Directing Effect on Electrophilic Aromatic Substitution. Electron-donor groups are known to lead to an increase in rate of electrophilic substitution whereas electron-withdrawing groups are known to lead to a decrease in rate. Furthermore, donors are known to favor *ortho* and *para* substitution products while acceptors are known to favor *meta* products. The working hypothesis is that substitution reactions initiate by addition of the positively charged electrophile, for example, Br^+. This in turn leads to a benzenium ion intermediate, the stability of which determines both the overall rate and the distribution of products.

Obtain energies for all molecules and benzenium ion intermediates needed to evaluate the energies of the following series of reactions. Consider only *meta* and *para* intermediates.



Which intermediate is favored for bromination of toluene? Is the other intermediate close enough in energy to be seen at room temperature? (Assume a minimum abundance of 5% in order to be detected.) Which intermediate is favored for bromination of nitrobenzene? Is the other intermediate likely to be seen? Is bromination of toluene leading to the lower-energy intermediate more or less favorable than bromination of benzene, that is, is the reaction above *exothermic* or *endothermic*? Is bromination of nitrobenzene leading to the lower-energy intermediate more or less favorable than bromination of benzene? Are your results consistent with the working hypothesis? Elaborate.

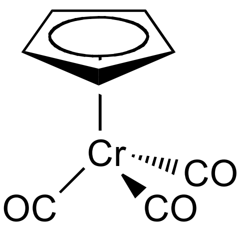
4. Nitration of Naphthalene. Electrophilic substitution in naphthalene can occur at one of two sites, leading to two different products. For example, nitration of naphthalene can lead either to 1 or 2-nitronaphthalene (or both). The working hypothesis is that the favored product is that which follows from the more stable intermediate "naphthalenium ion".



Compare energies for the two intermediate ions resulting from initial addition of NO_2^+ to naphthalene. Is the lower-energy ion that which leads to the experimentally observed nitration product? Is the energy difference between the two ions small enough such that both products are likely to be seen in a room-temperature equilibrium mixture, or is it sufficiently large such that only the lower-energy product will be seen? (Assume a minimum abundance of 5% in order to be detected.)

5. Acyl Cation. Acyl cation, CH_3CO^+, adds to benzene to give acetophenone. However, the "obvious" Lewis structure for acyl cation places the + charge on oxygen and not on carbon. Obtain atomic charges for acyl cation. Which is more positive, oxygen or one of the two carbons? If the latter, which carbon? Confirm (or refute) your result by examining the electrostatic potential map for the ion. Is what you find consistent with what is observed experimentally?

6. Chromium Tricarbonyl as a "Substituent". Organic chemists typically think about a substituent as a chemical group that is σ bonded to molecule. The substituent can then act as a σ or π donor or as a σ or π acceptor (or as both a donor and acceptor). There is another kind of "substituent" that can also act to donate or accept π electrons. This is group that "complexes" to the π system of a double bond or to one face of an aromatic ring. Such a group will generally (but not necessarily) involve a metal, a good example being the chromium tricarbonyl group. Chromium tricarbonyl complexes adopt roughly tetrahedral geometries, for example, benzene chromium tricarbonyl.



The images on screen correspond to electrostatic potential maps for dimethylaniline, nitrobenzene and benzene chromium tricarbonyl, as well as benzene itself (providing a "baseline"). The amino group is known to be a strong π-electron donor whereas the nitro group is known to be a strong π-electron acceptor. Are the electrostatic potential maps consistent with these descriptions? Elaborate. Is the $Cr(CO)_3$ group an electron donor or electron acceptor (or neither)? How does it compare to the appropriate strong donor or acceptor group?

16. Aldehydes and Ketones

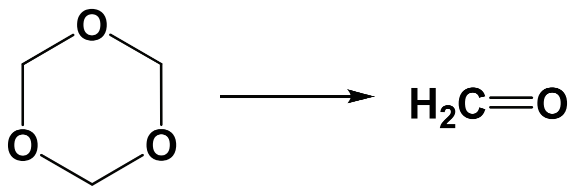
1. Dipole Moments in Carbonyl Compounds vs. Alkenes. Evidence that the CO double bond in carbonyl compounds is more polar than a CC double bond in alkenes, should follow from a comparison of dipole moments. Compare dipole moments for acetone and 2-methylpropene. Is the direction of the dipole moment the same in the two molecules, that is, does the common fragment remain at the same end? Is the magnitude of the dipole moment in acetone significantly larger than that in 2-methylpropene? Next, examine the magnitudes of dipole moments in cyclohexanone and methylenecyclohexane. Are they similar to those in acetone and 2-methylpropene, respectively? Is the difference between them similar to the difference between acetone and 2-methylpropene? Finally, obtain the dipole moment for perfluoroacetone, $(CF_3)_2CO$. Is the magnitude and direction similar to those for acetone? If one or both are not, try to provide an explanation as to why not. Use your results to predict the sign and direction of the dipole moment in the alkene analogue, $(CF_3)_2C{=}CH_2$. Test your prediction by calculating them.

2. Infrared Spectra of Carbonyl Compounds. A presence of a strong line in the infrared in the region of 1700-1750 cm^{-1} alerts an organic chemist that there is at least one carbonyl group in the molecule. In fact, one of the most common practical uses of infrared spectroscopy is to confirm that a molecule contains carbonyl functionality. Examine the infrared spectrum of acetone (access it from the database accessible from SpartanModel). Is there a strong absorption where anticipated? What is the vibrational motion associated with this line? Next, examine the infrared spectra of a series related carbonyl compounds. Acetaldehyde, propanal and 2-pentanone are available in the database, although there are many others for you to choose from.

> The infrared spectra included in the database have been obtained from quantum chemical calculations. They are not experimental infrared spectra, although the results are typically very close.

There are exceptions to the general rule that carbonyl compounds will always show a “strong” line between 1700 and 1750 cm^{-1}. Among them is perfluoroacetone, $(CF_3)_2CO$ (see previous problem). Examine its infrared spectrum. Why is it an exception? Is it because there is no line in the spectrum in the “right” region or because the absorption is very weak? If the former, locate the line in the infrared spectrum of perfluoroacetone that corresponds to the “characteristic vibration” exhibited by other carbonyl compounds. If the latter, suggest why it is weaker that that in other carbonyl compounds. Hint: the intensity of an infrared absorption is proportional to the change in the dipole moment during the vibration.

3. Preparation of Formaldehyde. Formaldehyde cannot easily be handled as a pure substance. Rather, it is normally prepared *in situ* from 1,3,5-trioxane, a reaction that may be viewed as swapping three CO π bonds for three CO σ bonds.



1,3,5-trioxane

Is decomposition of 1,3,5-trioxane to three molecules of formaldehyde an *exothermic* or *endothermic* process? Rationalize your result based on what you know about the relative CO σ and π bond energies. If the reaction is *endothermic*, point to any other factors that may furnish the driving force.

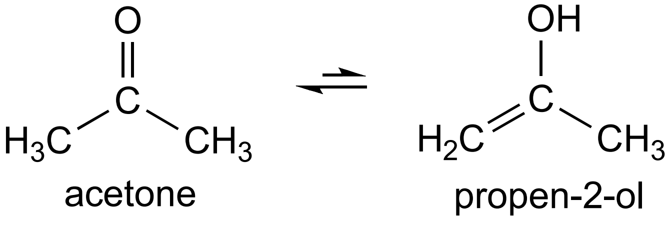
4. Molecular Orbitals of Formaldehyde. The Lewis structure of formaldehyde contains six electron pairs, three involved in σ bonds, one in a π bond and two non-bonded pairs (lone pairs). Examine the occupied molecular orbitals of formaldehyde. Are you able to say which correspond to the individual CO and CH σ bonds or to the lone pairs? Elabrorate.

Identify the molecular orbital that corresponds to the π bond. Is it the highest-occupied molecular orbital (the HOMO)? Is there experimental evidence for whether or not it is? Elaborate. Is the π orbital equally concentrated on the carbon and oxygen? If not, on which atom is it more heavily concentrated? Rationalize your result.

Is it the lowest-unoccupied molecular orbital (the LUMO) a π type orbital? (If not, find the unoccupied π type orbital.) Is their experimental evidence for whether or not it is? It is the same evidence that suggests that the HOMO of formaldehyde does or does not correspond to the π bond? Elaborate. Is this orbital equally concentrated on the carbon and oxygen? If not, on which atom is it more heavily concentrated? Rationalize your result in light of what you found for the occupied π orbital. Given that addition of a nucleophile should occur where the LUMO is concentrated, what does you result say about nucleophilic addition to carbonyl compounds?

5. Nucleophilic Reactivity of Carbonyl Compounds. As discussed in the previous problem, nucleophilic addition should occur onto the atom for which the LUMO is most heavily concentrated. It is reasonable to expect that LUMO energy will be a broad indicator of reactivity, that is, the lower the energy the greater the reactivity? Obtain LUMO energies for the series of aldehydes: formaldehyde, acetaldehyde, benzaldehyde and trichloroacetaldehyde. Based on the ordering of LUMO energies, rank the reactivity of the compounds. Provide any experimental evidence in support of (or refuting) your assignments.

6. Affecting Keto-Enol Distributions. Aldehydes and ketones are in equilibrium with their enol forms (vinylic alcohols). Equilibrium typically favors the former, sometimes significantly so. For example, acetone is estimated to be more than 40 kJ/mol more stable than its enol, 2-propenol.



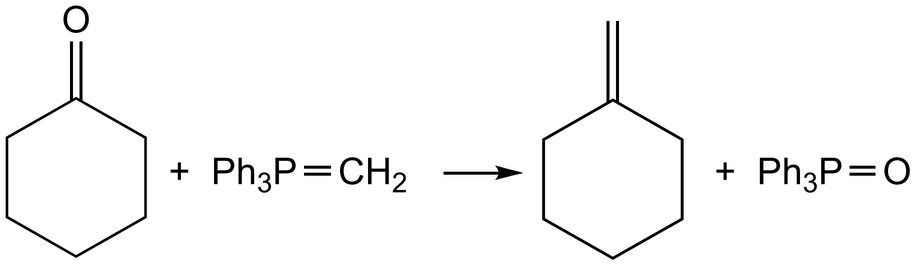
Calculate energies for acetone and 2-propenol. Verify that the ketone is lower in energy and that the keto-enol energy difference is in qualitative accord with the experimental estimate. Calculate keto-enol differences for methyl acetate and 1,1,1-trifluoroacetone. What effect does replacing a methyl group by a methoxy group (a stronger π-electron donor) have on the keto-enol energy difference? What effect does replacing methyl with trifluoromethyl (a π-electron acceptor group) have on the difference? Is it likely that the enol form of either methyl acetate or 1,1,1-trifluoroacetone will be seen in an equilibrium mixture at room temperature? (Assume that the enol would need comprise at least 5% of the total mixture in order to be detected.)

7. Phosphorus Ylides. Ylides of phorphorus such as methylene triphenylphosphine ylide can be represented either in terms of a Lewis structure with separated charges (a zwitterion) or as a structure in which phosphorus has more than eight valence electrons (a hypervalent structure).

$$\mathrm{Ph_3P^+{-}CH_2^-} \longleftrightarrow \mathrm{Ph_3P{=}CH_2}$$

Examine atomic charges and the electrostatic potential map of methylene triphenylphosphine ylide. Which Lewis structure appears to be the more appropriate? Explain how you reached your conclusion.

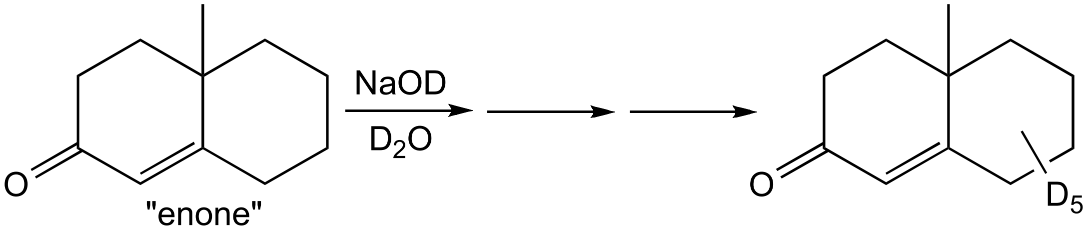
8. Wittig Reaction. CO double bonds are typically much stronger that CC double bonds, making it difficult obtain alkenes from carbonyl compounds. The Wittig reaction offers a way to accomplish this transformation by using a phosphorus ylide ("Wittig reagent"), for example, reaction of cyclohexanone and triphenylphosphine ylide to yield methylenecyclohexane and trimethylphosphine oxide.



Is this reaction *exothermic*? If it is, what does this say about the relative strengths of PC and PO double bonds?

17. Enols and Enolates

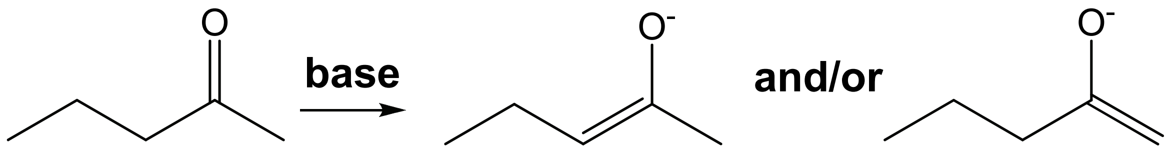
1. Enolates in H/D Exchange Reactions. Treatment of the bicyclic enone pictured below with deuterated sodium hydroxide in D_2O, leads to exchange of several hydrogen atoms for deuterium atoms.

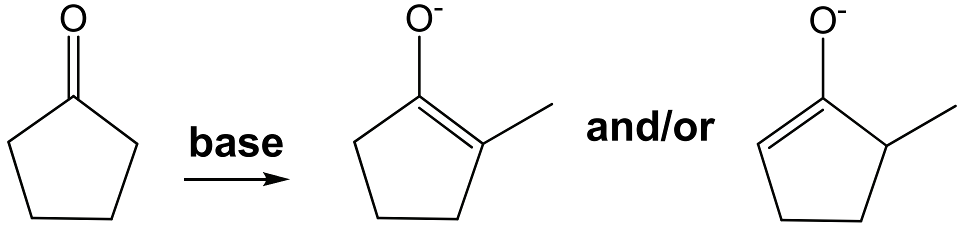


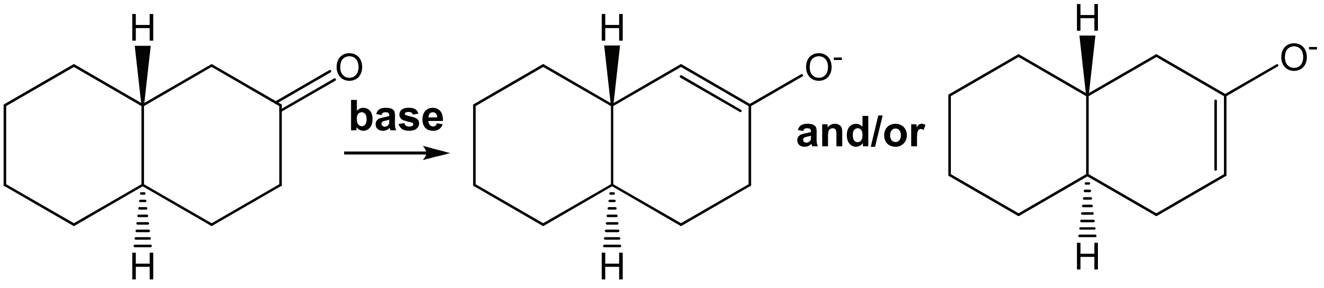
The reaction is presumed to involve initial deprotonation leading to an enolate anion followed by deuteration by D_2O. How many "reasonable" enolate anions may result from deprotonation? Identify the "best" (lowest energy) enolate. Identify any other enolates that would be expected to make up at least 1% of a room temperature equilibrium mixture. How many hydrogen atoms would you expect to be exchanged for deuterium atoms?

2. Using Enolate Stabilities to Anticipate Product Distributions. In the presence of strong base, unsymmetrical ketones may give rise to two (and possibly more) different enolates. Where the reaction is under thermodynamic control, knowledge of which enolate is the most stable allows assignment of the preferred product.

Assuming thermodynamic control, assign the product of each of the following reactions.

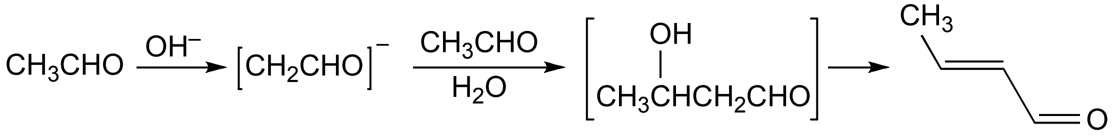




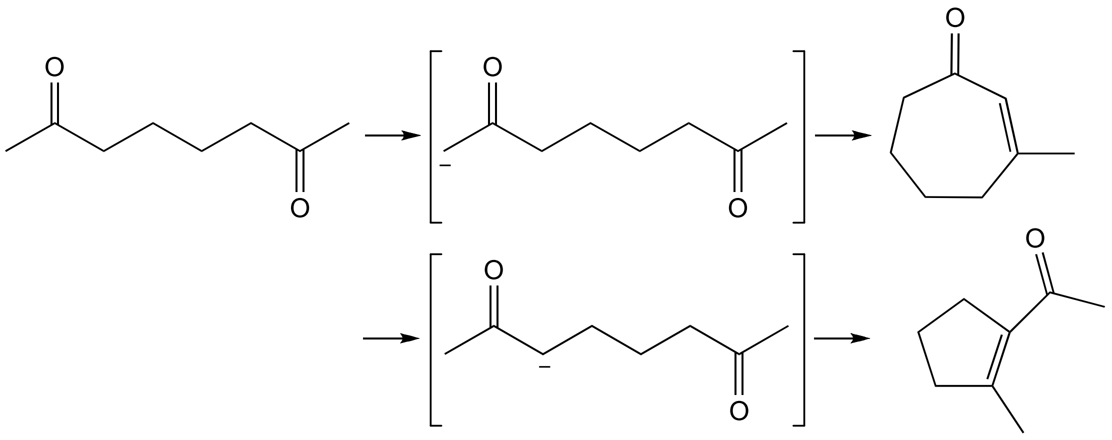


Try to rationalize your results based on difference in the structures of the different enolates.

3. Intramolecular Aldol Condensation. Aldol condensation involves addition of an enolate formed upon deprotonation of an aldehyde or ketone by strong base, to another aldehyde or ketone with subsequent loss of water, for example, the aldol condensation of acetaldehyde.



For some dicarbonyl compounds, intramolecular aldol condensation may also occur, leading to the possibility of two or more different products. Thus, aldol condensation of 2,7-octadione can give rise to either (or both) seven and five-member ring products.



Identify the lower-energy enolate? Assuming that the product distribution follows from the equilibrium distribution of enolates, what is the ratio of 5 to 7-member ring products at room temperature?

Ester Enolates/Claisen Condensation

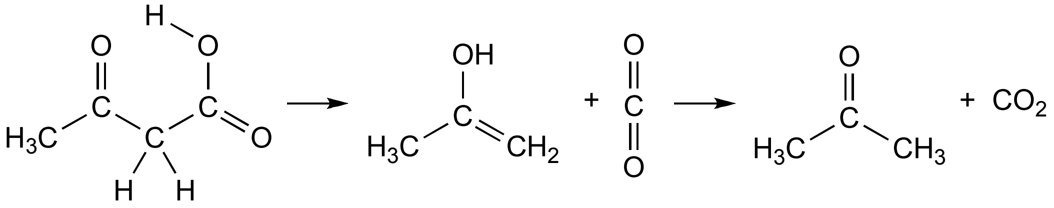
1. Claisen Condensation. The Claisen condensation involves base initiated attack of an ester enolate onto a carbonyl group, resulting in a 1,3-dicarbonyl compound containing a new carbon-carbon bond, for example, reaction of ethyl acetate with itself leading to ethanol and ethyl acetoacetate.

$$2\ CH_3CO_2Et \longrightarrow EtOH + CH_3COCH_2CO_2Et$$

Is the process for ethyl acetate *exothermic* or *endothermic*? To decide, either calculate energies for all molecules in the reaction or use data from the collection of heats of formation accessible from ***SpartanModel***. Justify your result using what you know about bond energies. If you conclude that the reaction is *endothermic*, provide a reason for why it actually proceeds.

2. Acidity of Ethyl Acetoacetate. Ethyl acetoacetate, the product of Claisen condensation of ethyl acetate with itself, has two sets of acidic hydrogens, one on the terminal methyl and the other on the methylene carbon in between the two carbonyl groups. Examine the electrostatic potential map to decide which is more acidic. Are the more acidic hydrogens on ethyl acetoacetate more or less acidic than the acidic hydrogens the reactant, ethyl acetate? Is it likely that the resulting enolate will attack ethyl acetate? Is such a reaction observed?

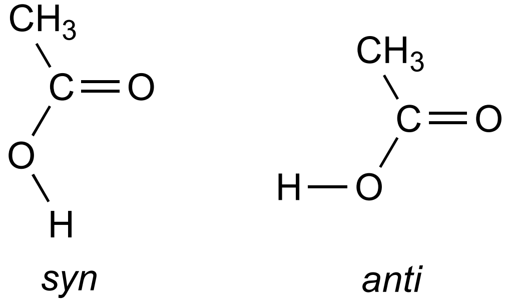
3. Acetyl Acetic Acid. So-called β-keto acids such as acetylacetic acid may lose carbon monoxide leading initially to 2-propenol which in turn rearranges to acetone. The mechanism typically written seems to demand that the reactant position itself into a six-member ring allowing transfer of hydrogen.



Why should you not be surprised to learn that the structure depicted above does not correspond to the lowest-energy conformer of acetylacetic acid? Hint: what is the structure of acetic acid? Find the lowest-energy conformer and calculate the energy difference between it and the conformer above. Is the latter likely to be seen in a room-temperature equilibrium? (Assume that it must contribute at least 5% to the total in order to be detected.)

18. Carboxylic Acids

1. Conformation of Acetic Acid. Conformer energy differences that arise due to rotation about single bonds are typically very small. For example, both the *trans* and *gauche* conformers of ethanol are present in equilibrium meaning that the energies of the two are nearly the same. A major exception to any generalization arises for rotation about the CO single bond in carboxylic acids and esters. Here, *cis* and *trans* conformers are plausible, as for example, in acetic acid, but only a single conformer is observed.



Obtain equilibrium geometries for both *cis* and *trans* conformers of acetic acid. Which conformer is lower in energy and by how much? Is it likely that the higher-energy conformer will be seen in equilibrium mixture at room temperature? (Assume that it needs comprise at least 5% of the total to be detected.) Which conformer has the lower dipole moment? Rationalize your result. Is the lower-energy conformer also the conformer with the smaller dipole moment? If so, why is this reasonable?

Repeat your calculations and analysis for methyl acetate.

2. Dimers of Carboxylic Acids. Both melting and boiling points of carboxylic acids are significantly higher than those of alcohols of comparable molecular weight. For example, the boiling point of acetic acid is 21° higher than that of 1-propanol, even though the two have nearly equal molecular weights. The usual explanation is that carboxylic acids form hydrogen-bonded dimers. Alcohols also form dimers, so the difference must be in the number and strengths of the hydrogen bonds.

Obtain structures of the dimers of both acetic acid and 1-propanol (or methanol as a simpler example). Is there a difference in the number of hydrogen bonds? Calculate the dimerization energy for acetic acid (subtract twice the energy of acetic acid from the energy of acetic acid dimer). Repeat for 1-propanol (or methanol) dimer. Is there a significant difference in the total hydrogen bond energy? Is there a significant difference in the energy per hydrogen bond?

3. Measuring Relative Acidities of Carboxylic Acids. Acetic acid is weaker than formic acid (its pKa is larger), whereas both trichloroacetic acid and trifluoroactetic acids are stronger. Is this ordering inherent to the isolated molecules, that is, is the same ordering observed in the gas phase, or is it due to the solvent? To tell, evaluate energies for reactions.

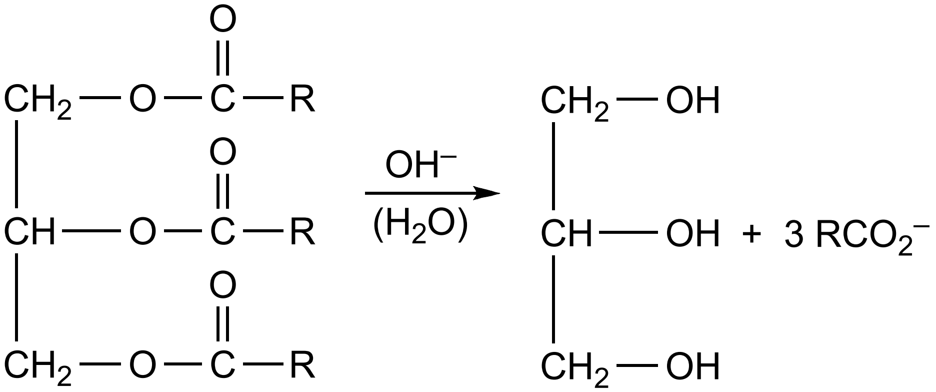
$$\mathrm{RCO_2H + HCO_2^{-} \longrightarrow RCO_2^{-} + HCO_2H \quad R{=}CH_3, CF_3 \text{ and } CCl_3}$$

Is the reaction of acetic acid *endothermic* or *exothermic*? Are reactions involving trifluoroacetic and trichloroacetic acids *endothermic* or *exothermic*? Is the ordering of acid strengths the same as found in solution? Elaborate.

Could the ordering of acid strengths in the gas phase have been anticipated by examining the value of the electrostatic potential of the (neutral) acids in the vicinity of the acidic hydrogen? This is much simpler than evaluating reaction energies as only the neutral compounds need to be considered. Display electrostatic potential maps for the four acids side-by-side on screen. Is the (maximum) value of the potential at the acidic hydrogen smaller for acetic acid compared to formic acid and larger for both trifluoroacetic acid and trichloroacetic acid compared to formic acid?

Order acidities for the following carboxylic acids, RCO_2H, where R is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cubyl and adamantyl. Use both reaction energies and electrostatic potential maps.

4. Soaps. Animal fats are long chain esters of glycerol ($HOCH_2CH(OH)CH_2OH$) known as triglycerides. Where the chains are alkyl groups, the fats are referred to "saturated fats". Where the contain double bonds, the fats are referred to as "unsaturated fats". Hydrolysis of animal fats in the presence of strong base leads to glycerol and the salts of long-chain carboxylic acids. These salts are commonly known as "soaps".



How does soap work in dissolving stains ("grease") in water? To help you decide, examine electrostatic potential maps for a long-chain (C_{15}-C_{20}) carboxylate anion, 2,2,3,3-tetramethylbutane (grease) and for water. Note, while the scale of the map for the carboxylate anion is different for those for the two neutral molecules, the color red indicates a negatively charged region, the color blue (not accessible for the anion) a positively-charged region and the color green a neutral region. Note also, that in the absence of Coulombic (charge-charge) interactions, molecules will weakly associate. Is 2,2,3,3-tetramethylbutane likely to associate with the carboxylate? Is water likely to associate? If you have answered yes to both questions, explain why.

Carboxylic Acid Derivatives

1. Nucleophilic Reactivity of Carboxylic Acid Derivative. Carboxylic acids and carboxylic acid derivatives all incorporate a polar carbon-oxygen double bond. Does this guarantee that they will be as reactive toward nucleophiles as “normal” carbonyl compounds, that is, aldehydes and ketones? One obvious “measure” is the energy and availability of the lowest-unoccupied molecular orbital (LUMO). Afterall, this is the orbital that receives the electron pair from the nucleophile. It is reasonable to expect that molecule in which the LUMO is of low energy and heavily localized on the carbonyl carbon will be more accessible to nucleophilic attack than one with a delocalized high energy LUMO.

Display LUMOs for acetaldehyde, acetone, acetic acid, methyl acetate, acetyl chloride and N,N-dimethylacetamide simultaneously on screen. Which compound has the lowest LUMO energy? Is this the same compound for which is the carbonyl carbon the most prominent? Which compound has the highest LUMO energy? Is this also the compound for which the LUMO is least prominent? On the basis of LUMO energies and the extent to which they are localized on the carbonyl carbon, assign an ordering of nucleophilic reactivity to these compounds. Is your result consistent with what is actually observed? Elaborate.

19. Amines and Amine Derivatives

1. Proton Affinities of Amines. The proton affinities (basicities) of amines depend on environment. It the gas phase, proton affinities increase dramatically with increasing alkyl substitution, for example: $NH_3 < MeNH_2 < Me_2NH < NMe_3$, whereas in water the effects are more subtle and ammonia is actually a stronger base than trimethylamine. To understand why, first calculate energies for both neutral and protonated forms of ammonia, methylamine, dimethylamine and trimethylamine. Determine proton affinities relative to that of ammonia, that is, the energies of the proton transfer reactions.

$$:B + NH_4^+ \longrightarrow BH^+ + :NH_3$$

What is the effect on the proton affinity of ammonia of adding a methyl group? Is the magnitude of the effect increased, decreased or remain the same with increased methyl substitution?

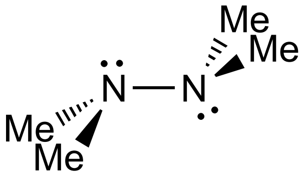
Next, repeat your calculations "in water". (It is sufficient to consider only the "end points", ammonia and trimethylamine.) A very primitive model is to "surround" each molecule with a several water molecules. The smallest number of water molecules that you can get away with is four. Why? Determine the energy of the "aqueous proton transfer reaction.

$$:NMe_3\text{---}(H_2O)_4 + NH_4^+\text{---}(H_2O)_4 \longrightarrow Me_3NH^+\text{---}(H_2O)_4 + :NH_3\text{---}(H_2O)_4$$

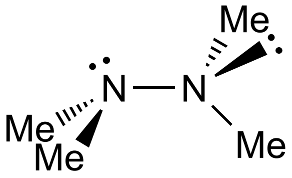
Make certain that the amine/protonated amine is "in the center" of the cluster. Water should be able to interact with all available electron pairs and acidic hydrogen atoms.

Is the reaction *exothermic* (trimethylamine is the stronger base) or *endothermic* (ammonia is the stronger base)? Is the difference in basicities "in water" comparable to the difference in the gas-phase or is it significantly smaller or larger? Rationalize you results.

2. Tetramethylhydrazine. Two different "staggered" conformers may be drawn for tetramethylhydrazine, one in which the nitrogen lone pairs are *anti* (180^o apart) and the other in which they are *gauche* (~60^o apart).



lone pairs *anti*

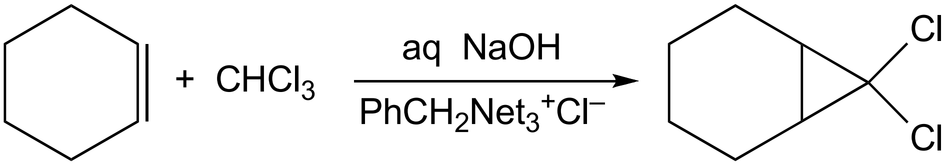


lone pairs *gauche*

Obtain equilibrium geometries for both *anti* and *gauche* conformers and compare their energies. Which conformer is more stable? Is this also the conformer with the smaller dipole moment? If it is not, provide a rationale why it is favored. Is the higher-energy conformer likely to be observed in an equilibrium mixture at room temperature? (Assume that it needs to make up >5% of the mixture to be detected.)

The procedure for finding an equilibrium geometry is not able to "jump out" of an energy well. This means that structures and energies for different conformers may be found by starting with different structures.

3. Phase-Transfer Catalysts. Phase transfer catalysts are agents that assist transfer of molecules between polar ("aqueous") and non-polar ("organic") solvents. In so doing, they allow molecules that would not normally be able to get close to react. For example, cyclohexene, chloroform and aqueous sodium hydroxide react only in the presence of a small amount of the phase-transfer catalysis, benzyltriethylammonium chloride. Without the catalyst, Na^+ and OH^- are confined to the aqueous layer and unable to reach chloroform and cyclohexene, which form the organic layer. Benzyltriethylammonium ion picks up hydroxide and carries it into the organic layer (or more likely to the interface between the two layers). Hydroxide deprotonates chloroform leading to dichlorocarbene, which in turn adds to the double bond.



Examine the electrostatic potential map for benzyltriethylammonium ion. Is it reasonable to expect that it will dissolve in both aqueous and organic solvents? Elaborate. Compare electrostatic potential maps for both tetraethylammonium and tetrabenzylammonium ions with that for benzyltriethylammonium ion. Would you expect either or both of these to be effective phase-transfer catalysts? Elaborate.

4. Electronegativities of Functional Groups. What is the electronegativity of a functional group? One way to put a bound on its value is to establish at what point the sign of the dipole moment changes along a series of molecules in which the functional group is attached to different atoms of known electronegativity.

Calculate dipole moments for the series of halogen nitriles, XCN, X=F, Cl, and I. For each, note whether the halogen or the nitrile group is at the positive end of the dipole moment vector. Based on your results and on halogen electronegativites given in your text, suggest a possible range of values for the electronegativity of the nitrile group.

Repeat your calculations and analysis for the analogous series of nitro compounds (XNO_2, X=F, Cl, and I). Is the electronegativity of the nitro group less, greater or about the same as the cyano group?

5. Are Amides Planar? The nitrogen in amines adopts a pyramidal geometry with a barrier to inversion through a planar nitrogen center on the order of 20 kJ/mol. On the other hand, organic chemists generally assume that the nitrogen in amides is planar. Is it?

Starting from a non-planar geometry, obtain the structure for N,N-dimethylacetamide. Is the nitrogen center planar? Add up the three CNC bond angles to tell. If it is not planar, calculate the energy of planar N,N-dimethylacetamide (start from a planar geometry). What is the barrier to inversion about nitrogen? How does this compare to the barrier in trimethylamine?

6. Energy Content of Hydrazine Fuels. Among numerous other applications, hydrazine, $H_2N\text{-}NH_2$, is a rocket fuel. Evaluate its heat of combustion using data from the collection of heats of formation accessible from ***SpartanModel***. (The heat of formation of O_2 is not in the collection. The value is 0 kJ/mol.)

$$H_2N{-}NH_2 + O_2 \longrightarrow N_2 + 2H_2O$$

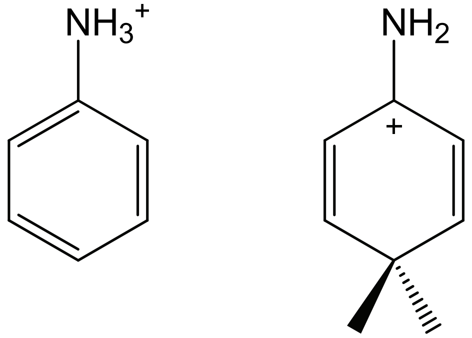
Also evaluate the heat of combustion of tetramethylhydrazine.

$$Me_2N{-}NMe_2 + 7O_2 \longrightarrow N_2 + 6H_2O + 4CO_2$$

Which delivers the greater energy on a per gram basis, hydrazine or tetramethylhydrazine? Make certain to include the mass of the oxidizer (O_2) in your calculations. How does the better of the two fuels compare with molecular hydrogen on a per gram basis?

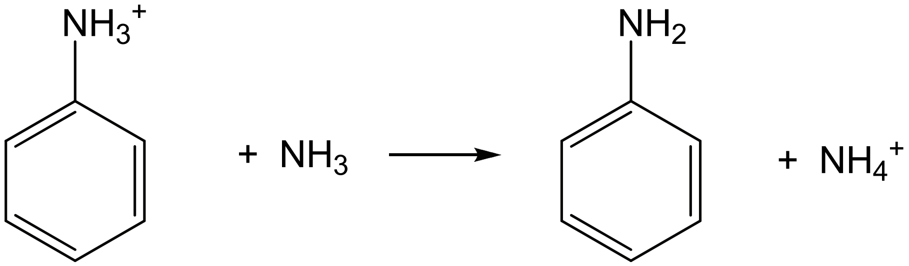
$$2\ H\text{-}H + O_2 \longrightarrow 2\ H_2O$$

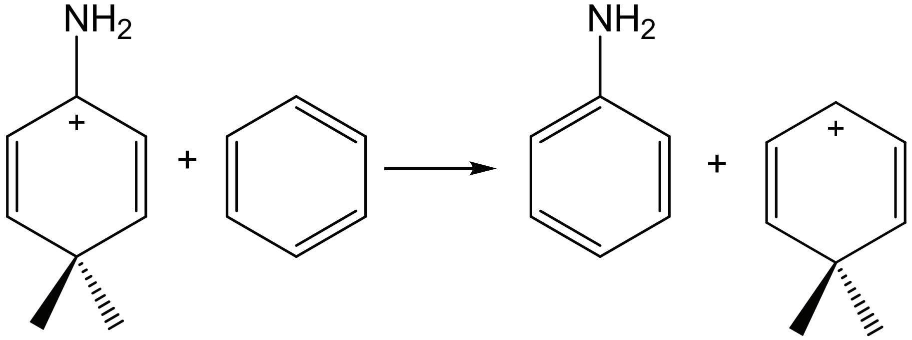
7. Protonation of Aniline. Does aniline protonate at nitrogen or on the ring?



A good argument can be made either way. Protonation on the ring would lead to loss of aromatic stabilization, but the resulting benzenium ion is delocalized and an NH_2 group (a very strong π donor) should stabilize the carbocation enter. On the other hand, protonation at nitrogen does not disrupt the aromaticity of aniline.

Calculate energies of both nitrogen and carbon protonated forms of aniline (assume that carbon protonation occurs *para* to the NH_2 group). Which ion is more stable? If the difference in energy between the two is small (<20 kJ/mol), obtain a "second opinion" by asking the calculations to calculate the difference in proton affinities between (nitrogen-protonated) aniline and ammonia and between (carbon-protonated) aniline and benzene.



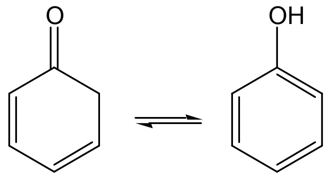


Combine your data with the known difference between the proton affinities of ammonia and benzene (104 kJ/mol in favor of ammonia). Does your previous result maintain? If not, you can assume that the second approach provides the more accurate result.

The quantum chemical model incorporated into ***SpartanModel*** is not sufficiently accurate to confidently assign differences in the energies of isomers that differ greatly in their bonding. Errors >20 kJ/mol may be common. This model is, however, able to properly account for energy differences between isomers with subtle differences in structure.

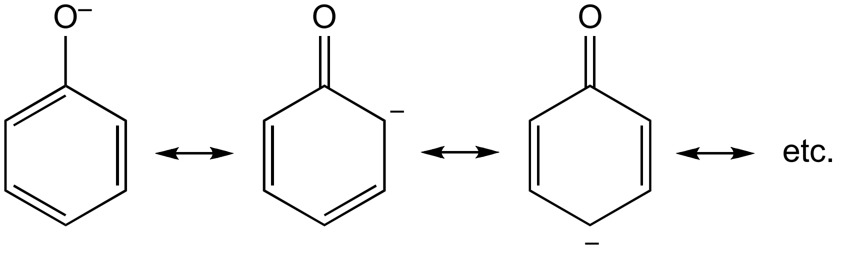
20. Chemistry of Substituents on Benzene

1. Tautomer of Phenol. Isomers are said to be tautomers if they are related by the shift of hydrogen from one heteroatom to another or from a heteroatom to carbon. The most common example of the latter is the relationship between vinylic alcohols and carbonyl compounds. Enols (vinylic alcohols) are almost always less stable than their keto tautomers (aldehydes and ketones). For example, acetone is known experimentally to be ~42 kJ/mol more stable than its enol, propen-2-ol. An exception to the rule might be expected for the keto-enol pair, 2,4-cyclohexenedione and phenol. The enol is an aromatic molecule and should benefit from additional "aromatic" stabilization".



Obtain equilibrium geometries for phenol and 2,4-cyclohexadienone as well as for acetone and propen-2-ol, and calculate keto/enol energy differences for both tautomer pairs. "Correct" the energy difference for the phenol/2,4-cyclohexadienone pair for the error in the difference for the acetone/propen-2-ol pair. According to the corrected data, is phenol favored over 2,4-cyclohexadienone? If it is, by how much is it favored? What temperature would be needed in order for the higher-energy structure to be present as 5% of the equilibrium mixture? Is the change in keto/enol energies between the two sets of tautomers of the same order of magnitude as the estimated stabilization energy of benzene due to aromaticity? Elaborate.

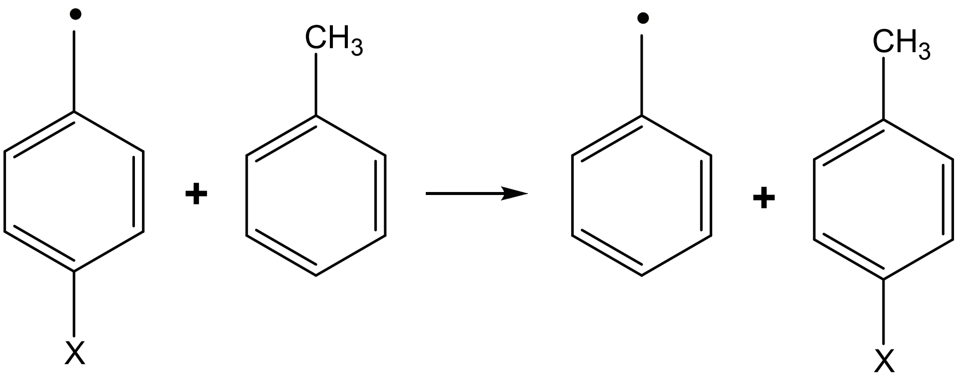
2. Acidity of Phenol. Lewis structures show that the negative charge on the phenoxide anion that results from loss of the OH proton in phenol is not restricted to the oxygen but is dispersed onto three of the six carbons on the ring.



This suggests that an electron-withdrawing group at one of these positions will stabilize the anion and lead to increased acidity, and furthermore that the same substituent placed on any of the remaining positions will have little if any effect on acidity. To test this hypothesis, obtain energies of deprotonation of phenol substituted in the *para* position and in the *meta* position by a nitro group (a strong π-electron acceptor), and compare these to the energy of deprotonation of the unsubstituted compound. Are both parts of the hypothesis supported by your results? If not, which part is not supported?

Repeat your calculations and analysis using a different electron-withdrawing substituent (cyano or trifluoromethyl would be good choices). Do you find that this group is more or less effective in increasing acidity than the nitro group?

3. Benzyl Radical. Lewis structures suggest that electron-donor groups placed on the *ortho* and *para* ring positions will stabilize benzyl cation, while electron-withdrawing groups placed in the same positions will stabilize benzyl anion. Lewis structures for benzyl radical are the same as those for benzyl cation and anion except that "•" has replaced "+" and "-", respectively. What is the effect of electron-donor and acceptor groups on benzyl radical? To decide, obtain energies for all molecules involved in reactions, where X is both NMe_2 (a strong electron donor) and NO_2 (a strong electron acceptor).



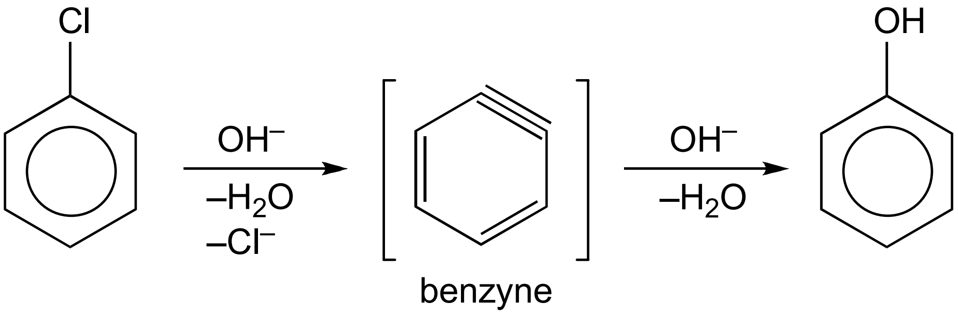
For reference, obtain the energies for the analogous reactions involving benzyl cation substituted with NH_2 and benzyl anion substituted with NO_2. Does an electron-donor group in the *para* position stabilize or destabilize benzyl radical? Is the magnitude of the effect smaller, larger or comparable to that for benzyl cation? Does an electron-acceptor group in the *para* position stabilize or destabilize benzyl radical? Is the magnitude of the effect smaller, larger or comparable to that for benzyl anion? Summarize your results with regard to the directions and magnitudes of substituent effects on radicals.

4. Azo Dyes. Aromatic azo compounds, ArN=NAr', are often brightly colored and used as dyes. The color arises because light absorption leading to an excited state occurs in the visible (most organic compounds do not absorb in this region). Assuming that absorption leads to promotion of an electron from the highest-occupied to lowest-unoccupied molecular orbitals, a simple model for dye color is the difference in energy between the two orbitals, the so-called HOMO-LUMO gap.

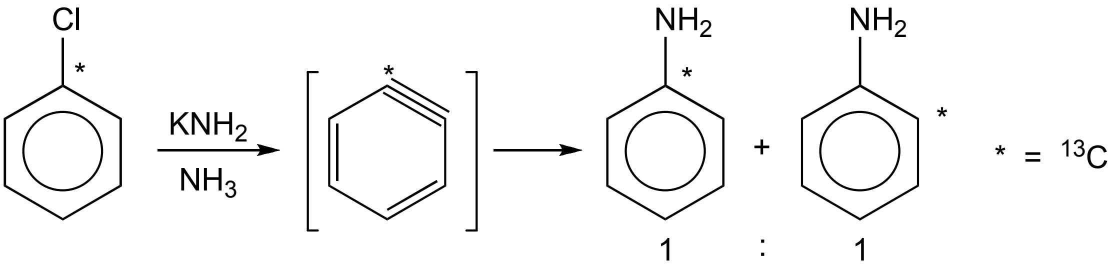
Obtain HOMO-LUMO gaps for azobenzene, 4-aminoazobenzene and 4-nitroazobenzene. What effect if any does the amino group (a π-electron donor) have on the HOMO-LUMO gap in azobenzene? If it does have an effect, is it primarily due to a change in the HOMO energy, a change in the LUMO energy or both? Azobenzene is orange. Based on your results, would you expect the color of 4-aminoazobenzene to be "more red" or "more blue"? Elaborate.

Answer the same questions with regard to the nitro group (a π-electron acceptor).

5. Structure of Benzyne. Benzyne is believed to be an intermediate in nucleophilic aromatic substitution, for example, in the reaction of chlorobenzene with strong base.



While the geometry of benzyne has yet to be established experimentally, the results of a ^{13}C labeling study leave little doubt that the two carbon atoms involved in the "triple bond" are equivalent.

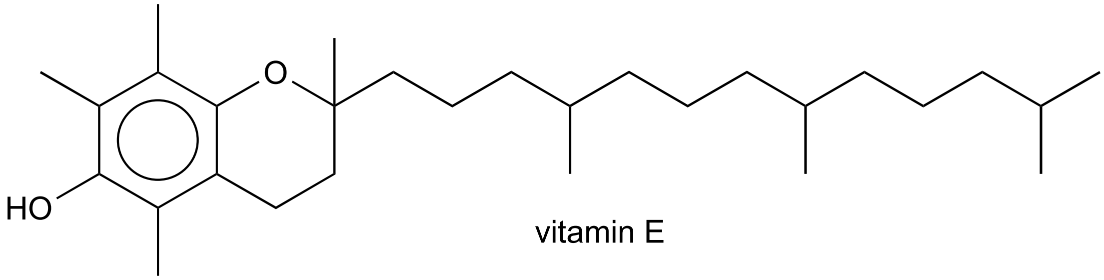


Obtain the geometry of benzyne. Does it incorporate a triple bond, as in a normal alkyne or is the length closer to that in benzene? Obtain geometries for 2-butyne and benzene to provide references.

To build benzyne, start with benzene and delete the hydrogen atoms on two adjacent carbons.

Examine the valence molecular orbitals of benzyne. Are there three π-type orbitals as in benzene? If there are, are the shapes and energies of the π orbitals relatively unchanged from those in benzene? Identify the orbital corresponding to the "in-plane" π bond in the Lewis structure. Is it the HOMO? Examine the electrostatic potential map for benzyne. Is it more negative (greater negative charge) in the plane of the ring or perpendicular to the plane (in the π system)? Compare maps for benzyne and benzene. Which shows the more reactive (toward electrophiles) π system?

6. Vitamin E. Molecules with unpaired electrons (“free radicals”) can cause biochemical damage through their reaction with unsaturated fatty acids found in cellular membranes. Vitamin E may play an active role in defending cells from attack by transferring a hydrogen atom to the radical to give stable products that can then be safely excreted. Such compounds are referred to as antioxidants.



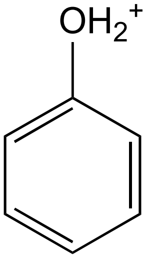
vitamin E

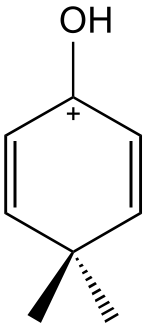
$$R^{\bullet} + \text{vitamin E} \longrightarrow \text{RH} + \text{vitamin E}^{\bullet}$$

The effectiveness of vitamin E is not surprising, given that loss of hydrogen atom leads to a stabilized “phenoxy” radical. However, why is vitamin E so large? A clue is that phenoxy radical by itself is a highly-polar molecule, but vitamin E needs to act in non-polar cellular membranes. Display an electrostatic potential map for vitamin E. Does it show a polar or non-polar molecule (or both)?

Vitamin E is fairly large and the calculation will probably require 2-3 minutes of computer time. Be patient.

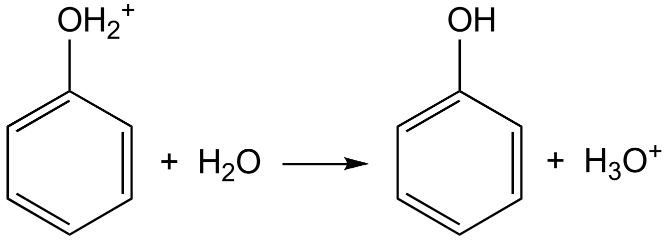
7. Protonation of Phenol. Does phenol protonate at oxygen or on the ring?

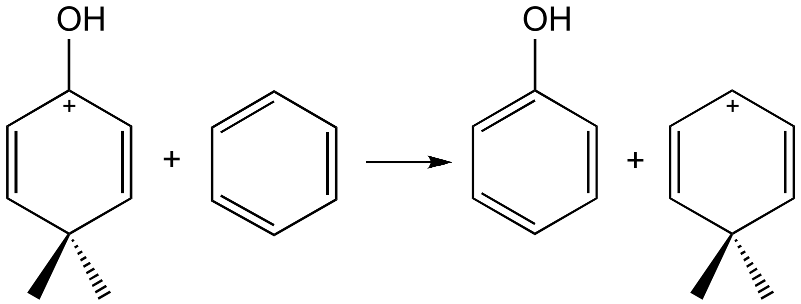




A good argument can be made either way. Protonation on the ring would lead to loss of aromatic stabilization, but the resulting benzenium ion is delocalized and an OH group (a moderately strong π donor) in the *para* position should stabilize the carbocation enter. On the other hand, protonation at oxygen does not disrupt the aromaticity of phenol.

Calculate energies of both oxygen and carbon protonated forms of phenol (assume that carbon protonation occurs *para* to the OH group). Which ion is more stable? If the difference in energy between the two is small (<20 kJ/mol), obtain a "second opinion" by asking the calculations to calculate the difference in proton affinities between (oxygen-protonated) phenol and water and between (carbon-protonated) phenol and benzene.



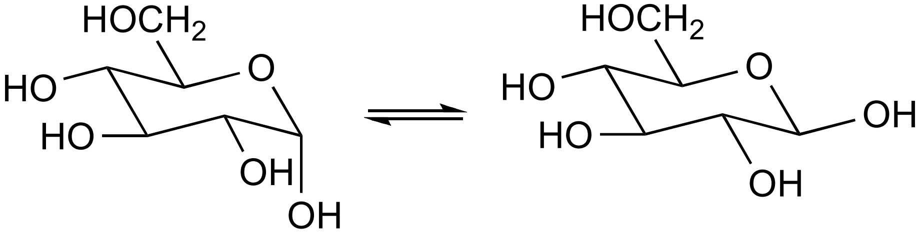


Combine your data with the known difference between the proton affinities of water and benzene (59 kJ/mol in favor of benzene). Does your previous result maintain? If not, you can assume that the second approach provides the more accurate result.

The quantum chemical model incorporated into ***SpartanModel*** is not sufficiently accurate to confidently assign differences in the energies of isomers that differ greatly in their bonding. Errors >20 kJ/mol may be common. This model is, however, able to properly account for energy differences between isomers with subtle differences in structure.

21. Carbohydrates

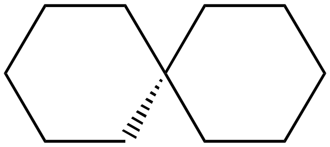
1. D-Glucose. D-glucose (glucopyranose) can be crystallized in so-called α and β forms which exhibit different properties. However, given sufficient time, they equilibrate in a process known as mutarotation.

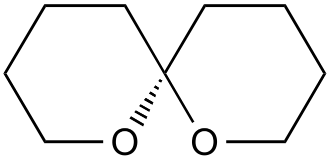


α-D-glucopyranose β-D-glucopyranose

What is the relationship between α and β forms of D glucose? Are they conformers, isomers, enantiomers or diastereomers? Does equilibration involve chemical change?

2. Spirocyclic Molecules and the Anomeric Effect. Two hydrocarbon rings may share an atom leading to a spirocyclic compound. For example, two cyclohexane rings lead to spiro[5.5]undecane, where the lengths of the two methylene chains are given inside the square brackets.





spiro[5.5]undecane 1,7-dioxaspiro[5.5]undecane

How many different conformers exist for spiro[5.5]undecane (consider only conformers in which both cyclohexane rings are chairs)? Obtain equilibrium geometries for all conformers and identify the lowest-energy structure. Are any higher-energy conformers likely to be present in a room-temperature Boltzmann distribution? (Assume a detection limit of >5%.)

Spiro compounds may also involve rings with heteroatoms, for example, tetrahydropyran rings. How may different (chair) conformers exist for 1,7-dioxaspiro[5.5]undecane? If there is more than one, identify the lowest-energy conformer. Are the two carbon-oxygen single bonds in this conformer both *equatorial*, both *axial* or one *equatorial* and one *equatorial*?

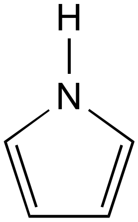
What you have uncovered is an example of the ***anomeric effect***, one of the primary factors that influence the conformations of carbohydrates. Are any higher-energy conformers likely to be present in a room-temperature Boltzmann distribution?

22. Heterocycles

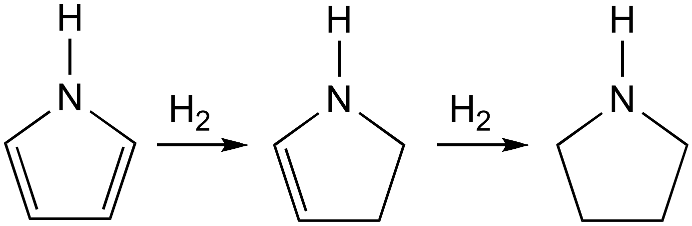
1. Benzene vs. Pyridine. At first glance, benzene and pyridine would appear to be nearly identical. Both involve six π electrons in a six-member ring. Space-filling models for the two molecules are nearly identical. Yet benzene and pyridine exhibit entirely different chemistry. Benzene undergoes electrophilic aromatic substitution and is a weak base. Pyridine is much less reactive with regard to aromatic substitution but is a much stronger base.

Compare electrostatic potential maps for benzene and pyridine. For which molecule is the electrostatic potential on the π system more negative? Which molecule is likely to be more susceptible to aromatic substitution? For which molecule is overall electrostatic potential more negative? Where is it most negative on this molecule?

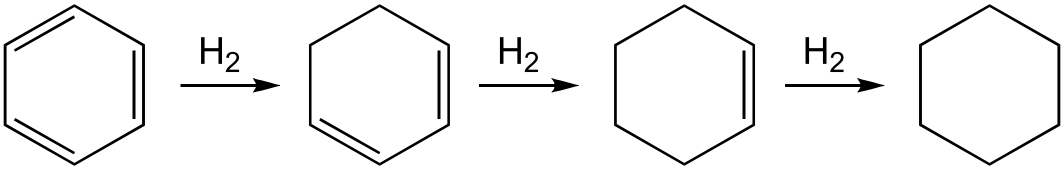
2. Pyrrole. Pyrrole is an essential building block for a number of biologically-important molecules, among them hemoglobin and vitamin B12.



Display the occupied molecular orbitals of pyrrole. How many π type orbitals are there? Is pyrrole a good candidate for an aromatic molecule? To decide, obtain energies for both steps in the complete hydrogenation of pyrrole. Either use reactant and product from the simple quantum chemical model supported in ***SpartanModel*** or (for more reliable results) access heats of formation from the database accessible from ***SpartanModel***.

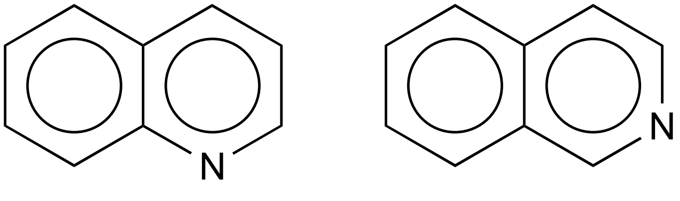


Both reactions involve trading a CC π bond and an HH bond for two CH bonds, but the first step destroys any aromatic character that may be present. Thus, the difference in energies between the two steps provides a qualitative estimate of extra stabilization due to aromaticity. For reference, obtain the difference in energy between the first and second (of three) steps in the complete hydrogenation of benzene. This provides a value for the aromaticity of benzene. Use the same source of data as you did for pyrrole.



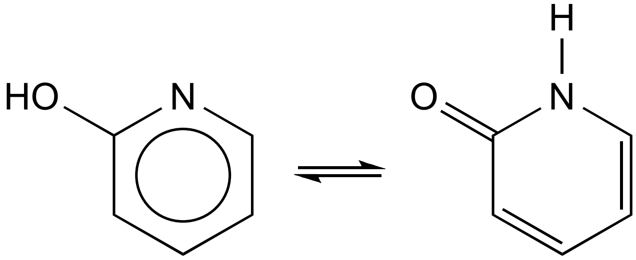
Is the extent of aromatic stabilization afforded pyrrole, less than, greater than or comparable to that afforded benzene? Do you conclude that pyrrole is an aromatic molecule?

3. Quinoline and Isoquinoline. Draw all Lewis structures for quinoline and isoquinoline. Assuming that each structure contributes equally, which if any of the carbon-carbons in the two molecules would be expected to be especially short or especially long. Are the calculate geometries in agreement with your assignments? If not, which Lewis structures appear to be the major contributors?



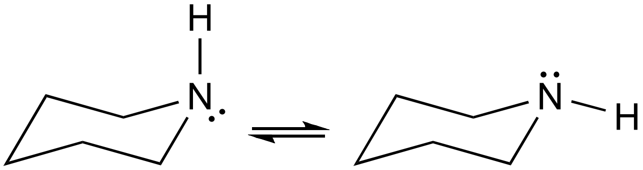
quinoline isoquinoline

4. Tautomer of 2-Hydroxypyridine. 2-hydroxypyridine should be a very stable molecule. It is aromatic and possibly benefits from an internal hydrogen bond between the OH hydrogen and the lone pair on the pyridine nitrogen. However, the molecule is known to possess a stable isomer (or tautomer), formed by proton transfer from the oxygen to nitrogen. This is 2-pyridone.



Which is lower in energy, 2-hydroxypyridine or 2-pyridone? If 2-pyridone is actually the more stable (or it the energies of the tautomers are close), provide an explanation why? Hint: consider the possibility that 2-pyridone is also an aromatic molecule. Examine its occupied molecular orbitals. How many π orbitals are there? Are they delocalized as in benzene?

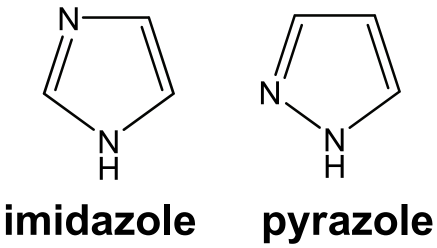
5. Piperidine. Like cyclohexane, piperidine may undergo ring inversion leading to the exchange of e*quatorial* and *axial* hydrogens. Unlike cyclohexane, the two conformers of pipeidine are different because there is only one hydrogen attached to nitrogen (the fourth tetrahedral direction is occupied by an electron pair).



Does the hydrogen prefer to be *equatorial* or a*xial*? Provide a rationale for your result.

Repeat your calculations for N-methylpiperidine. Rationalize any differences with the parent compound either in the direction or magnitude of the preference.

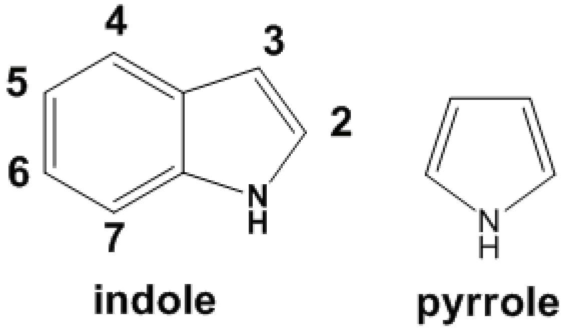
6. Protonation of Imidazole and Pyrazole. Both pyrazole and its isomer imidazole incorporate three different carbon atoms and two different nitrogen atoms. This means that each may possess as many as five different protonated forms.



Obtain equilibrium geometries for all five protonated forms of imidazole, and identify the lowest-energy form. Provide a rationale for your result. Hint: examine the molecular orbitals of the protonated forms. Are any alternatives forms low enough in energy to be seen in a room-temperature equilibrium mixture? Assume >5% abundance in order to be detected.

Repeat your calculations and analysis for pyrazole. Do the two isomers exhibit the same preference for protonation?

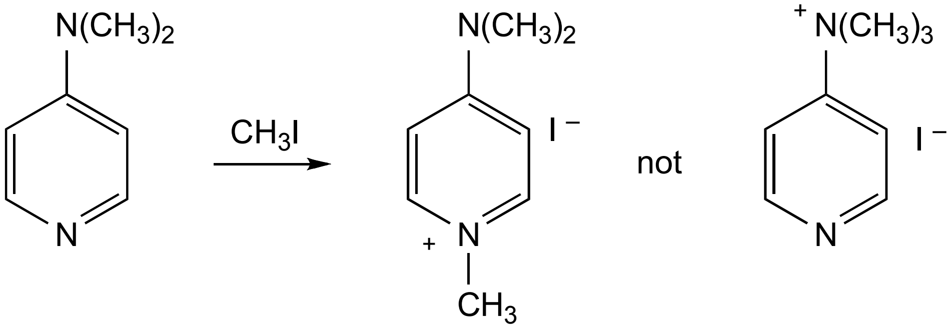
7. Electrophilic Substitution of Indole. The indole ring, made from "fusing" benzene and pyrrole rings, is among the most commonly encountered structures found in molecules of biological importance. It appears, for example, in the amino acid tryptophan and in the drug reserpine.



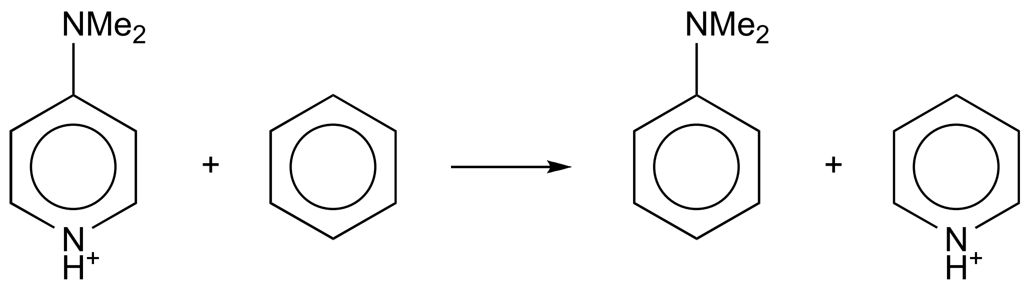
Excluding the possibility of reaction at nitrogen, electrophilic substitution in indole can lead to one of six products (or a mixture of two or more of them). These follow from the six intermediate "indolium" ions. Obtain energies for the six ions that could possibly result from protonation of indole at carbon. Which is most stable? Are any of the higher-energy ions likely to be seen at room temperature? (Assume a minimum abundance of 5% in order to be detected.)

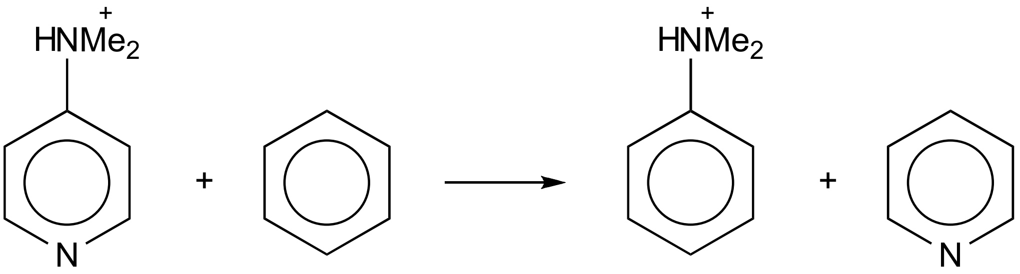
Obtain energies for the two different ions that can result from protonation of pyrrole at carbon. Is the difference in energies of protonation (proton affinities) at C_2 and C_3 in indole smaller, greater or about the same as the corresponding difference in pyrrole? Is the absolute proton affintity (larger of the C_2 and C_3 proton affinities) smaller, greater or about the same as the absolute proton affinity of pyrrole? Provide a rationalization for the latter result.

8. Protonation of Mixed Nitrogen Compounds. N,N-dimethylaniline is known to be more basic than pyridine, leading to the expectation that 4-(dimethylamino)pyridine will protonate on the "aniline nitrogen" instead of on the "pyridine nitrogen". However, addition of methyl iodide to 4-(dimethylamino)pyridine is known to lead exclusively to the "pyridine" adduct.



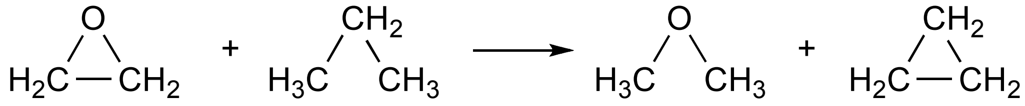
Calculate energies for both protonated forms of 4-(dimethylamino)pyridine. Which form is lower in energy? Is it likely that the alternative form will be seen in an equilibrium mixture at room temperature? (Assume that the minor form needs to make up at least 5% of the total in order to be detected.) If the favored form is that resulting from protonation at the pyridine nitrogen (despite the fact that N,N-dimethylaniline is more basic than pyridine, obtain and interpret the energies for reactions "measuring" the effect of a dimethylamino group on the proton affinity of pyridine and a pyridyl group on the proton affinity of dimethylamine.



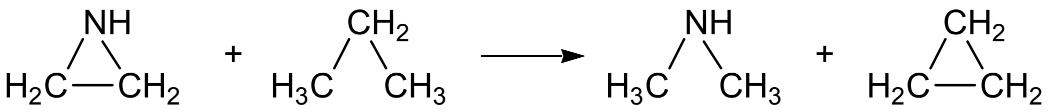


You can build the pyridine-protonated form, by starting from cyclohexane, replacing one of the sp^3 carbons by the ammonium fragment by *double clicking* on carbon, introducing three double bonds into the ring and finally adding the NMe_2 group.

9. ***Ring Strain in Oxirane and Aziridine.*** Which molecule is more strained oxirane or cyclopropane? To tell, compare the hydrogenation energy of oxirane (leading to dimethyl ether) relative to that of cyclopropane (leading to propane). (Hydrogen molecule appears on both sides of the equation and its energy is not needed.) Offer an explanation for your result.



Repeat the calculation for hydrogenation of aziridine (leading to dimethylamine) relative to hydrogenation of cyclopropane.



Which is more strained, aziridine or oxirane? Suggest an explanation for your result.

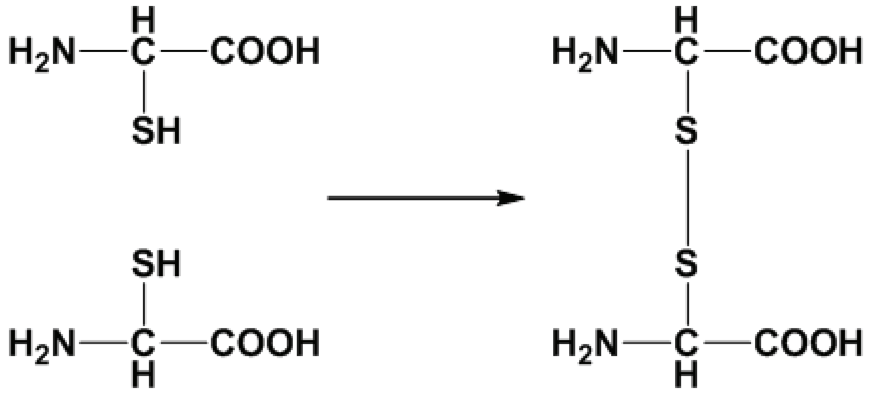
23. Amino Acids and Proteins

1. Glycine in the Gas Phase and in Water. Glycine and all other amino acids are almost always pictured as “zwitterions”, with nitrogen protonated and bearing positive charge and the carboxylic acid deprotonated and bearing negative charge. There is another tautomer with no charges. Which is actually the proper representation?

$$H_3N^+-CH_2-COO^- \qquad H_2N-CH_2-COOH$$

Obtain energies for both tautomers of glycine. This corresponds to the gas phase. Which tautomer is favored and by how much is it favored? Is it likely that the higher-energy tautomer will be seen at room temperature? (Assume that it needs to make up at least 5% of the mixture in order to be detected.) Next, obtain energies for both tautomers “surrounded” by a few water molecules (8 or 9 molecules should suffice). This provides a very crude model for glycine in water. Is the preference maintained? If it is, is the energy difference between tautomers reduced? Is it likely that the higher-energy tautomer will be seen at room temperature? Explain your results.

2. Sulfur-Sulfur Linkages in Proteins. Nearby cysteine residues in proteins may form sulfur-sulfur linkages. In so doing they impose geometrical constraints on the protein, in particular, on the distance between α carbons on the two cisteine residues. This in turn is likely to affect the secondary structure of the protein.

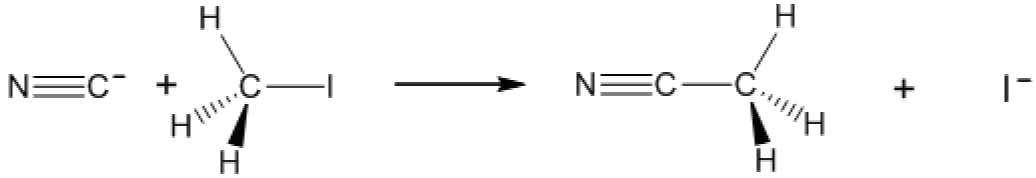


What is the structure of the residue pair formed as a result of SS bonding? Specifically, what is the largest distance that the two α carbons may achieve? (As there is likely to be more than one conformation about the SS bond, you will need to repeat the calculation starting with different conformations.)

Speculate why serine, the oxygen analogue of cysteine, does not link to itself by way of an OO bond.

24. Reactions

1. Charge Distributions in Transition States. Organic chemists have developed a powerful *nomenclature* to designate chemical reactions. Here, curved or "curly" arrows are used to indicate transfer of a pair or electrons (a bond or a lone pair) from one place in a molecule to another. A particularly simple example is found for the S_N2 reaction of cyanide anion and methyl iodide leading to acetonitrile and iodide anion. One arrow indicates that the lone pair on cyanide will be used to make a new carbon-carbon bond, while the second arrow indicates that the carbon-iodine bond will break with the pair of electrons going to iodine.



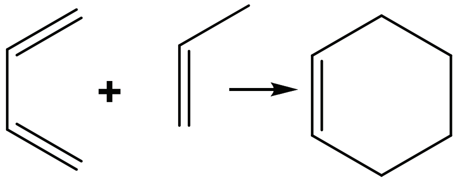
Curly arrows do not say anything either about the geometry or charge distribution in the transition state, or about changes in geometry and charge distribution that occur in moving from the reactants to the transition state and onto the product. All that they do is identity the product. On the other hand, quantum chemical calculations are able to provide insight into both the geometry and charge distribution of the transition-state. Comparison with the corresponding information for the reactants, reveal any changes that occur during the course of a chemical reaction.

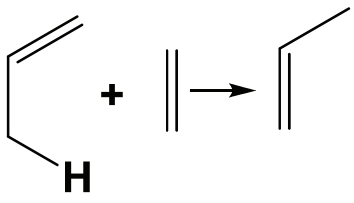
An electrostatic potential map for "one frame" in the S_N2 reaction cyanide anion and methyl iodide appears on screen. A plot of energy vs. CI distance is also provided. Step through the frames by *clicking* on ◀ ▶ at the bottom left of the screen, or animate the sequence by *clicking* on ▶. Does "cyanide" or "iodide" appear to hold the bulk of the negative charge at the transition state? Is cyanide or iodide the better leaving group? Elaborate. Is your conclusion consistent with the fact that the reaction as written is *exothermic*? Explain.

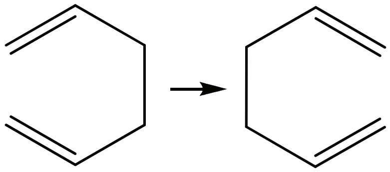
2. Geometries of Transition States. Organic chemists think about a transition state as a structure that lies at the top of a plot of energy vs. reaction coordinate (a reaction coordinate diagram). While this simple picture is conceptually useful, it is also deceptive. “Real” reactions are not one dimensional and may not be described by a one-dimensional energy diagram. Instead, they depend on as many as 3N-6 independent geometrical coordinates, where N is the number of atoms. Thus, the actual energy diagram for as simple a process as combination 1,3-butadiene and ethylene leading to cyclohexene is actually 42 dimensional. While such a plot cannot be drawn, it is possible to uniquely define and locate a transition state.

The mathematics involved are outside the scope of an elementary organic chemistry course. Suffice it to say, that a transition state is an energy maximum in one dimension (the reaction coordinate) and an energy minimum in all remaining dimensions. The one dimension will generally not be easily represented in terms of a single geometrical coordinate such as a bond length or bond angle, but rather is some combination of coordinates.

While the geometries of transition states cannot be known from experiment, they can be established from quantum chemical calculations. Transition states exemplifying three important reactions are presented on screen. On the top left is the reaction referred to above, a ***Diels-Alder*** reaction, on the right is the ***ene*** reaction of propene and ethylene leading to 1-pentene and on the bottom is the ***Cope*** reaction of 1,5-hexadiene leading back to 1,5-hexadiene.



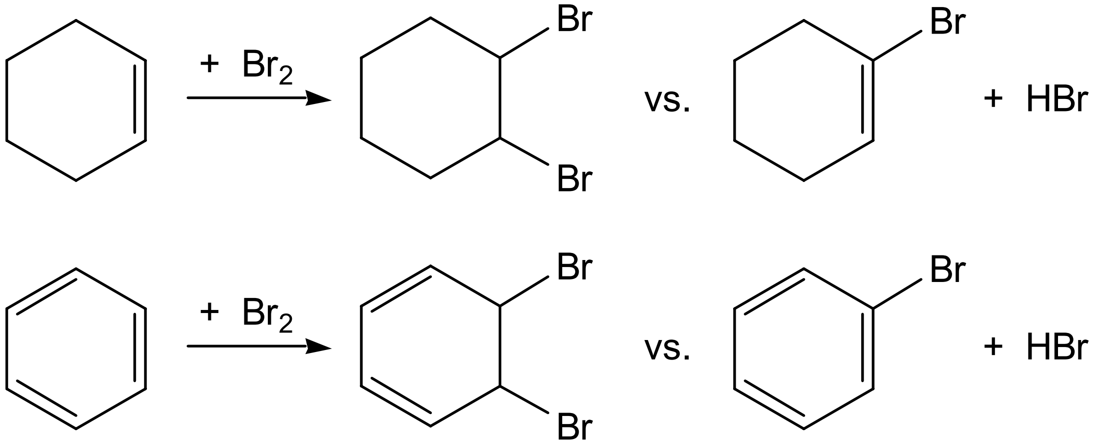




For each transition state, identify all partial carbon-carbon double bonds (that is, single bonds in the reactant that become double bonds in the product or *vice versa)* and measure bond distances. Are these similar to the carbon-carbon bonds in benzene (~1.40Å) or are they significantly different?

Identify all partial single bonds (that is, single bonds that are broken or formed during the reaction) and measure their distances. How do these compare to normal carbon-carbon single bond lengths (1.52-1.55Å)? How do they compare to twice the van der Waals radius of carbon (3.4Å)? Are partial double and partial single bond distances for all three transition states similar or are the significantly different?

3. Addition vs. Substitution. Alkenes undergo addition reactions whereas aromatics undergo substitution reactions. For example, *trans*-1,2-dibromocyclohexane, not 1-bromocyclohexene, results from reaction of bromine and cyclohexene whereas the product of bromine and benzene is bromobenzene, not *trans*-5,6-dibromo-1,3-cyclohexadiene.



Calculate energies for all reactants and products involved in the two sets of addition reactions and two sets of substitution reactions. (Alternatively, use heats of formation from the database accessible from ***SpartanModel***.) Are all four reactions *exothermic*? If not, which reactions are *endothermic*? Is addition or substitution favored for cyclohexene? Is addition or substitution favored for benzene? If there is a change in preferred reaction from cyclohexene to benzene, provide an explanation why.

Appendix A

Binding Energies and Heats of Formation

Binding Energies and Heats of Formation

The stability of a molecule is almost always given as a ***Heat of Formation***. This differs in four ways from the energy obtained from a quantum chemical calculation.

First, heat (enthalpy) and energy are not the same, but are related through a pressure-volume term.

$$\Delta H = \Delta E + P\Delta V \quad \text{at constant pressure}$$

However, at normal pressures this term is very small and the energy and enthalpy are nearly identical.

Second, experimental measurements are carried out at finite temperature (typically room temperature) whereas quantum chemical calculations refer to systems at 0K.

Third, the energy obtained from a quantum chemical calculation refers to a molecule at the bottom of an energy well, whereas a measured enthalpy refers to a molecule in its lowest ("zeroeth") vibrational state. The difference is known as the zero-point energy.

Finite temperature and zero-point energy corrections may be important for accurate description of the energies for some types of chemical reactions, in particular, reactions where bond counts are not maintained. The corrections can be obtained from calculation and require the mass, geometry and vibrational (infrared) spectrum of the molecule. However, the corrections largely cancel and may be ignored for reactions that involve more subtle changes in bonding, for example, differences between stereoisomers.

Fourth, while both calculated energies and heats of formation refer to the energies (heats) of specific chemical reactions, the reactions are different. Heats of formation refer to a reaction in which a molecule is converted to a set of standard products, each corresponding to the most stable form of the element at room temperature. The heat of formation of each standard is defined as zero. For example, the heat of formation of ethylene is defined by the reaction.

$$C_2H_4 \rightarrow 2C\ (\text{graphite}) + 2H_2\ (\text{gas})$$

Graphite and hydrogen molecule are the carbon and hydrogen standards, respectively. Experimental measurements are not actually carried out for this reaction, but most commonly (but not necessarily) for a combustion reaction (reaction with O_2), for example, for ethylene.

$$C_2H_4 + 3O_2 \rightarrow 2CO_2 + 2H_2O$$

Heats of formation may be either positive or negative quantities and generally span a range of only a few hundred kJ/mol. Molecules with positive heats of formation much greater than 500 kJ/mol are likely to the thermodynamically unstable, making their detection and characterization difficult.

Heats of formation may not be obtained ***directly*** from quantum chemical calculations, simply because some of the standards are not isolated species on which calculations may be performed. The alternative is to use a different reaction. Most commonly, this is a hypothetical reaction that splits a molecule into isolated nuclei (not atoms) and electrons, for example, for ethylene.

$$C_2H_4 \rightarrow 2C^{+6} + 4H^{+} + 16e^{-}$$

Each of the products (H^+, C^{+6} and e^-) contains a single particle and, therefore, its energy is zero. ***Total Energy***, as the energy of such a reaction is termed, is necessarily a negative number and can be very large (several tens of thousands to several million kJ/mol). One way to reduce the size of this number is to subtract the energies of the constituent atoms from the energy of the molecule. This is referred to as the ***Binding Energy***.

SpartanModel allows for calculation of the binding energy for any molecule that can be built as well as for lookup of the heat of formation for any molecule contained in its associated database. Heats of formation in the database are not experimental. Rather, they are total energies obtained from high-quality quantum chemical calculations that have been empirically corrected to account for finite temperature and zero-point energy as well as the difference in the reference reactions. The heats are believed to be accurate to within 8 kJ/mol. Either calculated binding energies or heats of formation from the database are suitable for calculations of the energies (heats) of mass-balanced chemical reactions (the “standards” cancel). Heats of formation from the database will, however, generally provide more accurate reaction energies.

Appendix B

Molecular Orbitals

Molecular Orbitals

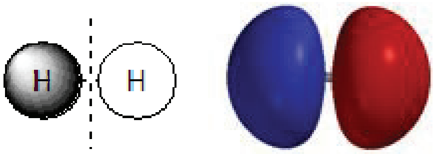
Molecular orbitals “descriptions of molecules” are assembled from atomic orbitals, “descriptions of atoms”. 1s, 2s, $2p_x$, … atomic orbitals correspond to the exact solutions of the Schrödinger equation for the hydrogen atom. 1s is the lowest-energy solution, 2s is the next up in energy and so forth. The lowest-energy state (the ***ground state***) of the hydrogen atom has its electron in the 1s atomic orbital, and that higher-energy (***excited***) states have the electron in higher-energy atomic orbitals.

Atomic orbitals for atoms with more than a single electron ***are assumed*** to be qualitatively the same as those for hydrogen atom. They are occupied in order of their energies (1s, 2s, 2p), each with a maximum of two electrons. Thus, the five-electron boron atom has two electrons in a 1s orbital, two electrons is a 2s orbital and one electron in a 2p orbital. The full set of atomic orbitals may be divided into ***core*** and ***valence orbitals***. Core orbitals are very low in energy and do not participate to any significant extent in bond formation. Valence orbitals are higher in energy and are involved in bond formation. The valence orbitals for an element in the first long row of the *Periodic Table* are 2s, $2p_x$, $2p_y$ and $2p_z$, and for the second long row are 3s, $3p_x$, $3p_y$ and $3p_z$. In the case of first-row elements, a single core orbital, 1s, lies underneath while in the case of second-row elements, a set of five core orbitals, 1s, 2s, $2p_x$, $2p_y$ and $2p_z$, lie underneath.

Molecular Orbitals and Chemical Bonds

Molecular orbitals are commonly related to the bonds and lone pairs in a Lewis structure. Whereas Lewis structures provide ***localized*** descriptions, that is, they assign pairs of electrons either to single atoms (lone pairs) or pairs of atoms (bonds), molecular orbitals are almost always spread over several atoms or throughout the entire molecule, that is, they are ***delocalized***. While both molecular orbitals and Lewis structures may be used to describe electron distributions in molecules, they approach this in different ways. Lewis structures are useful for “counting” the number of bonding and non-bonding electrons (lone pairs) around each atom. On the other hand, molecular orbitals are of little value for this purpose. Rather, molecular orbitals (and the energies of molecular orbitals) are useful for describing differences in chemical bonds and non-bonded electron pairs. These differences may in turn be used to assess variations in molecular properties or in chemical reactivity.

To see how molecular orbitals can provide important clues about molecular structure and chemical reactivity, we first need to understand what they look like. The following figure shows two representations of the lowest-energy unoccupied molecular orbital of hydrogen molecule, H_2, a “hand” drawing and an image generated using ***SpartanModel***.

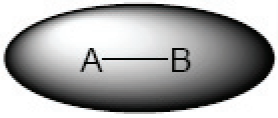


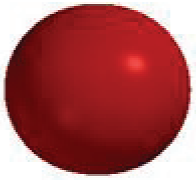
The hand drawing shows the orbital as two circles and a dashed line. The circles identify regions where the orbital takes on a significant value, either positive (***shaded***) or negative (***unshaded***). The dashed line identifies locations where the sign of the orbital changes, that is, where its value is exactly zero (a ***node***). The hand drawing is certainly useful, but it is also limited. It portrays the orbital only as a boundary, and does not show how the orbital builds and decays inside and outside of this boundary. More important, it is two dimensional.

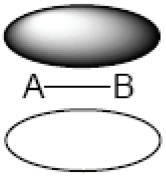
The orbital generated using ***SpartanModel*** also depicts a boundary. This surface unlike the hand drawn image is three-dimensional and can be manipulated and be looked at from a variety of different perspectives. Note, that the image actually consists of two distinct surfaces represented by different colors. The two surfaces have the same meaning as the two circles in the orbital drawing, in that they identify regions where the orbital takes on significant positive value (red) or negative value (red). The node is not shown, but we can imagine that it lies midway between the two surfaces (the value of the orbital surface can only change from positive to negative by passing through zero).

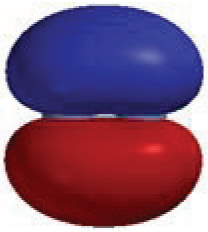
Molecular Orbitals of Nitrogen

Molecular orbital surfaces can extend over two or more atoms. If the orbital surface (or surfaces) is confined to a single atom (or more generally to atoms that are not close together), the orbital is said to be ***non-bonding***. Adding to or removing electrons from a non-bonding orbital will have little overall effect on molecular geometry. If the orbital contains a surface that extends continuously over two neighboring atoms, the orbital is regarded as ***bonding*** with respect to these atoms. Adding electrons to such an orbital will strengthen the bond between these atoms and cause them to draw closer together, while removing electrons will have the opposite effect. Two different kinds of bonding orbitals are depicted below, both as hand drawings and as 3D surfaces obtained from ***SpartanModel***. The drawing and surface on the left correspond to a ***σ bonding*** orbital while the drawing and surface on the right correspond to a ***π bonding*** orbital.



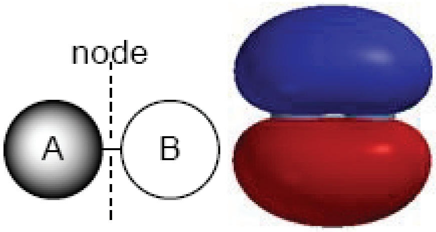


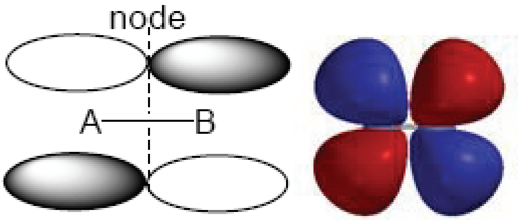




Note that the σ orbital is a single surface (insofar as NN bonding is concerned) while the π orbital is made up of two (red and blue). There is a node (change in color from red to blue) in the π orbital, although it does not involve the NN bond.

It is also possible for an orbital to contain a node that divides the region between two neighboring atoms into separate “atomic” regions. Such an orbital is regarded as ***antibonding*** with respect to these atoms. Adding electrons to an antibonding orbital weakens the bond and pushes the atoms apart, while removing electrons has the opposite effect. Two different kinds of antibonding orbitals are depicted below, both as hand drawings and as 3D surfaces obtained from ***SpartanModel***. The drawing and surface on the left correspond to a σ antibonding orbital (a so-called σ^* orbital) while the drawing and surface on the right correspond to a π antibonding orbital (a so-called π^* orbital).





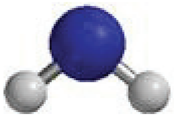
Note that the σ* orbital has a single node (change in color from red to blue) in the middle of the NN bond, while the π* orbital has two nodes, one in the middle of the NN bond and the other along the bond.

In summary, bonds can be strengthened either by adding electrons to bonding orbitals or by removing electrons from antibonding orbitals. Conversely, bonds can be weakened either by removing electrons from bonding orbitals or by adding electrons to antibonding orbitals.

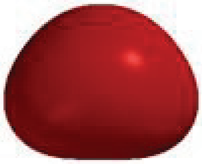
Molecular Orbitals of Singlet Methylene

Molecular orbitals in molecules with three or more atoms are almost always spread throughout the molecule. They may have complicated shapes with different parts reflecting bonding, antibonding or non-bonding character. Despite their complexity, most molecular orbitals can be broken down into two-atom interactions and analyzed using the principles outlined earlier. The highly reactive singlet methylene molecule (CH_2) provides a simple example. The designation "singlet" means that the molecule's eight electrons are organized into four pairs.

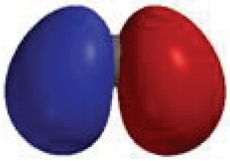
The lowest-energy molecular orbital of singlet methylene closely resembles the 1s atomic orbital on carbon atom. The electrons occupying this orbital restrict their motion to the immediate region of the carbon nucleus and do not significantly affect bonding. This is a core molecular orbital.



The next orbital consists of a single surface that is delocalized over all three atoms. This means that it is simultaneously (σ) bonding with respect to each CH atom pair.



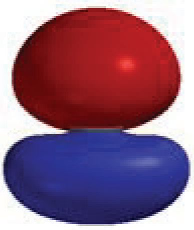
The next higher-energy orbital is made up of two surfaces. A positive (blue) surface encloses one CH bonding region and a negative (red) surface encloses the other CH bonding region. Since each surface encloses CH atom pair, this orbital is also (σ) bonding and reinforces the bonding character of the previous orbital. The node that separates the two surfaces does not pass through either of the CH bonding regions and, therefore, does not weaken bonding.



Thus, the two CH bonds in the Lewis structure for singlet methylene are replaced by two delocalized σ bonding molecular orbitals.

> Note that both σ bonding molecular orbitals of singlet methylene reflect the fact that the two hydrogens (and the two CH bonds) are equivalent. More generally, all molecular orbitals must show any equivalences that exist in the geometry of the molecule. This means that the orbital surface covering one section of a molecule must either be the same or the negative of the surface covering an equivalent section. The reason that the surface can either be the same (***symmetric***) or the negative (***antisymmetric***) is a consequence of the fact that the observable (electron density) does not depend on the orbital but rather on the **square** of the orbital. The lower-energy σ bonding molecular orbital of singlet methylene is symmetric whereas the higher energy orbital is antisymmetric.

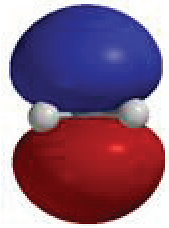
The highest-occupied molecular orbital (the HOMO) of singlet methylene is also described by two surfaces. The larger surface is directed from carbon away from the two hydrogens and may be described as non bonding. The smaller surface encompasses both CH bonding regions. Although it is hard to track the path of the node, it actually passes almost exactly through the carbon. This means that this surface possesses only weak CH bonding character (although it is H---H bonding). The non-bonding character of the HOMO dominates, consistent with the fact that singlet methylene behaves as an electron-pair donor (a nucleophile).



In summary, the four molecular orbitals of singlet methylene divide into two groups, one core orbital and three valence orbitals. The latter consist of two CH bonding orbitals and a non-bonding orbital. Note that it is not possible to directly associate these orbitals to the bonds and electron pair depicted in the Lewis structure. The two CH bonding orbitals are both associated with all three atoms rather than with a particular bond, and the non-bonding orbital is actually weakly bonding.

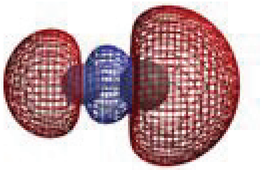
The molecular orbital description of singlet methylene also gives rise to unoccupied molecular orbitals. These have higher (more positive) energies than any of the occupied orbitals, and because they are unoccupied, play no role in the electron distribution (or size and shape) of the molecule. Nevertheless, the shapes of unoccupied orbitals are worth considering because they provide insight into the molecule's chemical reactivity. In particular, the lowest-unoccupied molecular orbital (LUMO) is the orbital into which the next pair of electrons (a nucleophile) will go. It anticipates how susceptible the molecule is likely to be toward nucleophilic attack.

The LUMO in methylene is localized entirely on carbon (it looks like a 2p atomic orbital) and is therefore non-bonding in character. Were this orbital to accept electrons, the CH bonds would not be affected.

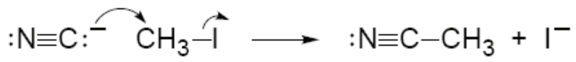


Molecular Orbitals Anticipate Chemical Reactivity

Not only may molecular orbitals provide insight into molecular geometry and changes in geometry with changing number of electrons, but they may also be used to suggest why a particular chemical reaction occurs as it does, or why a chemical reaction does not occur as expected. For example, the fact that the HOMO in cyanide anion is more concentrated on carbon (on the right) than on nitrogen,

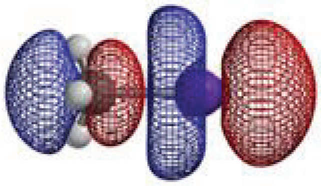


suggests, as is observed, that cyanide will act as a carbon nucleophile and not a nitrogen nucleophile.



This might seem counterintuitive, as nitrogen is more electronegative than carbon, and thus more likely to hold the negative charge. However, it is entirely reasonable. The fact that nitrogen is holds on to its electrons better than does carbon, means that it will be the poorer nucleophile.

Unoccupied molecular orbitals may also be informative. For example, the LUMO of methyl iodide clearly reveals why iodide leaves following attack by cyanide.



The LUMO is antibonding between carbon and iodine, meaning that donation of the electron pair from cyanide will cause the CI bond to weaken and eventually break.

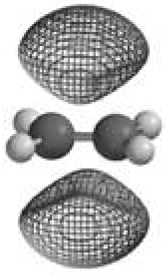
The energies of the HOMO and LUMO (the ***frontier molecular orbitals***) and the difference in energy between them are commonly related to quantities that can be measured. The HOMO is related to the ***ionization potential***, the energy required to completely remove an electron from an atom or molecule. The LUMO is related to the ***electron affinity***, the gain in energy following capture of an electron. The difference in energy between the HOMO and LUMO (the so-called ***HOMO-LUMO gap***) is related to the energy of a UV/visible spectral transition.

Appendix C

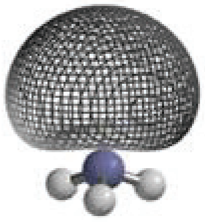
Electrostatic Potential Maps

Electrostatic Potentials and Electrostatic Potential Maps

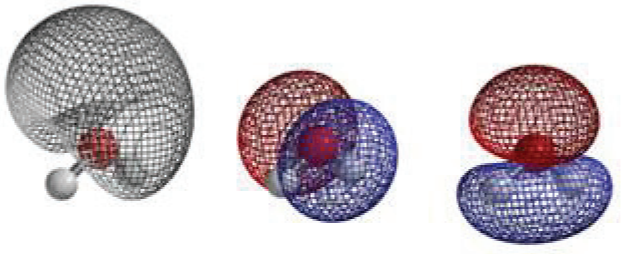
The ***electrostatic potential*** is the energy of interaction of a positive point charge located in the vicinity of a molecule with the nuclei and electrons of the molecule. Regions of negative electrostatic potential are associated with electrons that are most available. In ethylene, for example, a negative potential (left) reveals the location of the π electrons. It closely resembles the highest-occupied molecular orbital (HOMO) of ethylene (right), although the HOMO is made up of two surfaces distinguished by their sign (color).

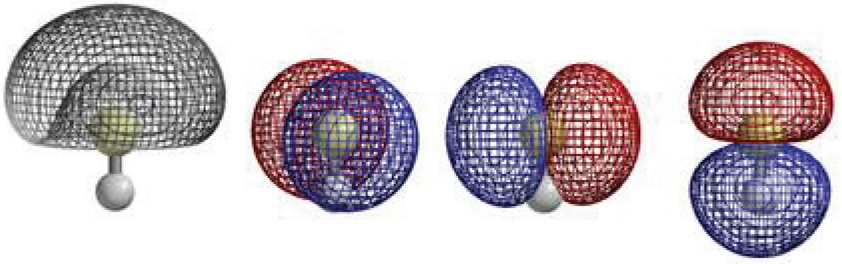


A surface of negative potential for ammonia (left) is also similar to the HOMO (right). Both reveal the location of the non-bonded pair of electrons (the lone pair). Note, however, that the HOMO has significant contributions from the hydrogen atoms.



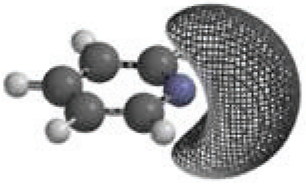
A negative electrostatic potential surface for a molecule with two or more high-energy lone pairs reflects the features of each, for example, surfaces for water (top left) and hydrogen fluoride (bottom left).





The surface for water is crescent shape, suggesting large contributions from the two highest-energy molecular orbitals (top right), while that for hydrogen fluoride is a hemisphere, suggesting large contributions from the three highest-energy molecular orbitals (bottom right).

Negative electrostatic potential surfaces may be used to distinguish among molecules that are structurally very similar. For example, whereas the overall size and shape of benzene and pyridine are nearly identical, their electrostatic potential surfaces are completely different.

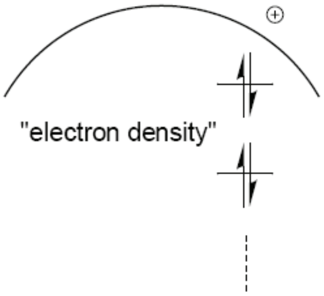


As expected, the surface for benzene shows that the highest-energy “π electrons” extend above and below the plane of the ring, while the highest-energy electrons of pyridine lie in the plane of the ring. The “chemistry” of the two molecules should be and is entirely different.

Positive electrostatic potential surfaces are almost always less informative, as they are dominated by regions close by the nuclei (and not available “to do chemistry”). However, as will be illustrated in the next section, they may offer a good indicator of acid strength.

Electrostatic Potential Map

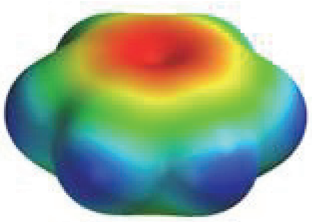
A surface of electron density surface may be constructed to portray overall molecular size and shape, and be used to identify how close a molecule can get to its environment or to an incoming reagent. Therefore, it may be thought of as the quantum chemical equivalent of a space-filling (CPK) model. The distribution of charge on an electron density surface may be obtained by displaying the value of electrostatic potential at all locations.



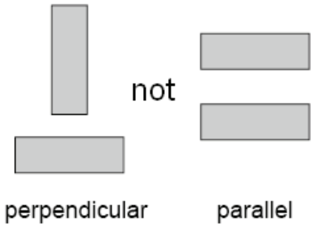
This is known as an ***electrostatic potential map***. In practice, each location on the density surface is colored according to the value of the potential evaluated at that location. By convention, colors toward the "red" end of the spectrum represent negative values of the potential, colors toward the "blue" end represent positive values of the potential and colors in the "green" represent values of the potential that are close to zero.

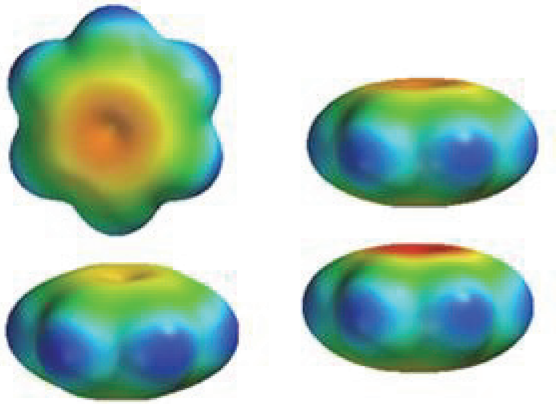
Consider as an example, constructing an electrostatic potential map for benzene. The first step is to specify an electron density surface that depicts the molecule's overall size and shape.

Then, the value of the electrostatic potential is evaluated for "all points" on this surface, and the regions surrounding these points are colored accordingly. In the case of benzene, the potential in regions above and below the plane of the ring is negative and colored red, whereas the potential in regions around the periphery of the ring is positive and colored blue. Note that, except for coloring, the electron density surface is unchanged. That is to say, an electrostatic map conveys both structural and charge information.

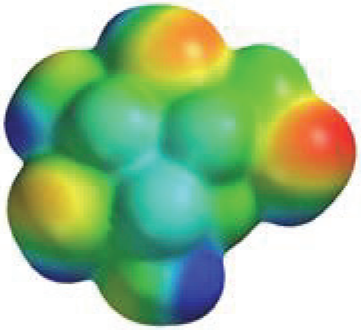
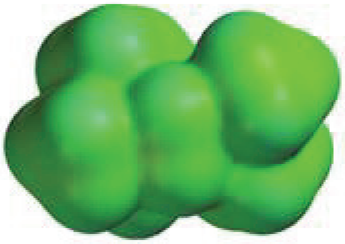


Note, that the observed “perpendicular” geometry of benzene dimer is easily rationalized from the electrostatic potential map of the monomer. In order to benefit from favorable electrostatic interactions rather than suffer from them, the two rings need to be positioned such that the negative π system of one “sees” the positive σ system of the other.

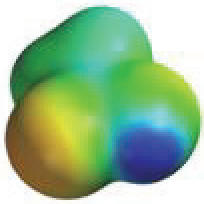
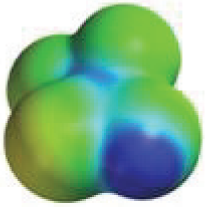




Electrostatic potential maps have found a myriad of uses. Perhaps the most obvious is to provide an indicator of the overall charge distribution in a molecule, distinguishing positively and negatively regions from each other and from neutral regions. In so doing, the map provides a measure of the extent to which a molecule is hydrophilic or hydrophobic. For example, large regions of the electrostatic potential map for glucose (left) are either positively or negatively charged suggesting that sugar dissolves in water, whereas the corresponding surface of 2,2,4-trimethylpentane or “isooctane” (right) is neutral suggesting that gasoline does not dissolve in water.

More subtle, is the use of electrostatic potential maps to measure changes in charge distributions in response to changes in structure. For example, the fact that the potential at the acidic hydrogen in trifluoromethylacetic acid (right) is significantly larger than that in acetic acid (left) suggests that the former is the stronger acid.

Glossary

Common Terms and Acronyms

3-21G. A **Split-Valence Basis Set** in which each **Core Basis Function** is written in terms of three **Gaussians**, and each **Valence Basis Function** is split into two parts, written in terms of two and one **Gaussians**, respectively.

6-31G*. A **Polarization Basis Set** in which each **Core Basis Function** is written in terms of six **Gaussians**, and each **Valence Basis Function** is split into two parts, written in terms of three and one **Gaussians**, respectively. Non-hydrogen atoms are supplemented by a set of single **Gaussian** d-type functions.

***Ab Initio* Models**. The general term used to describe methods seeking approximate solutions to the **Electronic Schrödinger Equation**, but which do not involve empirical parameters.

Acid. A molecule which “desires” to give up a proton.

Acidity. The **Energy** (**Enthalpy**) of the reaction: $AH \rightarrow A^- + H^+$. Typically given relative to a “standard” acid, A_SH, that is Δ**E**(Δ**H**) for $AH + A_S \rightarrow A^- + A_SH$.

Activation Energy. The energy of a **Transition State** above that of reactants. Activation energy is related to reaction rate by way of the **Arrhenius Equation**.
Anion. An atom or molecule with a net charge of -1.

Antibonding Molecular Orbital. A **Molecular Orbital** which has a “break” or a “**Node**” between particular atomic centers. Adding electrons to such an orbital will weaken the bond while removing electrons will strengthen the bond. The opposite is a **Bonding Molecular Orbital**.

Arrhenius Equation. An equation governing the rate of a chemical reaction as a function of the **Activation Energy** and the temperature.

Atomic Orbital. A **Basis Function** centered on an atom. Atomic orbitals typically take on the form of the solutions to the hydrogen atom (s, p, d, f... type orbitals).

Atomic Units. The set of units which remove all of the constants from inside the **Schrödinger Equation**. The **Bohr** is the atomic unit of length and the **Hartree** is the atomic unit of energy.

Base. A molecule which "desires" to accept a proton.

Basicity. The **Energy** (**Enthalpy**) of the reaction: $B + H^+ \rightarrow BH^+$. Typically given relative to a "standard" base, B_S, that is $\Delta\mathbf{E}(\Delta\mathbf{H})$ for $B + B_SH^+ \rightarrow BH^+ + B_S$.

Basis Functions. Functions usually centered on atoms which are linearly combined to make up the set of **Molecular Orbitals**. Except for **Semi-Empirical Models** where basis functions are **Slater** type, basis functions are **Gaussian** type.

Basis Set. The entire collection of **Basis Functions**.

Bohr. The **Atomic Unit** of length. 1 bohr = 0.529167Å.

Boltzmann Equation. The equation governing the distribution of products in **Thermodynamically-Controlled Reaction**.

Bonding Molecular Orbital. A **Molecular Orbital** which has strong positive overlap between two particular atomic centers. Adding electrons to such an orbital will strengthen the bond, while removing electrons will weaken the bond. The opposite is an **Antibonding Molecular Orbital**.

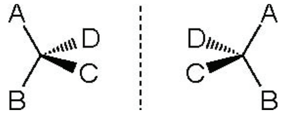
Bond Surface. An **Isodensity Surface** used to elucidate the bonding in molecules. The value of the density is typically taken as 0.1 electrons/**bohr**.^{3}

Born-Oppenheimer Approximation. An approximation based on the assumption that nuclei are stationary. Applied to the **Schrödinger Equation**, it leads to the **Electronic Schrödinger Equation**.

Cation. An atom or molecule with a net charge of +1.

Chiral. A molecule with a non-superimposible mirror image.

Chiral Center. A tetrahedral atom (most commonly carbon) with four different groups attached. Two different arrangements ("stereoisomers") are possible and these are mirror images.



Chiral centers are labelled "R" or "S" depending on the arrangement of groups. Also known as a **Stereocenter**.

Closed Shell. An atom or molecule in which all electrons are paired.

Conformation. The arrangement about single bonds and of flexible rings.

Core. Electrons which are primarily associated with individual atoms and do not participate significantly in chemical bonding (1s electrons for first-row elements, 1s, 2s, 2px, 2py, 2pz electrons for second-row elements, etc.).

Coulombic Interactions. Charge-charge interactions which follow Coulomb's law. Stabilizing when charges are of opposite sign and destabilizing when they are of the same sign.

Covalent Bond. A chemical bond which involves a significant sharing of a pair of electrons between the two atoms.

CPK Model. A molecular model in which atoms are represented by spheres, the radii of which correspond to **van der Waals Radii**. Intended to portray molecular size and shape. Also known as a **Space-Filling Model**.

Diastereomers. Stereoisomers which differ in the stereochemistry (R or S) of one or more (***but not all***) **Chiral Centers**.

Diffusion-Controlled Reactions. Chemical reactions without **Transition States** (or **Activation Energies**), the rates of which are determined by the speed in which molecules encounter each other and how likely these encounters are to lead to reaction. The combination of two radicals proceeds without **Activation Energy** and are examples of diffusion-controlled reactions.

Dipole Moment. A measure of the overall polarity of a molecule, taking into account differences in nuclear charges and electron distribution.

Electron Density. The number of electrons per unit volume at a point in space. This is the quantity which is measured in an X-ray diffraction experiment.

Electronic Schrödinger Equation. The equation which results from incorporation of the **Born-Oppenheimer Approximation** to the **Schrödinger Equation**.

Electrophile. An electron pair acceptor. A molecule (or part of a molecule) which desires to interact (react) with an electron-rich reagent or **Base**.

Electrostatic Charges. Atomic charges chosen to best match the **Electrostatic Potential** at points surrounding a molecule, subject to overall charge balance.

Electrostatic Potential. The energy of interaction of a positive point charge with the nuclei and fixed electron distribution of a molecule.

Electrostatic Potential Map. A graph that shows the value of **Electrostatic Potential** on an **Electron Density Isosurface** corresponding to a **van der Waals Surface**.

Enantiomers. Stereoisomers which differ in the stereochemistry (R or S) of all **Chiral Centers**. Enantiomers are non-superimposible mirror images.

Endothermic Reaction. A chemical reaction in which the **Enthalpy** is positive.

Energy(ΔE). The heat given off (negative energy) or taken in (positive energy) by a chemical reaction at constant volume. Quantum chemical calculations give the energy.

Enthalpy (ΔH). The heat given off (negative enthalpy) or taken in (positive enthalpy) by a chemical reaction. Enthalpy is commonly equated to **Energ**y from which it differs by a (small) pressure-volume (PV) term: $\Delta\mathbf{H} = \Delta\mathbf{E} + P\Delta V$.

Entropy (ΔS). The extent of ordering (negative entropy) or disordering (positive entropy) which occurs during a chemical reaction.

Equilibrium Geometry. A **Local Minimum** on a **Potential Energy Surface**.

Excited State. An electronic state for an atom or molecule which is not the lowest-energy or **Ground State**.

Exothermic Reaction. A chemical reaction in which the **Enthalpy** is negative.

Force Field. The set of rules underlying **Molecular Mechanics Models**. Comprises terms which account for distortions from ideal bond distances and angles and for **Non-Bonded van der Waals** and **Coulombic Interactions**.

Frontier Molecular Orbitals. The **HOMO** and **LUMO**.

Formal Charge. A “recipe” to assign charges to atoms: formal charge = number of valence electrons - number of electrons in lone pairs - number of bonds (single bond equivalents).

Free Energy; *See* **Gibbs Energy**

Gaussian. A function of the form $x^l y^m z^n \exp(\alpha r^2)$ where l, m, n are integers (0, 1, 2 . . .) and α is a constant. Used in the construction of **Basis Sets**.

Gaussian Basis Set. A **Basis Set** made up of **Gaussian Basis Functions**.

Gibbs Energy (ΔG). The combination of **Enthalpy** and **Entropy** which dictates whether a reaction is favorable (spontaneous) or unfavorable at temperature T: $\Delta G = \Delta H - T\Delta S$.

Global Minimum. The lowest energy **Local Minimum** on a **Potential Energy Surface**.

Ground State. The lowest energy electronic state for an atom or molecule.

Hammond Postulate. The idea that the **Transition State** for an *exothermic* reaction will more closely resemble reactants than products. This provides the basis for “modeling” properties of **Transition States** in terms of the properties of reactants.

Hartree. The **Atomic Unit** of energy. 1 hartree = 627.47 kcal/mol.

Hartree-Fock Approximation. Separation of electron motions in many-electron systems into a product form of the motions of the individual electrons.

Hartree-Fock Energy. The energy resulting from **Hartree-Fock Models**.

Hartree-Fock Models. Methods in which the many-electron wavefunction in written terms of a product of one-electron wavefunctions. Electrons are assigned in pairs to functions called **Molecular Orbitals**.

Heterolytic Bond Dissociation. A process in which a bond is broken and a cation and anion result. The number of electron pairs is conserved, but a non-bonding electron pair has been substituted for a bond.

HOMO. **H**ighest **O**ccupied **M**olecular **O**rbital. The highest-energy molecular orbital which has electrons in it.

Homolytic Bond Dissociation. A process in which a bond is broken and two **Radicals** result. The number of electron pairs is not conserved.

Hybrid Orbital. A combination of **Atomic Orbitals**. For example, 2s and 2px, 2py, 2pz orbitals may be combined to produce four equivalent sp^3 hybrid orbitals, each pointing to different corners of a tetrahedron.

Hypervalent Molecule. A molecule containing one or more main-group elements in which the normal valence of eight electrons has been exceeded. Hypervalent molecules are common for second-row and heavier main-group elements but are uncommon for first-row elements.

Imaginary Frequency. A frequency which results from a negative curvature of the **Potential Energy Surface**. **Equilibrium Geometries** are characterized by all real frequencies while **Transition States** are characterized by one imaginary frequency.

Infrared Spectrum. The set of **Energies** corresponding to the vibrational motions which molecules undergo upon absorption of infrared light.

Ionic Bond. A chemical bond in which the pair of electrons is not significantly shared by the two atoms.

Isodensity Surface. An **Electron Density Isosurface**. **Bond Surfaces** and **Size Surfaces** may be used to elucidate bonding or to characterize overall molecular size and shape, respectively.

Isopotential Surface. An **Electrostatic Potential Isosurface**. It may be used to elucidate regions in a molecule which are particularly electron rich and subject to electrophilic attack and those which are particularly electron poor, subject to nucleophilic attack.

Isosurface. A three-dimensional surface defined by the set of points in space where the value of the function is constant.

Isotope Effect. Dependence of molecular properties and chemical behavior on atomic masses.

Kinetically-Controlled Reaction. A chemical reaction which has not gone all the way to completion, and the ratio of products is not related to the relative **Activation Energies**.

Kinetic Product. The product of a **Kinetically-Controlled Reaction**.

LCAO Approximation. **L**inear **C**ombination of **A**tomic **O**rbitals approximation. Approximates the unknown **Hartree-Fock Wavefunctions** (**Molecular Orbitals**) by linear combinations of atom-centered functions (**Atomic Orbitals**).

Local Ionization Potential. A measure of the relative ease of electron removal ("ionization") as a function of location.

Local Ionization Potential Map. A graph of the value of the **Local Ionization Potential** on an **Isodensity Surface** corresponding to a **van der Waals Surface**.

Local Minimum. Any **Stationary Point** on a **Potential Energy Surface** for which all coordinates are at energy minima.

Lone Pair. A **Non-Bonded Molecular Orbital** which is typically associated with a single atom.

LUMO. **L**owest **U**noccupied **M**olecular **O**rbital. The lowest-energy molecular orbital which does not have electrons in it.

LUMO Map. A graph of the absolute value of the **LUMO** on an **Isodensity Surface** corresponding to a **van der Waals Surface**.

Mechanism. The sequence of steps connecting reactants and products in an overall chemical reaction. Each step starts from an equilibrium form (reactant or intermediate) and ends in an equilibrium form (intermediate or product).

Merck Molecular Force Field; *See* **MMFF94**.

Meso Compound. A molecule with two (or more) **Chiral Centers** with a superimposible mirror image.

Minimal Basis Set. A **Basis Set** which contains the fewest functions needed to hold all the electrons on an atom and still maintain spherical symmetry.

MMFF94. **M**erck **M**olecular **F**orce **F**ield. A **Molecular Mechanics Force Field** for organic molecules and biopolymers developed by Merck Pharmaceuticals incorporated into Spartan.

Molecular Mechanics Models. Methods for structure, conformation and strain energy calculation based on bond stretching, angle bending and torsional distortions, together with **Non-Bonded Interactions**, and parameterized to fit experimental data.

Molecular Orbital. A one-electron function made of contributions of **Basis Functions** on individual atoms (**Atomic Orbitals**) and delocalized throughout the entire molecule.

Molecular Orbital Models. Methods based on writing the many-electron solution of the **Electronic Schrödinger Equation** in terms of a product of one-electron solutions (**Molecular Orbitals**).

Multiplicity. The number of unpaired electrons (number of electrons with "down" spin) +1. 1=singlet; 2=doublet; 3=triplet, etc.

Node. A change in the sign of a **Molecular Orbital**. Nodes involving bonded atoms indicate that a particular **Molecular Orbital** is **Antibonding** with respect to the atoms.

Non-Bonded Interactions. Interactions between atoms which are not directly bonded. **van der Waals Interactions** and **Coulombic Interactions** are non-bonded interactions.

Non-Bonded Molecular Orbital. A molecular orbital which does not show any significant **Bonding** or **Antibonding** characteristics. A **Lone Pair** is a non-bonded molecular orbital.

Non-Polar Bond. A **Covalent Bond** which involves equal or nearly equal sharing of electrons.

Nucleophile. An electron-pair donor. A molecule (or region of a molecule) which "desires" to interact (react) with an electron-poor reagent or **Acid**.

Octet Rule. The notion that main-group elements prefer to be "surrounded" by eight electrons (going into s, px, py, pz orbitals).

Orbital Symmetry Rules; *See* **Woodward-Hoffmann Rules**.

Open Shell. An atom or molecule in which one or more electrons are unpaired.

Radicals are open-shell molecules.

PM3. **P**arameterization **M**ethod **3**. A **Semi-Empirical Model** incorporated into Spartan.

Point Group. A classification of the **Symmetry Elements** in a molecule.

Polar Bond. A **Covalent Bond** which involves unequal sharing of electrons.

Polarization Basis Set. A **Basis Set** which contains functions of higher angular quantum number (**Polarization Functions**) than required for the **Ground State** of the atom, in particular, d-type functions for non-hydrogen atoms. **6-31G*** is a polarization basis set.

Polarization Functions. Functions of higher angular quantum than required for the **Ground State** atomic description. Added to a **Basis Set** to allow displacement of **Valence Basis Functions** away from atomic positions.

Potential Energy Surface. A function of the energy of a molecule in terms of the geometrical coordinates of the atoms.

Property Map. A representation or "map" of a "property" on top of an **Isosurface**, typically an **Isodensity Surface**. **Electrostatic Potential Maps**,

LUMO Maps and **Spin Density Maps** are useful property maps.

Pseudorotation. A mechanism for interconversion of *equatorial* and *axial* sites around trigonal bipyramidal centers, e.g., fluorines in phosphorous pentafluoride.

Quantum Mechanics. Methods based on approximate solution of the **Schrödinger Equation**.

Radical. A molecule with one or more unpaired electrons.

Rate Limiting Step. The step in an overall chemical reaction (**Mechanism**) which proceeds via the highest-energy **Transition State**.

Reaction Coordinate. The coordinate that connects the **Local Minima** corresponding to the reactant and product, and which passes through a **Transition State**.

Reaction Coordinate Diagram. A plot of energy vs. **Reaction Coordinate**.

Schrödinger Equation. The quantum mechanical equation which accounts for the motions of nuclei and electrons in atomic and molecular systems.

Semi-Empirical Models. **Quantum Mechanics** methods that seek approximate solutions to the **Electronic Schrödinger Equation**, but which involve empirical parameters. **PM3** is a semi-empirical model.

Size Surface. An **Isodensity Surface** used to establish overall molecular size and shape. The value of the density is typically taken as 0.002 electrons/**bohr**^{3}.

Slater. A function of the form $x^l y^m z^n \exp(-\zeta r)$ where l, m, n are integers (0, 1, 2 . . .) and ζ is a constant. Related to the exact solutions to the **Schrödinger Equation** for the hydrogen atom. Used as **Basis Functions** in **Semi-Empirical Models**.

SOMO. **S**ingly **O**ccupied **M**olecular **O**rbital. An orbital which has only a single electron in it. The **HOMO** of a **Radical**.

Space-Filling Model; *See* **CPK Model**.

Spin Density. The difference in the number of electrons per unit volume of "up" spin and "down" spin at a point in space.

Spin Density Map. A graph that shows the value of the **Spin Density** on an **Isodensity Surface** corresponding to a **van der Waals Surface**.

Split-Valence Basis Set. A **Basis Set** in which the **Core** is represented by a single set of **Basis Functions** (a **Minimal Basis Set**) and the **Valence** is represented by two or more sets of **Basis Functions**. This allows for description of aspherical atomic environments in molecules. **3-21G** is a split-valence basis set.

Stationary Point. A point on a **Potential Energy Surface** for which all energy first derivatives with respect to the coordinates are zero. **Local Minima** and **Transition States** are stationary points.

Stereocenter; *See* **Chiral Center**

Symmetry Elements. Elements which reflect the equivalence of different parts of a molecule. For example, a plane of symmetry reflects the fact that atoms on both sides are equivalent.

T1. A thermochemical recipe incorporated into Spartan, designed to provide highly accurate Heats of Formation for organic molecules.

Theoretical Model. A "recipe" leading from the **Schrödinger Equation** to a general computational scheme. A theoretical models needs to be unique and well defined and, to the maximum extent possible, be unbiased by preconceived ideas. It should lead to **Potential Energy Surfaces** which are continuous.

Theoretical Model Chemistry. The set of results following from application of a particular **Theoretical Model**.

Thermodynamically-Controlled Reaction. A chemical reaction which has gone all the way to completion, and the ratio of different possible products is related to their thermochemical stabilities according to the **Boltzmann Equation**.

Thermodynamic Product. The product of a reaction which is under **Thermodynamic Control**.

Transition State. A **Stationary Point** on a **Potential Energy Surface** for which all but one of the coordinates is at an energy minimum and one of the coordinates is at an energy maximum. Corresponds to the highest-energy point on the **Reaction Coordinate**.

Transition-State Geometry. The geometry (bond lengths and angles) of a **Transition State**.

Transition State Theory. The notion that all molecules react through a single well-defined **Transition State**.

Valence. Electrons which are delocalized throughout the molecule and participate in chemical bonding (2s, 2px, 2py, 2pz for first-row elements, 3s, 3px, 3py, 3pz for second-row elements, etc.).

van der Waals Interactions. Interactions which account for short-range repulsion of non-bonded atoms as well as for weak long-range attraction.

van der Waals Radius. The radius of an atom (in a molecule), which is intended to reflect its overall size.

van der Waals Surface. A surface formed by a set of interpreting spheres (atoms) with specific **van der Waals radii**, and which is intended to represent overall molecular size and shape.

Vibrational Frequencies. The energies at which molecules vibrate. Vibrational frequencies correspond to the peaks in an **Infrared** and Raman **Spectrum**.

VSEPR Theory. **V**alence **S**tate **E**lectron **P**air **R**epulsion theory. A simple empirical model used to predict the geometries of molecules given only the total number of electrons associated with each center.

Wavefunction. The solutions of the **Electronic Schrödinger Equation**. In the case of the hydrogen atom, a function of the coordinates which describes the motion of the electron as fully as possible. In the case of a many-electron system a function which describes the motion of the individual electrons.