

# **SpartanModel . . . An Electronic Model Kit**

Tutorial and User's Guide  
2nd Edition



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# Introduction

## SpartanModel. An Electronic Model Kit

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SpartanModel is an “electronic” model kit. As such, it offers significant advantages over conventional “plastic” models used by past generations of organic chemistry students. Molecules of any size and complexity can be easily constructed, manipulated and explored. In addition to organic molecules, inorganic and organometallic compounds and polypeptides and polynucleotides may be built. Once constructed, molecules may be displayed in a variety of different styles. Students may highlight aspects of molecules that may be of particular interest. For example, the location of bonds or overall size and shape may be emphasized. Atom chiralities (R/S assignments) may be obtained. Finally, high-quality images of molecules may be pasted into other programs.

SpartanModel uses a molecular mechanics procedure to turn what has been built into a more accurate and ultimately more realistic structure. Bond lengths and angles, surface areas and molecular volumes may be queried. Strain energies for different conformers may be compared and the “best” conformation identified.

SpartanModel includes a database comprising several thousand organic and inorganic molecules. Structures, energies, infrared spectra and selected properties for each molecule have been obtained from high-quality quantum mechanical calculations, the same types of calculations that are extensively used by research chemists. While the calculated data are not identical to experimental results, they are sufficiently close to be of significant value in the study of chemistry. The database also includes the necessary information to rapidly generate electrostatic potential maps. These allow visualization of the charge distribution in molecules. Taken as a whole, the information

in SpartanModel's database not only allows quantitative comparisons of molecular properties to be made among diverse molecules, but also facilitates answers to such questions as whether a particular chemical reaction is likely to proceed as written, or which of several possible acid sites in a molecule is likely to be the strongest.

Information available to SpartanModel is not limited to the database. Any file generated from the Spartan line of molecular modeling software may be read and information about molecular structure and properties may be examined and queried.

This guide comprises four chapters and an appendix. The first two chapters, **Operating SpartanModel** and **Tutorials**, provide introductory materials for the program as well as "hands-on" tutorials illustrating its capabilities. Here, the emphasis is on model building and display, retrieval and use of information from SpartanModel's database and display and interpretation of electrostatic potential maps. The third chapter, **Modeling Topics**, provides brief discussions on the use and interpretation of information available in SpartanModel's database. The fourth and longest chapter, **Activities**, comprises a series of activities that call on SpartanModel's ability to build and examine molecules, access calculated structures, energies and infrared spectra and other properties, and generate electrostatic potential maps. The activities are intended to provide students with "a taste" of what computer technology brings to the study of organic chemistry, and instructors with "templates" on which to base new materials. Finally, the **Appendix** details a number of important capabilities of SpartanModel available under its menus.

# Table of Contents

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<b>Chapter 1</b>	<b>Operating SpartanModel .....</b>	<b>1</b>
<b>Chapter 2</b>	<b>Tutorials .....</b>	<b>5</b>
	Basic Operations .....	6
	Acrylonitrile: Atoms and Groups .....	15
	Camphor: Atoms and Rings .....	17
	Lysergic Acid: Atoms, Groups and Rings .....	18
	Ethinamate: Retrieving a Molecule by Structure .....	20
	Adamantyl Cation: Retrieving an Ion by Structure. ....	21
	Vitamin E: Retrieving a Molecule by Name .....	22
	Benzoic Acid Dimer: Retrieving a Molecular Complex ....	23
	Electrostatic Potential Maps and Acid Strengths .....	24
<b>Chapter 3</b>	<b>Modeling Topics .....</b>	<b>25</b>
	Energy and Thermodynamics .....	26
	Molecular Shape .....	28
	Infrared Spectra .....	32
	Atomic Charges .....	33
	Electrostatic Potential Maps .....	34
<b>Chapter 4</b>	<b>Activities .....</b>	<b>39</b>
	Nomenclature .....	40
	Structure and Bonding .....	44
	Acids and Bases .....	49
	Alkanes and Cycloalkanes .....	52
	Saturated Compounds with Heteroatoms .....	55
	Alkenes and Alkynes .....	59
	Dienes .....	65
	Aromatics .....	71
	Electrophilic Aromatic Substitution .....	78
	Nucleophilic Additions .....	82
	Carbonyl Compounds .....	85
	IR/UV Spectra .....	90
	Biomolecules .....	96
<b>Appendix</b>	<b>SpartanModel Overview .....</b>	<b>99</b>
	Menus .....	99
	Model Kits and Builder Functions .....	101
	Properties Dialogs .....	105



# Chapter 1

## Operating SpartanModel

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### Starting and Quitting SpartanModel

To start on Windows, *click* on the **Start** button, *click* on **All Programs**, and *click* on **SpartanModel**. To quit, select **Exit** from the **File** menu. To start on Macintosh, *double click* on its icon on the desktop. To quit, select **Quit SpartanModel** from the **SpartanModel** menu.




























### Menus

Program functions may be accessed using pull-down menus.

<b>File</b>	Allows you to create a new molecule, read in a Spartan file, or to access SpartanModel's database using a molecule's name.
<b>Edit</b>	Allows you to access the clipboard for moving structures and graphics between SpartanModel and other applications.
<b>Model</b>	Allows you to control the style of your model.
<b>Geometry</b>	Allows you to measure bond lengths and angles.
<b>Build</b>	Allows you to build and edit molecules.
<b>Display</b>	Allows you to query molecular and atomic properties, and display electrostatic potential maps and infrared spectra.

### Icons

Windows/Macintosh icons access selected functions.

  New	  Add Fragment	  Measure Distance
  Open	  Delete	  Measure Angle
  Close	  Make Bond	  Measure Dihedral
  Retrieve	  Break Bond	 Help
  View	  Minimize	

## Using the Mouse

The following operations require the mouse.

### Windows

<b>select molecule</b>	<i>click</i> (left mouse button)
<b>rotate molecule</b>	<i>press</i> the left button and <i>move</i> the mouse
<b>translate molecule</b>	<i>press</i> the right button and <i>move</i> the mouse
<b>scale molecule</b>	<i>press</i> both the <b>Shift</b> key and the right button and <i>move</i> the mouse “up and down”
<b>rotate about bond</b>	<i>press</i> the <b>Alt</b> key and the left button and <i>move</i> the mouse “up and down”

### Macintosh (one-button mouse)

<b>select molecule</b>	<i>click</i>
<b>rotate molecule</b>	<i>press</i> the button and <i>move</i> the mouse
<b>translate molecule</b>	<i>press</i> the <b>option</b> key and the button and <i>move</i> the mouse
<b>scale molecule</b>	<i>press</i> both the <b>Apple</b> and <b>option</b> keys in addition to the button and <i>move</i> the mouse “up and down”
<b>rotate about bond</b>	<i>press</i> the <b>spacebar</b> and the button and <i>move</i> the mouse “up and down”

### Macintosh (two-button mouse)

<b>select molecule</b>	<i>click</i> (left mouse button)
<b>rotate molecule</b>	<i>press</i> the left button and <i>move</i> the mouse
<b>translate molecule</b>	<i>press</i> the right button and <i>move</i> the mouse
<b>scale molecule</b>	<i>press</i> the <b>Apple</b> key and the right button and <i>move</i> the mouse “up and down” or use the scroll wheel if available
<b>rotate about bond</b>	<i>press</i> the <b>spacebar</b> and the left button and <i>move</i> the mouse “up and down”

## 3-Dimensional Displays

A molecule may be viewed in 3D (stereo) using “red/blue” glasses. 3D is turned “on” and “off” by toggling the “**3**” key.



## Changing Colors and Setting Preferences

**Colors** and **Preferences...** from the **Options** menu (**Edit** menu for **Colors** and **SpartanModel** menu for **Preferences** on Macintosh) allows for changing default colors, and for setting program defaults.

## Retrieving Molecules from SpartanModel's Database


SpartanModel accesses a database of several thousand molecules. Each entry includes structure, energy, infrared spectrum, electrostatic potential map, and additional properties from quantum mechanics calculations. Molecules can be retrieved from the database either by structure or by name.

### a) By Structure:

Following building, the existence of a molecule in the database is signaled by its name appearing to the right of the **Retrieve** button at the bottom of the screen. *Clicking* on the **Retrieve** button replaces what has been built by the molecule in the database. Note that where two or more different structures for the same molecule are present in the database (for example, *anti* and *gauche* conformers of *n*-butane) only the lowest-energy structure will be retrieved, irrespective of which structure was built. The only way to access higher-energy structures is by name retrieval (see below).

Structure retrieval of charged molecules (Windows version only) requires that a formal charge be assigned to the atom bearing the charge. This is done following building by first entering the view mode (**View** from the **Build** menu), then selecting **Properties** from the **Display** menu, then *clicking* on the atom bearing the charge and finally changing the entry in the menu to the right of **Formal Charge** from “unspecified” to 1 (for a cation) or -1 (for an anion).

### b) By Name:

Name retrieval follows selection of **Retrieve** from the **File** menu (*clicking* on the  icon), and typing a character string (all or part of the name of the molecule) into the box at the top of the **Retrieve Molecule** dialog. For Macintosh, all database entries

that contain the character string will be identified. Scroll through the list. For Windows, only the first database entry that starts with the character string will be identified. To find additional entries that incorporate the string, *click* on the **Look For** button. Once the molecule has been identified, *click* on the **Retrieve** button at the bottom of the dialog.

# Chapter 2



## Tutorials

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Each of the “hands-on” tutorials in this chapter focuses on a particular aspect of SpartanModel: building, displaying and manipulating molecules, retrieving and using information from the database and displaying and interpreting electrostatic potential maps.

Dialogs illustrated in the tutorials are for the Windows version of SpartanModel. Those for the Macintosh version are very similar. Both Windows and Macintosh icons accessing commonly-used functions under the menus are provided in the format Windows icon/Macintosh icon. Finally, a two-button mouse is assumed for Macintosh.

## Basic Operations

1. Click (left button) on **File** from the menu bar and select (click on) **Open** from the menu that appears. Alternatively, click on / . Locate and move into the *tutorials* directory in the dialog that appears, click on *basic operations* and click on **Open** (or double click on *basic operations*).

Ball-and-spoke models for *ethane*, *acetic acid dimer*, *carvone R enantiomer*, *carvone S enantiomer*, *propene*, *ammonia*, *hydrogen peroxide*, *acetic acid*, *water*, *cyclohexanone*, *ethylene*, *benzene* and *aniline* appear on screen. You can select a molecule by clicking on it with the left mouse button. Once selected, a molecule may be manipulated (rotated, translated and scaled). (See *Using the Mouse* in **Chapter 1**).

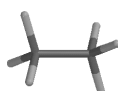
2. Identify *ethane* on the screen, and click on it (left button) to make it the selected molecule. Practice rotating (move the mouse while pressing the left button) and translating (move the mouse while pressing the right button) *ethane*. Click on a different molecule, and then rotate and translate it.
3. Return to *ethane*. Click on **Model** from the menu bar.



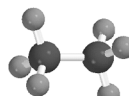
Wire



Ball-and-Wire



Tube



Ball-and-Spoke

One after the other, select **Wire**, **Ball and Wire**, **Tube** and finally **Ball and Spoke** from the **Model** menu. All four models for *ethane* show roughly the same information. The wire model looks like a conventional line formula, except that all atoms, not just the carbons, are found at the end of a line or at the intersection of lines. The wire model uses color to distinguish different atoms, and one, two and three lines between atoms to indicate single, double and triple bonds, respectively. The ball-and-wire model is similar to the wire model, except that atom positions are represented by small spheres. This makes it easy to identify atom locations. The tube model is useful for conveying the three-dimensional shape

of a molecule. Single bonds are rendered as cylinders and double and triple bonds as cylinders that have been split into two and three parts, respectively. The ball-and-spoke model is a variation on the tube model; atom positions are represented by colored spheres, making it easy to see atom locations.

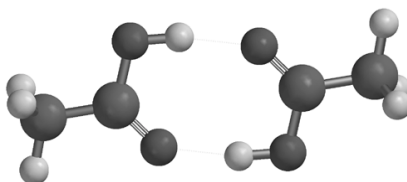
Select **Space Filling** from the **Model** menu.



Space-Filling

This model is different from the others in that bonds are not shown. Rather, each atom is displayed as a colored sphere that represents its approximate “size”. Thus, the space-filling model provides a measure of a molecule’s size. While lines between atoms are not drawn, the existence (or absence) of bonds can be inferred from the amount of overlap between neighboring atomic spheres. If two spheres substantially overlap, then the atoms are almost certainly bonded, and conversely, if two spheres marginally overlap, then the atoms are not bonded. Intermediate overlaps suggest “weak bonding”, for example, hydrogen bonding.

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



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




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



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


Chiral centers may be identified and R/S chirality assigned, using **Configure** from the **Model** menu.



Select *carvone R enantiomer* from the molecules on screen. Select **Configure** from the **Model** menu to bring up the **Configure** dialog. Click on **R/S** under “Atom” and then on **OK**. The chiral center will be designated. Repeat for *carvone S enantiomer*. Manipulate the two enantiomers so that you can see that they are in fact non-superimposable mirror images.




Select **Hydrogens** from the **Model** menu to remove the hydrogens from the model. (Select it again to put the hydrogens back.) Because they are less crowded, models without hydrogens may be easier to examine and query than those with hydrogens.

4. Distances, angles, and dihedral angles may easily be measured with Spartan using **Measure Distance**, **Measure Angle**, and **Measure Dihedral**, respectively, from the **Geometry** menu. Alternatively, the measurement functions may be accessed from the   and  icons.

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

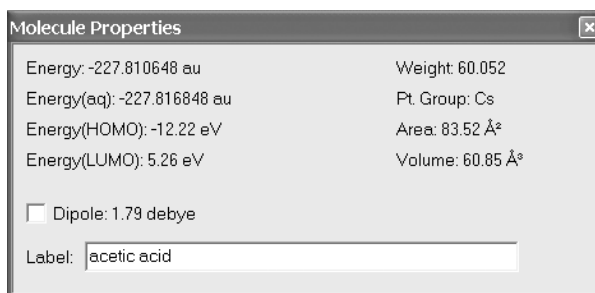
b) **Measure Angle**: This measures the angle around a central atom. Select *ammonia* from the molecules on screen, and then select **Measure Angle** from the **Geometry** menu (or click on ). Click first on H, then on N, then on another H. Alternatively, click on two NH bonds. The HNH angle (in

degrees) will be displayed at the bottom of the screen. Click on   when you are finished.

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

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

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

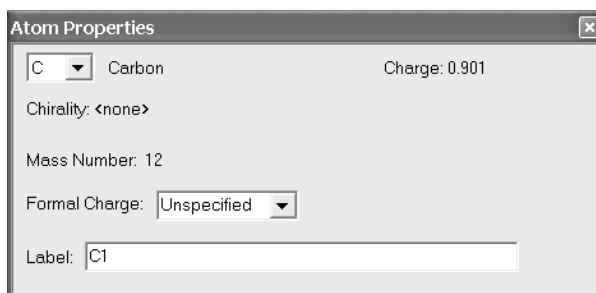




This provides the energy for acetic acid in atomic units (au). See “*Energy and Thermodynamics*” in **Chapter 3** for a discussion of energy units.

- b) **Dipole Moment:** The magnitude of the dipole moment (in debyes) is also provided in the **Molecule Properties** dialog. A large dipole moment indicates large separation of charge. You can attach the dipole moment vector, “ $\text{+}\text{---}\text{+}$ ” where the lefthand side “+” refers to the positive end of the dipole, to the model on the screen, by checking **Dipole** near the bottom

of the dialog. The vector will not be displayed if the magnitude of the dipole moment is zero, or if the molecule is charged.

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

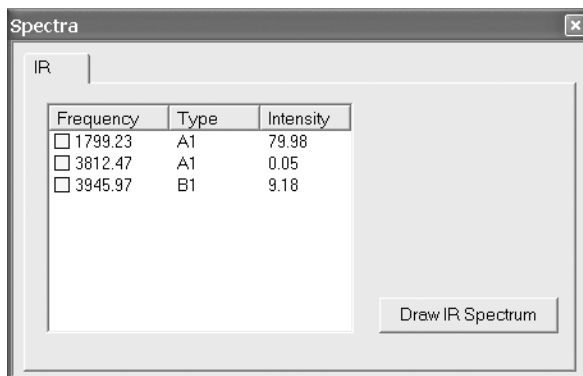


Atomic charges are given in units of electrons. A positive charge indicates a deficiency of electrons on an atom and a negative charge, an excess of electrons. Repeat the process as necessary by *clicking* on other atoms. Confirm that the positively-charged atom(s) lie at the positive end of the dipole moment vector. When you are finished, remove the dialog from the screen by *clicking* on the  in the top right-hand corner ( in the top left hand corner for Macintosh).

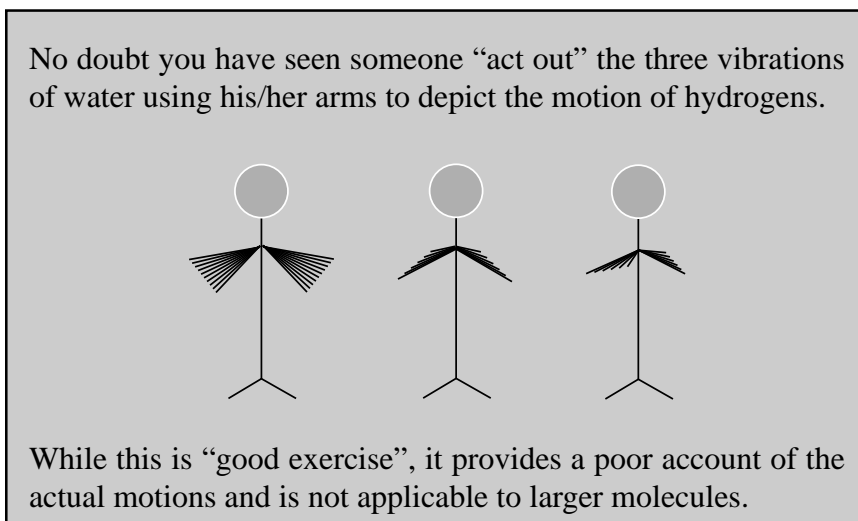
- d) **Infrared Spectra:** Molecules vibrate (stretch, bend, twist) even if they are cooled to absolute zero. This is the basis of infrared spectroscopy, where absorption of energy occurs when the frequency of molecular motions matches the frequency of the "light". Infrared spectroscopy is important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

Select **water** from the molecules on screen. Select **Spectra** from the **Display** menu. This leads to the **Spectra** dialog.



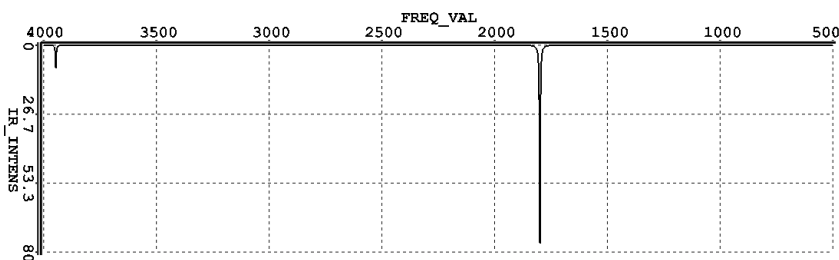




This displays the three vibrational frequencies for the water molecule\*, corresponding to bending and symmetric and antisymmetric stretching motions. One after the other, *double click* on each frequency and animate the motion. Turn “off” the animation when you are finished.



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

\* In general, vibrational frequencies from the quantum mechanics calculations from Spartan files included with SpartanModel and from SpartanModel’s database will be 10-12% larger than experimental frequencies.

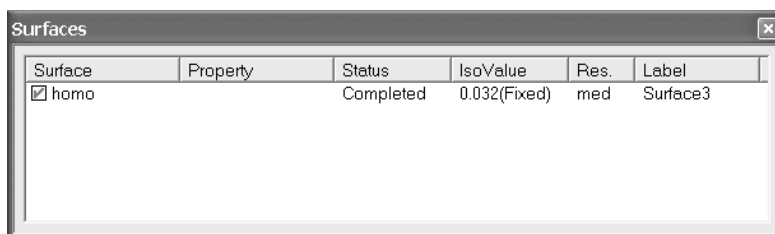


You can move the spectrum around the screen by first *clicking* on it to select it and then *moving* the mouse while *pressing* the right button. You can size it by *moving* the mouse “up and down” while *pressing* both the **Shift** key (⌘ key for Macintosh) and the right button. Identify the line in the spectrum associated with the CO stretch (a small gold ball moves from line to line as you step through the frequencies in the **Spectra** dialog). Note that this line is separated from the other lines in the spectrum and that it is intense. This makes it easy to find and is the primary reason why infrared spectroscopy is an important diagnostic for carbonyl functionality. When you are finished, *click* on  ( for Macintosh) at the top of the **Spectra** dialog to remove it from the screen.

6. SpartanModel permits display, manipulation and query of a number of important quantities resulting from a Spartan calculation in “visual” format. Most important are the electron density (which reveals “how much space” a molecule actually takes up) and key molecular orbitals (which provide insight both into bonding and chemical reactivity). In addition, the electrostatic potential map, an overlaying of a quantity called the electrostatic potential (the attraction or repulsion of a positive charge for a molecule) onto the electron density, is valuable for describing overall molecular charge distribution as well as anticipating sites of electrophilic addition. For further discussion, see “***Electrostatic Potential Maps***” in **Chapter 3**. (Electrostatic potential maps based on van der Waals surfaces rather than electron density surfaces and approximating the electrostatic potential using atomic charges are available for all entries in SpartanModel’s database.) Another indicator of electrophilic addition is provided

by the local ionization potential map, an overlaying of the energy of electron removal (“ionization”) onto the electron density. Finally, the likelihood of nucleophilic addition can be ascertained using a LUMO map, an overlaying of the lowest-unoccupied molecular orbital (the LUMO) onto the electron density.

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



*Click* on the selection box next to “homo...” inside the dialog. This will result in the display of ethylene’s highest-occupied molecular orbital as a solid. This is a  $\pi$  orbital, equally concentrated above and below the plane of the molecule. The colors (“red” and “blue”) give the sign of the orbital. Changes in sign often correlate with bonding or antibonding character. Turn “off” the graphic by *clicking* on the selection box.



Select *benzene* from the molecules on screen and *click* on the selection box next to “density potential...” inside the **Surfaces** dialog. An electrostatic potential map for benzene will appear. Change the display from solid to transparent to allow you to see the molecular model underneath. On Windows, *click* on the map and select **Transparent** from the menu that appears at the bottom right of the screen. On Macintosh, position the cursor over the map while holding down on either the left or right button and select **Transparent** from the menu that appears. Note, that the surface is colored “red” in the  $\pi$  system (indicating negative potential and the fact that this region is attracted to a positive charge), and “blue” in the  $\sigma$  system (indicating positive potential and the fact that this region is repelled by a positive charge).

Select *aniline* from the molecules on screen, and *click* on the selection box for “density ionization...” inside the **Surfaces** dialog. A local ionization potential map appears. Colors in red regions on the density surface from which electron removal (ionization) is relatively easy, meaning that they are subject to electrophilic attack. These are easily distinguished from regions where ionization is relatively difficult (colored in blue). Note that the *ortho* and *para* ring carbons are more red than the *meta* carbons, consistent with the known directing ability of the amino substituent.

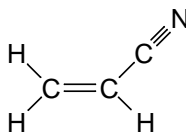
Finally, select *cyclohexanone* from the molecules on screen, and *click* on the selection box for “lumo...” in the **Surfaces** dialog. The resulting graphic portrays the lowest unoccupied molecular orbital (the LUMO) of cyclohexanone. This is a  $\pi^*$  orbital that is antibonding between carbon and oxygen. Note that the LUMO is primarily localized on carbon, meaning that this is where a pair of electrons (a nucleophile) will “attack” cyclohexanone.

A better portrayal is provided by a LUMO map, which displays the (absolute) value of the LUMO on the electron density surface. Here, the color blue is used to represent maximum value of the LUMO and the color red, minimum value. First, remove the LUMO from your structure (*click* on the selection box for “lumo...” in the **Surfaces** dialog) and then turn on the LUMO map (*click* on the selection box for “density lumo...” in the dialog). Note that the blue region is concentrated directly over the carbonyl carbon. Also, note that the so-called *axial* face shows a greater concentration of the LUMO than the *equatorial* face. This is consistent with the known stereochemistry of nucleophilic addition.

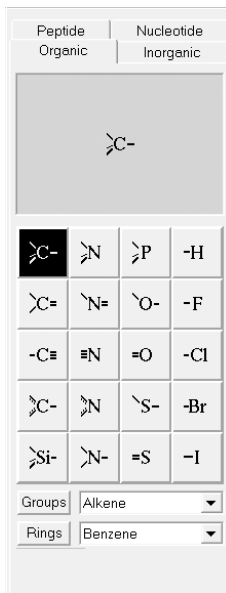
Small collections of molecules which include molecular orbitals, local ionization potential maps and LUMO maps are found in the *molecular orbitals*, *local ionization potential maps* and *LUMO maps* directories on the SpartanModel CD-ROM.

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

## Acrylonitrile: Atoms and Groups



1. Select **New** from the **File** menu (or *click* on / ).



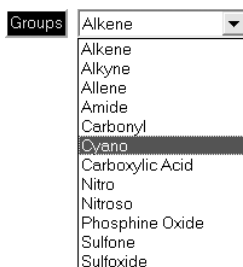
*Click* on trigonal planar  $sp^2$  hybridized carbon () from the palette of atomic fragments. A model of the fragment appears at the top of the model kit. Position the cursor anywhere on screen and *click*. Rotate the carbon fragment (move the mouse while holding down the left button) so that you can see both the (yellow colored) double free valence (“=”) and the two single free valences (“-”).

SpartanModel connects atomic fragments (as well as groups, rings and ligands) through free valences. Unless they are “used” or “deleted”, free valences will automatically be converted to hydrogen atoms.







2.  $sp^2$  carbon is still selected. *Click* on the double free valence. The two fragments are connected by a double bond, leaving ethylene.

SpartanModel allows only the same type of free valences to be connected, e.g., single to single, double to double, etc.



3. Click on **Groups** and select **Cyano** from the menu.



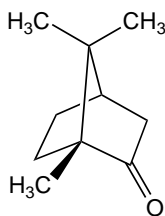
Click on one of the free valences on ethylene, to make acrylonitrile.\* If you make a mistake, you can select **Undo** from the **Edit** menu to “undo” the last operation or **Clear** (**Edit** menu) to clear the screen and start over.

4. Select **Minimize** from the **Build** menu (or click on  ). The “strain energy” and symmetry point group ( $C_s$ ) for acrylonitrile are provided at the bottom right of the screen. (To see the strain energy on the Macintosh, bring up the **Molecule Properties** dialog by selecting **Properties** from the **Display** menu.)
5. Select **View** from the **Build** menu (or click on  ) to remove the model kit from the screen.
6. Select **Close** from the **File** menu (or click on  ) to remove acrylonitrile from the screen.

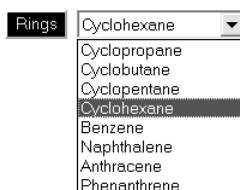
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
\* Acrylonitrile could also have been built without using the **Groups** menu. First, clear the screen by selecting **Clear** from the **Edit** menu. Then build ethylene from two  $sp^2$  carbons (as above), select  $sp$  hybridized carbon () from the model kit and then click on one of the free valences on ethylene. Next, select  $sp$  hybridized nitrogen () from the model kit and click on the triple free valence on the  $sp$  carbon. Alternatively, the molecule could have been built entirely from groups. First, clear the screen. Then click on **Groups**, select **Alkene** from the menu and click anywhere on screen. Then select **Cyano** from the same menu and click on one of the free valences on ethylene. Most molecules can be constructed in several ways.

## Camphor: Atoms and Rings

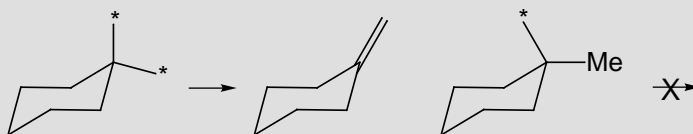





1. Click on / ). Click on **Rings** and select **Cyclohexane** from the menu of rings.















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

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

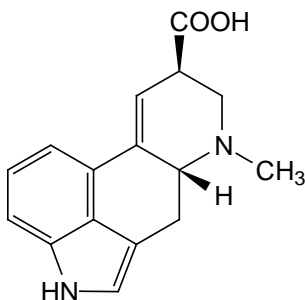







Select  $sp^2$  oxygen  from the model kit. Click on the double free valence on the  $sp^2$  carbon. You have made cyclohexanone. Click on / .

2. Select  $sp^3$  carbon  from the model kit and then *click* on the *axial* free valence two positions removed from the carbonyl carbon. You have made *axial* 3-methylcyclohexanone.



3. Select **Make Bond** from the **Build** menu (or *click* on / ). *Click* on one of the free valences of the  $sp^3$  carbon which you have just added and then on the *equatorial* free valence on the opposite side of the six-membered ring (adjacent to the carbonyl group). A bond will be drawn. *Click* on /  to produce a refined (intermediate) structure. Finish the structure by adding three methyl groups (*click* on  from the model kit and, one after the other, *click* on the three appropriate free valences). Finally, *click* on /  to give a minimized camphor geometry with  $C_1$  symmetry. *Click* on /  to remove the model kit.
4. Select **Configure...** from the **Model** menu. *Check* **R/S** under “Atom” in the dialog which results, and *click* on **OK**. R/S labels now appear (only) on the two bridgehead carbons. Both should be R (or both S), depending on which enantiomer you have built. You can if you wish turn “off” the labels by selecting **Labels** from the **Model** menu.
5. *Click* on /  to remove camphor from the screen.

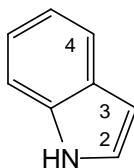
### Lysergic Acid: Atoms, Groups and Rings







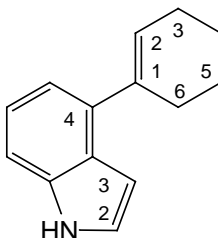
1. *Click* on / . *Click* on **Rings** and select **Benzene** from the **Rings** menu in the model kit, and *click* anywhere on screen.
2. Select **Alkene** from the **Groups** menu and *click* on any free valence on benzene. You have made styrene. Next, select planar trigonal nitrogen () from the model kit and *click* on the free valence on benzene that is adjacent to the vinyl group you have just added and near the terminus of this group. *Click* on / .














and, one after another, *click* on free valences on the vinyl group (terminal carbon) and nitrogen that are proximate. *Click* on  . You have made indole.



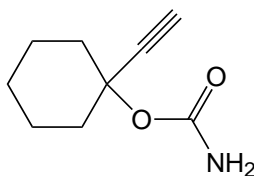
3. Select **Cyclohexane** from the **Rings** menu and *click* on free valence at C<sub>4</sub> (see figure above). *Click* on   and one after another *click* on free valences on the cyclohexane carbon that is bonded to indole and on an adjacent carbon. *Click* on  . Orient the two rings as shown below. To rotate about a bond, hold down both the **Alt** key (**spacebar** on Macintosh) and the left button and move the mouse up and down. The appropriate bond should be selected (circled by a red marker); if it is not, *click* on it.






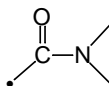
4. Select sp<sup>3</sup> carbon () from the model kit and *click* on the free valence at C<sub>3</sub> on the indole ring. *Click* on   and, one after another, *click* on free valences on the sp<sup>3</sup> carbon that you have just added and on C<sub>6</sub> on the cyclohexene ring. You need to pay attention to the stereochemistry of lysergic acid and use the free valence (on cyclohexene) that “points down”. *Click* on  .
5. Select **Carboxylic Acid** from the **Groups** menu and *click* on the free valence at C<sub>3</sub> on the cyclohexene ring that “points up”.
6. Select sp<sup>3</sup> nitrogen () and *double click* on C<sub>5</sub> on the cyclohexene ring (not on a free valence). Nitrogen will replace carbon.





7. Select  $\text{sp}^3$  carbon () and *click* on the free valence of the  $\text{sp}^3$  nitrogen. *Click* on / to produce a refined structure. If you have done everything correctly, the name “lysergic acid” will appear at the bottom of the screen. This indicates that the molecule is available in SpartanModel’s database.
8. *Click* on / to remove lysergic acid from the screen.

### Ethinamate: Retrieving a Molecule by Structure





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

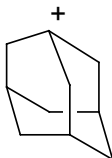





You can move the bonding position by repeatedly *clicking* on the icon. When you are satisfied, add the amide to the free valence on oxygen to make the carbamate functionality. Finally, select **Alkyne** from the **Groups** menu and add to the same carbon on the cyclohexane ring as occupied by the carbamate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

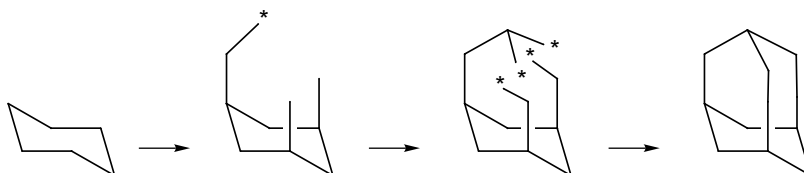
2. Note that the name “ethanimatate” appears at the bottom of the screen. This indicates that it is already available in SpartanModel’s database. *Click* on **Retrieve** to the left of the name to replace the model you have built with the one from the database.









3. Select **Properties** from the **Display** menu. The **Molecule Properties** dialog provides the energy and dipole moment for ethinamate. *Click* on an atom to bring up the **Atom Properties** dialog which provides the atomic charge.
4. *Click* on /  to remove ethinamate from the screen.

### Adamantyl Cation: Retrieving an Ion by Structure





1. Bring up the organic model kit (/ ). *Click* on **Rings**, select **Cyclohexane** and *click* anywhere on screen.
2. *Click* on  $sp^3$  carbon (). Add “methyl groups” to the three *axial* free valences on one face of the cyclohexane ring. Next, *click* on the free valence (—\*) on one of the “methyl groups” that points toward the other two groups.





3. *Click* on /  and, one after the other, connect free valences on the terminus of the “ethyl group” to those proximate on the two “methyl groups” (two bonds in total). *Click* on / . You have made adamantane (its name should appear at the bottom of the screen).
4. Select **Delete** from the **Build** menu (or *click* on / ). *Click* on a free valence on one of the bridgehead carbons (carbons with only one free valence).
5. *Click* on / . Select **Properties** from the **Display** menu and *click* on the carbon from which you have just deleted the free

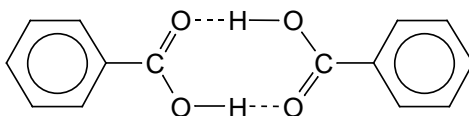
valence. This brings up the **Atom Properties** dialog. Change **Formal Charge** from **Unspecified** to **1** and dismiss the dialog.




6. The name “adamantyl cation” should appear at the bottom of the screen. *Click* on **Retrieve** to the left of the name to replace the model you have built with the entry in SpartanModel’s database.
7. *Click* on / to remove adamantyl cation from the screen.

### Vitamin E: Retrieving a Molecule by Name

1. Select **Retrieve...** from the **File** menu (or *click* on /). Type “vitamin E” into the box at the top of the **Retrieve Molecule** dialog. The name “vitamin E” will appear highlighted at the top of the list of molecules (Windows) or as the sole entry (Macintosh). *Click* on **Retrieve** at the bottom of the dialog.
2. Vitamin E incorporates three chiral centers. To assign them as R or S, select **Configure...** (**Model** menu) and *check* **R/S** under “Atom” in the dialog which appears. *Click* on **OK**. R/S labels will appear next to each of the chiral centers.
3. Select **Surfaces** from the **Display** menu to bring up the **Surfaces** dialog. *Check* the box to the left of the line “van derWaals potential (charges)” to display an electrostatic potential map. Notice the “long green tail” on the molecule. This is a neutral (“hydrophobic”) region which facilitates vitamin E dissolving in lipids. *Click* on the map. The **Style** menu will appear at the bottom right of the screen. Select **Transparent** from this menu to present the map as a translucent solid. This will allow you to see the molecular skeleton underneath. (On Macintosh, position the cursor over the map while holding down either the left or right button, and select **Transparent** from the menu which appears.)
4. Close vitamin E and any open dialogs when you are finished.

## Benzoic Acid Dimer: Retrieving a Molecular Complex



1. Bring up the organic model kit (). *Click* on **Rings**, select **Benzene** and *click* anywhere on screen. *Click* on **Groups**, select **Carboxylic Acid** and *click* on a free valence on benzene.
2. *Click* on **Rings**, select **Benzene**, hold down the **Insert** key (option key on Macintosh) and *click* on screen. You now have two molecules on screen, benzoic acid and benzene. *Click* on **Groups**, select **Carboxylic Acid** and *click* on a free valence on the benzene molecule (not the benzoic acid molecule).
3. (Optional) You can manipulate the two benzoic acid molecules into an appropriate complex geometry. On Windows, the default mouse operations pertain to the complex as a whole. To manipulate an individual molecule, first *click* on it to select and then hold down the **Ctrl** key while carrying out mouse operations. On Macintosh, *click* on the background to specify that mouse operations pertain to the complex as a whole and on an individual molecule to specify that mouse operations pertain only to it.
4. The name “benzoic acid dimer” will appear at the bottom of the screen. *Click* on **Retrieve** to the left of the name to replace the model you have built with the entry in SpartanModel’s database.
5. Select **Hydrogen Bonds** from the **Model** menu to show the two hydrogen bonds. Compare their lengths with those of the “normal” OH single bonds in the complex. *Click* on  and *click* on one of the hydrogen bonds (--- in the model) and then one of the OH single bonds.
6. *Click* on  to remove benzoic acid dimer from the screen.

## Electrostatic Potential Maps and Acid Strength

Chemists know that nitric and sulfuric acids are strong, acetic acid is weak, and that ethanol is very weak. What these compounds have in common is their ability to undergo heterolytic bond fracture, leading to a stable anion and a “proton”. What distinguishes a strong acid from a weak acid is the stability of the anion.  $\text{NO}_3^-$  and  $\text{HOSO}_3^-$  are very stable anions,  $\text{CH}_3\text{CO}_2^-$  is somewhat less stable and  $\text{CH}_3\text{CH}_2\text{O}^-$  is even less stable.

One way to reveal differences in acidity is to compare electrostatic potential maps for different acids, with particular focus on the potential in the vicinity of the “acidic hydrogen”. The more positive the potential, the more likely that dissociation will occur, and the stronger the acid.

1. One after another, build nitric acid, sulfuric acid, acetic acid and ethanol. For nitric acid, start with **Nitro** from the **Groups** menu; for sulfuric acid, start with **Sulfone** from the **Groups** menu. Replace all of your structures with those from the database.
2. Bring up the **Surfaces** dialog (**Display** menu). Select each molecule in turn and then *check* the box to the left of “vanderWaals potential(charges)...” inside the **Surfaces** dialog to display its potential map. Examine the potential in the vicinity of the acidic hydrogen (one of the two equivalent acidic hydrogens for sulfuric acid). “Blue” regions identify acidic sites, the more blue the greater the acidity. On this basis, rank the acid strength of the four compounds.
3. Remove all four models and the **Surfaces** dialog from the screen.

# Chapter 3

## Modeling Topics

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This section comprises a series of short “essays” discussing a number of important aspects of computer modeling. These include topics that may be directly related to experiment, for example, energy as related to thermodynamics, as well as those for which there are no direct parallels, for example, atomic charges.

## Energy and Thermodynamics

The energy of a molecule is an important quantity. It can be used to reveal which of several isomers is most stable. It can also be used to determine whether a particular chemical reaction will have a thermodynamic driving force (an “*exothermic*” reaction) or be thermodynamically uphill (an “*endothermic*” reaction).

There is more than one way to express the energy of a molecule. Most common to chemists is as a heat of formation,  $\Delta H_f$ . This is the enthalpy of a hypothetical chemical reaction that creates a molecule from well defined (but arbitrary) “standard states” of each of its constituent elements. For example,  $\Delta H_f$  for methane is the enthalpy required to create the molecule from graphite and  $H_2$ , the “standard states” of carbon and hydrogen, respectively.

An alternative to heat of formation is the total energy. This is the enthalpy of a hypothetical reaction that creates a molecule from a collection of separated nuclei and electrons. Total energies are always negative numbers and, in comparison with the energies of chemical bonds, are very large. By convention, total energies are expressed in “so-called” atomic units or au, but may be converted to other units as desired:

$$1 \text{ au} = 2625 \text{ kJ/mol}$$

It makes no difference whether heats of formation or total energies are used to calculate the thermochemistry of balanced chemical reactions:

$$\Delta E(\text{reaction}) = E_{\text{product 1}} + E_{\text{product 2}} + \dots - E_{\text{reactant 1}} - E_{\text{reactant 2}} - \dots$$

SpartanModel uses total energies. A negative  $\Delta E$  indicates an *exothermic* (thermodynamically favorable) reaction, while a positive  $\Delta E$  indicates an *endothermic* (thermodynamically unfavorable) reaction.

There are situations where energies (enthalpies) need to be replaced by “free energies” in order to account for the role of entropy. For example, accounting for the equilibrium concentrations of reactants and products requires the equilibrium constant,  $K_{eq}$ , which according to the Boltzmann equation, is related to the Gibbs energy of reaction,  $\Delta G_{rxn}$ :



$$K_{eq} = \exp(-\Delta G_{rxn}/RT)$$

Here R is the gas constant and T is the temperature (in K). At room temperature (298K) and for  $\Delta G_{rxn}$  in au, this is given by:

$$K_{eq} = \exp(-1060 \Delta G_{rxn})$$

$\Delta G_{rxn}$  has two components, enthalpy,  $\Delta H_{rxn}$ , and entropy,  $\Delta S_{rxn}$ :

$$\Delta G_{rxn} = \Delta H_{rxn} - T\Delta S_{rxn}$$

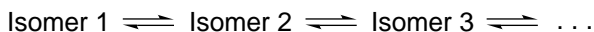
$$\Delta H_{rxn} \approx \Delta E_{rxn} = E_{product\ 1} + E_{product\ 2} + \dots - E_{reactant\ 1} - E_{reactant\ 2} - \dots$$

$$\Delta S_{rxn} = S_{product\ 1} + S_{product\ 2} + \dots - S_{reactant\ 1} - S_{reactant\ 2} - \dots$$

Often, the entropy contribution is small and can be neglected. Further assuming that  $\Delta H_{rxn} \approx \Delta E_{rxn}$ , equilibrium constants can then be estimated according to the Boltzmann equation:

$$K_{eq} \approx \exp(-\Delta E_{rxn}/RT) = \exp(-1060 \Delta E_{rxn})$$

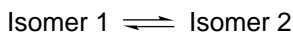
A particularly important “reaction” involves the interconversion of isomers:



Given that the isomers are of similar structure, the  $\Delta S_{rxn}$  would be expected to be small, and the approximate Boltzmann equation based on energy may be used to establish the equilibrium composition of a mixture of isomers:

$$\% \text{ Isomer } i = \frac{100 \exp(-1060 E_{\text{Isomer } i})}{\sum_k \exp(-1060 E_{\text{Isomer } k})}$$

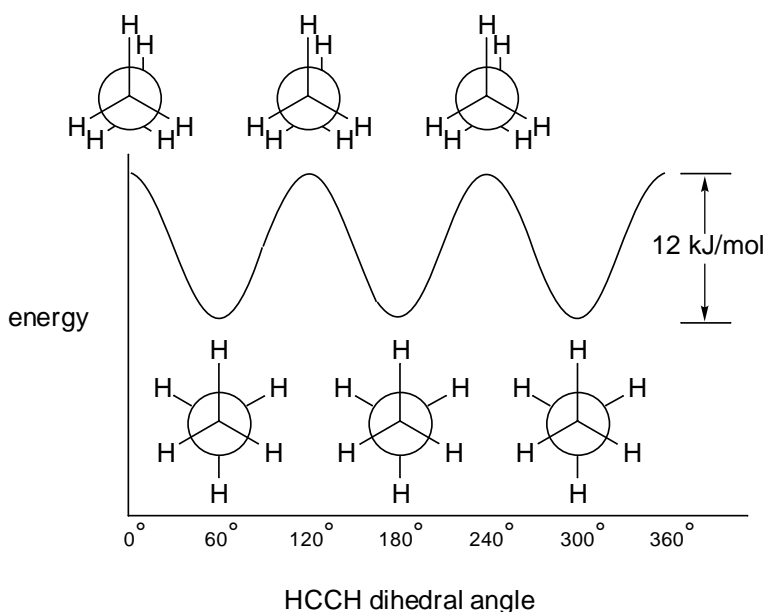
Isomer energies,  $E_{\text{isomer}}$ , are given in atomic units relative to the energy of the lowest-energy isomer. Where only two isomers are involved, the equilibrium composition is given by:



$$\frac{[\text{Isomer 1}]}{[\text{Isomer 2}]} = \exp[-1060 (E_{\text{isomer1}} - E_{\text{isomer2}})]$$

## Molecular Shape

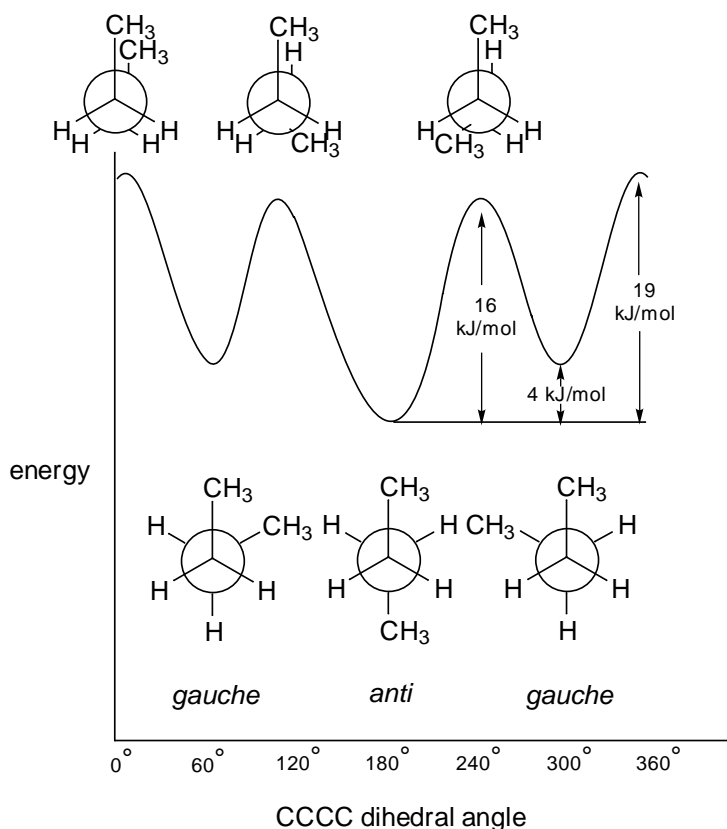
The energy of ethane changes with the dihedral angle around the carbon-carbon bond.



Full 360° rotation leads to three identical “staggered” structures that are energy minima, and three identical “eclipsed” structures that are energy maxima. The difference in energy between eclipsed and staggered structures of ethane, termed the barrier to rotation, is known experimentally to be around 12 kJ/mol. Note, that any physical measurements on ethane pertain only to its staggered structure. Eclipsed ethane is not a stable molecule and it is not possible to isolate it or to measure its properties.

Open “*ethane rotation*” in the *modeling topics* directory. The image that appears is one frame in a sequence depicting rotation about the carbon-carbon bond in ethane. Click on the ◀ and ▶ keys at the bottom left of the screen to look at other frames. Examine the plot of energy vs. HCCH dihedral angle to verify that the staggered structures correspond to minima on the energy plot and that the eclipsed structures correspond to maxima. Click on the ▶ key to animate the sequence. Close “*ethane rotation*” when you are finished.

Closely related in the change in energy with change in the dihedral angle involving the central carbon-carbon bond in *n*-butane.



Here too there are three energy minima, corresponding to staggered structures, and three energy maxima, corresponding to eclipsed structures. Unlike ethane, however, the three structures in each set are not identical. Rather, one of the minima, corresponding to a dihedral angle of 180° (the *anti* structure), is lower in energy and distinct from the other two *gauche* minima (dihedral angles around 60° and 300°), that are identical. Similarly, one of the energy maxima corresponding to a dihedral angle of 0°, is distinct from the other two maxima (with dihedral angles around 120° and 240°), that are identical. As with ethane, eclipsed forms of *n*-butane do not exist. Unlike ethane, which is a single compound, any sample of *n*-butane is made up of two distinct compounds, *anti n*-butane and *gauche n*-butane. The relative abundance of the two compounds as a function

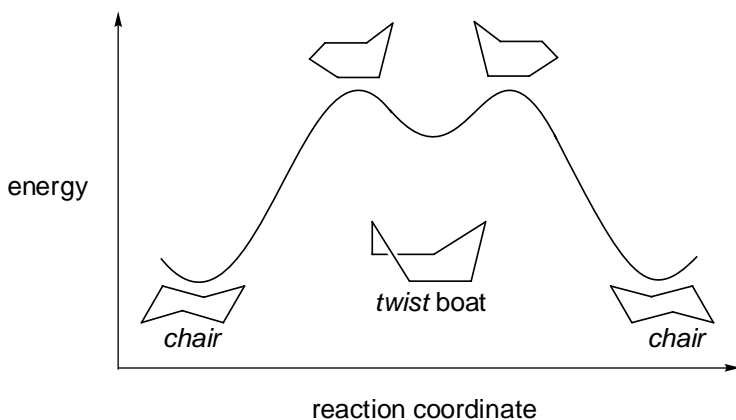
of temperature is given by the Boltzmann equation (see “*Energy and Thermodynamics*” earlier in this chapter).

Open “*n-butane rotation*” in the *modeling topics* directory. The image that appears is one frame of a sequence depicting rotation about the central carbon-carbon bond in *n*-butane. Click on the ◀ and ▶ keys at the bottom left of the screen to look at other frames. Examine the plot of energy vs. CCCC dihedral angle to verify that the staggered structures correspond to minima on the energy plot and that the eclipsed structures correspond to maxima. Verify that the *anti* structure is lower in energy than the *gauche* structure. Click on ▶ to animate the sequence. Close “*n-butane rotation*” when you are finished.

The “important” geometrical coordinate in both ethane and *n*-butane may clearly be identified as a torsion involving one particular carbon-carbon bond. This is an oversimplification, as bond lengths and angles also change during rotation around the carbon-carbon bond.

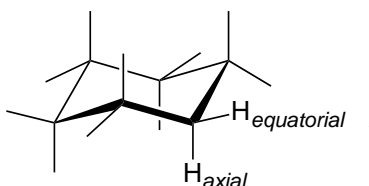
Open “*n-butane angle variation*” in the *modeling topics* directory. Examine the plot of the CCC bond angle vs. CCCC dihedral angle. Note that the bond angle is insensitive to conformation except in the region of the *syn* ( $0^\circ$  torsional angle) structure where it has opened up by several degrees. Close “*n-butane angle variation*” when you are finished.

It is often impossible to identify a “simple” geometrical coordinate to properly describe conformational change. An important example of this is provided by the ring inversion of cyclohexane.



The energy surface for ring inversion, like that for rotation in *n*-butane, contains three distinct energy minima, two identical structures identified as “chairs”, and one of higher energy identified as a “twist boat”. However, the energy difference between the chair and twist boat structures is large (around 23 kJ/mol) and only the former can be observed at normal temperatures. The twist boat alternative to chair cyclohexane is unfamiliar to many chemists.

All six carbons are equivalent in the chair form of cyclohexane, but the hydrogens divide into two sets of six equivalent “*equatorial*” hydrogens and six equivalent “*axial*” hydrogens.



Only one kind of hydrogen can normally be observed, which means that *equatorial* and *axial* positions interconvert via some low-energy process. This is the ring inversion process just described. As shown in the reaction coordinate diagram on the previous page, the overall process actually occurs in two steps, with a twist boat structure as a midway point (an “intermediate”). The two (equivalent) energy maxima leading to this intermediate adopt structures in which five of the ring carbons lie (approximately) in one plane.

Open “*cyclohexane ring inversion*” in the *modeling topics* directory. The image that appears is one frame in a sequence depicting ring inversion in cyclohexane. Click on the ◀ and ▶ keys at the bottom left of the screen to look at other frames. Examine the plot of energy vs. the “frame number” (position along the reaction coordinate) to verify that the three minima on the energy plot correspond to staggered structures and that the two maxima correspond to eclipsed structures. Also, verify that the twist boat structure is higher in energy than the “chair” structures. Click on ▶ to animate the sequence. Note that the overall ring inversion occurs in two distinct steps, the first leading up to the “twist” boat and the second leading away from it. Close “*cyclohexane ring inversion*” when you are finished.

## Infrared Spectra

Molecules vibrate in response to their absorbing infrared light. Absorption occurs only at specific wavelengths, which gives rise to the use of infrared spectroscopy as a tool for identifying chemical structures. The vibrational frequency is proportional to the square root of a quantity called a “force constant” divided by a quantity called the “reduced mass”. The force constant reflects the “flatness” or “steepness” of the energy surface in the vicinity of the energy minimum. The steeper the energy surface, the larger the force constant and the larger the frequency. Large force constants (and large frequencies) will be associated with molecular distortions that are “difficult”, for example, stretching strong bonds, while small force constants (frequencies) will be associated with “easy” distortions, for example, torsions around single bonds.

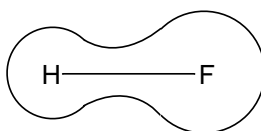
Open “*acetone*” in the *modeling topics* directory and select **Spectra** from the **Display** menu. The dialog that results contains all the vibrational frequencies for acetone. One after the other, *click* on the frequencies to display the associated vibrational motions. The smallest frequency is associated with torsional motion of the methyl rotors. The largest frequency is associated with stretching motion of CH bonds. Methyl torsion is characterized by a flat potential energy surface (small force constant), while CH stretching is characterized by a steep potential energy surface (large force constant). Leave acetone on screen.

The reduced mass reflects the masses of the atoms involved in the vibration. The smaller the reduced mass, the larger the frequency.

Open “*perdeuteroacetone*” from the *modeling topics* directory. This contains frequencies for acetone in which all six hydrogens have been replaced by deuteriums. While the vibrational motions in acetone and perdeuteroacetone are identical, the vibrational frequencies for perdeuteroacetone are consistently smaller than those for acetone. This follows from the fact that the mass of deuterium is larger than that of hydrogen. Close both “*acetone*” and “*perdeuteroacetone*” when you are finished.

## Atomic Charges

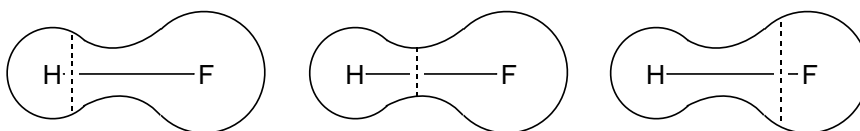
What is the charge on an atom in a molecule? Surprisingly, there is no simple answer. While it is easy to assign a total charge on a molecule, assigning a charge for an individual atom requires accounting both for the nuclear charge and for the charge of any electrons “associated” with the atom. The nuclear charge is simply the atomic number, but it is not obvious how to partition the electrons among the atoms in a molecule. Consider, for example, the electron distribution in hydrogen fluoride.



Here, the surrounding “line” is a surface corresponding to particular value of the electron density, say that corresponding to a van der Waals surface and enclosing a large fraction of the molecule’s electrons. In this picture, the surface has been drawn to suggest that more electrons are associated with fluorine than with hydrogen. This is entirely reasonable, given the known polarity of the molecule, i.e.,  $\delta^+\text{H}-\text{F}\delta^-$ , as evidenced by the direction of its dipole moment.



It is, however, not obvious how to divide this surface between the two nuclei. Is one of the divisions shown below better than the others?



Clearly not! In fact, there is no “best” division simply because it is not possible to say how many electrons “belong” to each atom.

Despite their ambiguity, charges are part of the everyday vocabulary of chemists. Most common are so-called “formal charges” which follow from a “back-of-the-envelope” recipe:

$$\text{formal charge} = \text{number of valence electrons} - \text{number of lone-pair electrons} - \text{number of bonds (single bond equivalents)}$$

For many (uncharged) molecules, it is possible to write a Lewis structure that will lead to formal charges for all atoms of zero. For these molecules, it is clear that formal charges are of no use in differentiating among different atoms.

Several alternatives to formal charges have been proposed. Among the most widely used are so-called electrostatic charges. These are obtained by fitting the energy that a “test” charge feels as it approaches a molecule, to a model in which the molecule’s nuclei and electrons are replaced by atom centered charges. Like formal charges, electrostatic charges are not unique. However, they are based on a qualitatively correct description of molecular structure and would be expected to yield a “realistic” portrayal of charge distributions.

## Electrostatic Potential Maps

The charge distribution in a molecule can provide critical insight into its physical and chemical properties. For example, molecules that are charged, or highly polar, tend to be water-soluble and “stick together” in specific geometries, such as the “double helix” in DNA. Chemical reactions are also associated with charged sites, and the most highly-charged molecule, or most highly-charged site in a molecule, is often the most reactive. Positively-charged sites invite attack by bases and nucleophiles, while negatively-charged sites are usually targeted by acids and electrophiles.

SpartanModel allows you to describe molecular charge distributions using a quantity termed the “electrostatic potential”. This is the hypothetical energy that a positive test charge “feels” at some location around a molecule. If the charge is placed in a region of excess positive charge (an electron-poor region), the charge-molecule interaction will be repulsive and the electrostatic potential will be positive. Conversely, if the charge is placed in a region of excess negative charge (an electron-rich region), the interaction will be attractive and the electrostatic potential will be negative.



A good way to show the electrostatic potential is to “map” it onto a surface which depicts the “size” of the molecule. One can use either a space-filling (CPK) model or employ a surface of electron density. As shown for benzene, the two surfaces are quite similar.

Open “*benzene space-filling, electron density*” in the *modeling topics* directory. The image on the left corresponds to a space-filling model for benzene, while that on the right corresponds to an electron density surface obtained from a quantum mechanical calculation. Close “*benzene space-filling, electron density*” when you are finished.

The value of the electrostatic potential at the surface is conveyed using different colors to represent the different values of the electrostatic potential. SpartanModel uses the color red to depict regions of most negative (least positive) electrostatic potential, and the color blue to depict regions of most positive (least negative) electrostatic potential. Intermediate colors represent intermediate values of the electrostatic potential, so that potential increases in the order: red < orange < yellow < green < blue.

The electrostatic potential maps provided in Spartan files in the *modeling topics* directory differ in three ways from those generated from SpartanModel’s database. First, they are based on actual electron density surfaces and not “smoothed out” van der Waals surfaces. Second, they are all calculated “exactly” and not approximated from atomic charges. Third, the maps generated from the database are all on the same scale which is symmetrical around “zero potential” (green color), whereas the scale of the maps from Spartan files have been adjusted for best presentation.

An electrostatic potential map for benzene conveys both the molecule’s size and shape as well as its charge distribution in a compact and easy to interpret manner. The faces of the ring, the  $\pi$  system, are “red” (electron rich), while the periphery of the molecule and especially the hydrogens are “blue” (electron poor).

Open “*benzene electrostatic potential map*” in the *modeling topics* directory. The map for benzene clearly distinguishes between the  $\sigma$  and the  $\pi$  systems insofar as their likely interaction with an electrophile. Close “*benzene electrostatic potential map*” when you are finished.

Electrostatic potential maps can be a very powerful tool for thinking about a variety of chemical and physical phenomena. For example, an electrostatic potential map for water suggests that two water molecules will be attracted to each other in a way that brings a hydrogen in one molecule close to the oxygen in the other molecule. This type of intermolecular bonding is called a “hydrogen bond”.

Open “*water dimer*” in the *modeling topics* directory. For clarity, this map is based on an electron density surface that is much smaller than that chosen to represent a space-filling model. Switch to a transparent or mesh model to see the underlying molecular skeleton. For Windows, *click* on the graphic and select the appropriate entry from the menu that appears at the bottom right of the screen. For Macintosh, position the cursor over the graphic, hold down either the left or the right button and select from the menu that appears. Note that the electron-poor hydrogen of one water is positioned near the electron-rich oxygen of the other water. Close “*water dimer*” when you are finished.

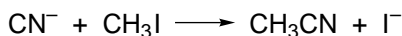
Electrostatic potential maps can also serve as useful predictors of chemical reactivity. For example, the nitrogens in both ethylamine and formamide are bonded to two hydrogens and one carbon, suggesting that the two molecules might be expected to exhibit similar chemical reactivity. Electrostatic potential maps tell a different story. The map for ethylamine shows a region of negative potential that coincides with the location of the lone-pair. This nitrogen is a good electron donor and can act as a base or nucleophile. On the other hand, the map for formamide suggests that while the oxygen atom might act as an electron donor, the nitrogen atom will not. The nitrogen atoms in these compounds are very different.

Open “*ethylamine, formamide*” in the *modeling topics* directory. Note that the nitrogen in ethylamine is electron rich in contrast to that in formamide, where only the oxygen is electron rich. Close “*ethylamine, formamide*” when you are finished.



Electrostatic potential maps for *n*-butyl cation,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^+$ , and *tert*-butyl cation,  $(\text{CH}_3)_3\text{C}^+$ , reveal that these reactive intermediates differ in significant ways. The electrostatic potential for *n*-butyl cation varies over a wider range, and the positive charge is clearly associated with the terminal “CH<sub>2</sub>” group. The map for *tert*-butyl cation, by comparison, shows a much smaller range of potentials. The central carbon is positively charged as its structure drawing suggests, but the potential never becomes as positive as that in *n*-butyl cation. *n*-Butyl cation should be the more reactive of the two.

Open “*n-butyl cation, tert-butyl cation*” in the *modeling topics* directory. Note that the positive charge in the *tert*-butyl cation is delocalized over the molecule to a much greater extent than that in the *n*-butyl cation. Close “*n-butyl cation, tert-butyl cation*” when you are finished.

Electrostatic potential maps for the sequence of structures in the S<sub>N</sub>2 reaction,



clearly show a shift in negative charge from cyanide to iodide. The map corresponding to the energy maximum (the so-called transition state) shows that negative charge is spread over all the atoms (it is “delocalized”). Perhaps the most interesting aspect of the sequence follows from a comparison of CN<sup>−</sup> in the “reactants” and I<sup>−</sup> in the “products”. The former shows greater extremes in the negative potential than the latter. This means that iodide better distributes the excess negative charge better than cyanide. Iodide is the better “leaving group” and one should conclude that the reaction as written is thermodynamically favorable (“*exothermic*”).

Open “*Sn2 cyanide+methyl iodide*” in the *modeling topics* directory. One “frame” of a sequence of electrostatic potential maps for the S<sub>N</sub>2 reaction will appear. Animate by *clicking* on  at the bottom left of the screen (stop the animation by *clicking* on ). Note that the negative charge (red color) flows smoothly from cyanide to iodide during the reaction. Note also, that cyanide (as the reactant) is “more red” than iodide (as the product). Switch to mesh or transparent map to “see” the making and breaking of “bonds”. Close “*Sn2 cyanide+methyl iodide*” when you are finished.

# Chapter 4

## Activities

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This section comprises a selection of “hands-on” activities for individual or group study. Each activity is intended to illustrate how molecular modeling can contribute to the understanding of a particular topic. Most of the activities are “open ended”, meaning that other examples could be used in place of those chosen here. The activities are brief and “focused”, and most can be completed in a few minutes. Where appropriate, they contain “hints” on using SpartanModel, but a working knowledge of the basic operation of the program is assumed. Students should complete the tutorials provided in **Chapter 2** before attempting this material.

Most activities draw on results in SpartanModel’s database.\* A few that involve sequences of molecules and/or graphical surfaces not available in the database require Spartan files available in the *activities* directory. Finally, some activities rely only on SpartanModel’s builder.

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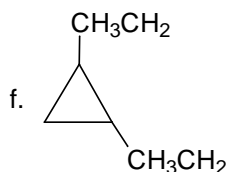
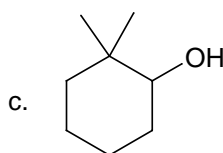
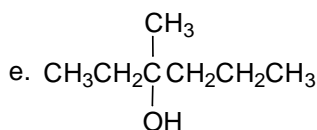
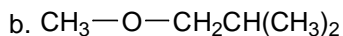
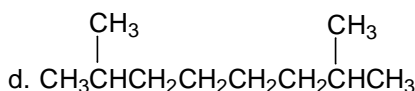
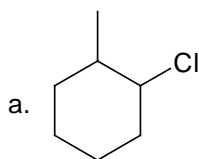
\* Molecules may be retrieved either by structure or by name. Structure retrieval requires that the molecule be built with the proper bond types and (in the case of an ion) that the charged atom be designated. This may be problematic for some molecules (for example, transition states) and is certainly tedious for others. In addition, only the lowest-energy conformer and only one enantiomer may be retrieved by structure. Name retrieval requires knowledge of the name associated with the molecule in the database. With few exceptions, systematic names are used throughout. Note, however, that the terms *cis* and *trans* have been used in lieu of Z and E. Conformer and enantiomer designations follow the molecule name (for example, *n*-butane *anti* conformer). Finally, transition states are named by designating the reactants followed by the phrase “transition state” (for example, cyclopentadiene + acrylonitrile transition state).

**Nomenclature (Use *SpartanModel*'s database to check your results for 1-3.)**

1. Build models of the following compounds:

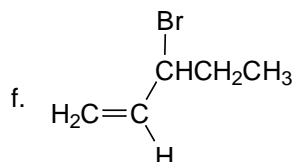
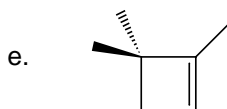
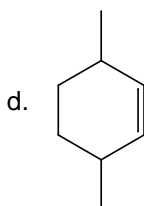
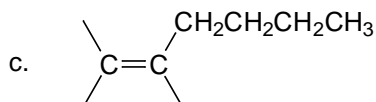
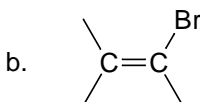
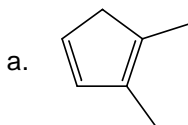
- |                            |                                  |
|----------------------------|----------------------------------|
| a. 1-methylcycloheptanol   | d. cyclopropylcyclohexane        |
| b. 3-ethoxy-2-methylhexane | e. 5-chloro-2-methyloctane       |
| c. dimethylamine           | f. 3-ethyl-2,2,3-trimethylhexane |

2. Name the following compounds:



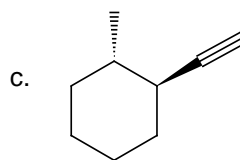
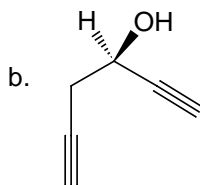
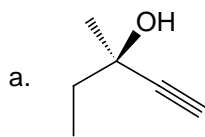
Are any of the structures ambiguous? If so, draw and name all possible isomers.

3. Name the following compounds:

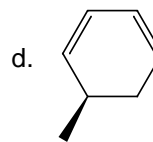
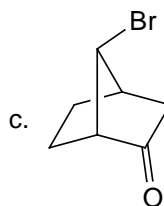
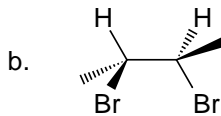
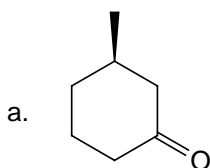


Are any of the structures ambiguous? If so, draw and name all possible isomers.

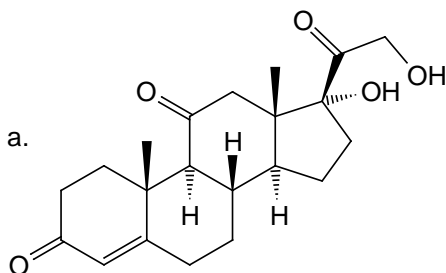
4. Assign R/S labels to all chiral centers in the following compounds:



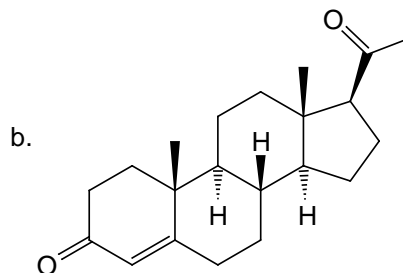
5. Assign R/S labels to all chiral centers in the following compounds:



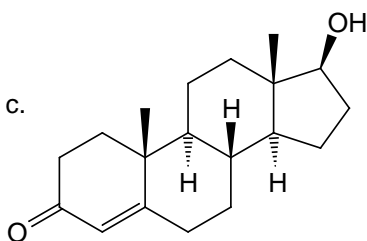
6. Assign R/S labels to all chiral centers in the following compounds:



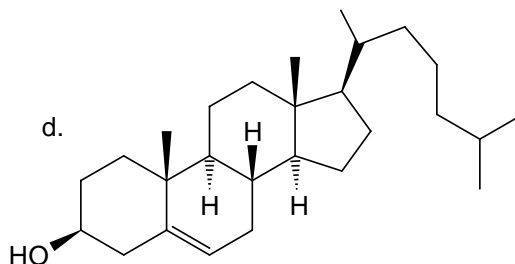
Cortisone



Progesterone

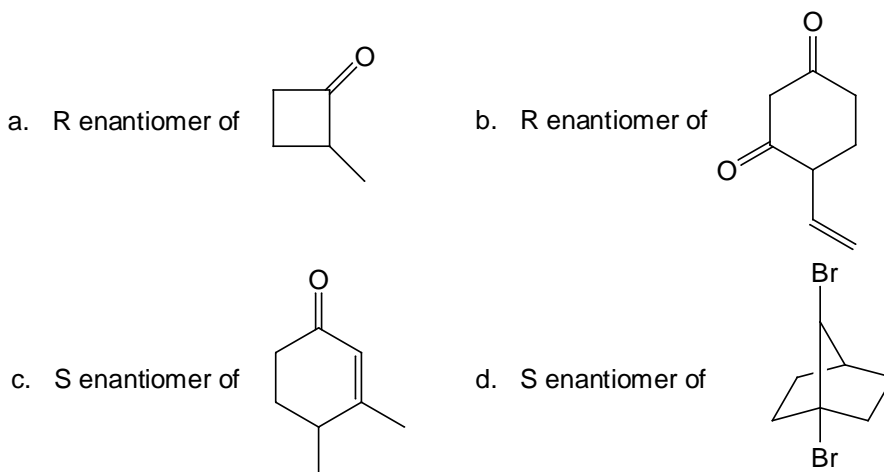


Testosterone

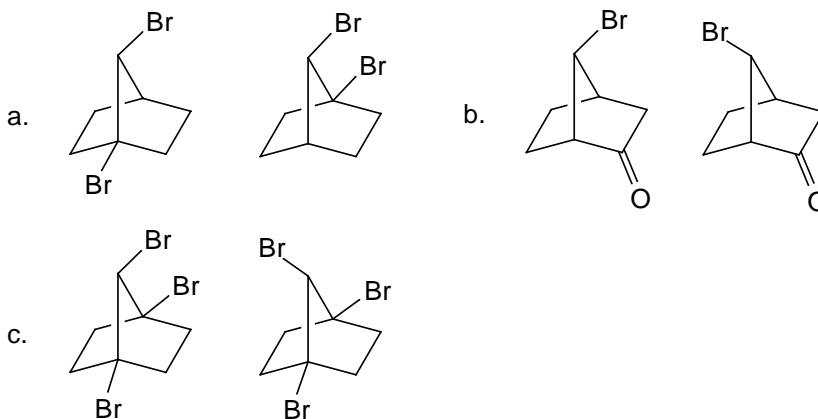


Cholesterol

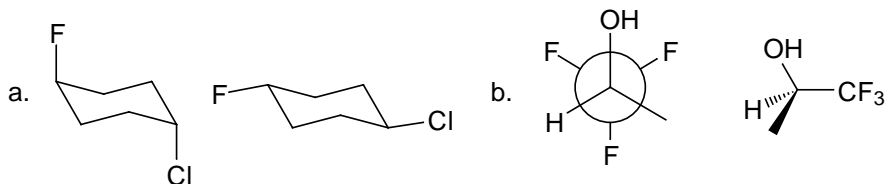
7. Sketch:



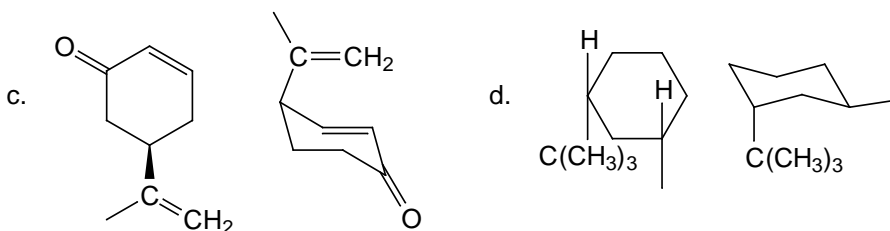
8. What is the relationship between the structures in each of the pairs drawn below: same molecule, enantiomers, diastereomers? Use molecular mechanics strain energies to help you decide.



9. What is the relationship between molecules in each pair: same molecule, enantiomers, diastereomers?





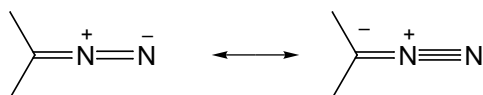


Use molecular mechanics strain energies to help you decide.

10. Draw all four forms of 2-chloro-3-fluorobutane and assign R/S chirality. Next, build the four structures according to your drawings and R/S labels to verify your assignments. Put all four structures into the same conformation and minimize the strain energy of each. How many different sets of strain energies are there? Are molecules with the same strain energy enantiomers (non-superimposable mirror images) or do they have a different relationship to each other? Try to superimpose them to find out what is the relationship between molecules with different strain energies.
11. Draw all four forms of 2,3-difluorobutane and assign R/S chirality. Next, build all the four structures according to your drawings and attach R/S labels to verify your assignments. Put all four structures into the same conformation and minimize the strain energy of each. How many different sets of strain energies are there? Are molecules with the same strain energy enantiomers or do they have a different relationship to each other? Try to superimpose the molecules to find out. What is the relationship between molecules with different strain energies?

## Structure and Bonding

- 2p atomic orbitals are higher in energy and extend further from carbon than the corresponding 2s orbital. Therefore, the higher the “fraction of 2p” in a hybrid, the further it will extend from carbon, that is,  $sp^3$  hybrids will extend further than  $sp^2$  hybrids, which in turn will extend further than  $sp$  hybrids. As a consequence, bonds made using  $sp^3$  hybrids should be longer than analogous bonds made using  $sp^2$  hybrids, which should in turn be longer than bonds made using  $sp$  hybrids.
  - Measure CH bond lengths in ethane, ethylene and acetylene. Is the ordering consistent with the use of different hybrids in the three compounds? Elaborate. Using the CH bond length in ethane as a standard, what is the % reduction in CH bond lengths in ethylene? In acetylene? Is there a rough correlation between % reduction in bond length and % of 2p in the hybrid?
  - Measure the CH bond length in cyclopropane. Based on your experience in the previous part, would you say that the carbons are  $sp^3$  hybridized? Elaborate. Repeat for cyclobutane, cyclopentane and cyclohexane. Which, if any, of the four cycloalkanes might be expected to be different chemically?
- Diazomethane is usually described as a composite of two resonance structures, both of which involve separated charges.



Compare the geometry of diazomethane with those of molecules incorporating “normal” CN single and double bonds and NN single double and triple bonds. Which resonance structure provides the better description or are both required for adequate representation?

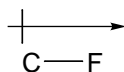
- Molecular geometry depends not only on the constituent atoms, but also on the total number of electrons. Molecules with the same stoichiometry but with varying numbers of electrons may

prefer different geometries. Compare geometries of 2-methyl-2-propyl cation, radical and anion.

To build, first make 2-methyl propane, and delete a hydrogen (free valence) from the 2 position. Formal charge needs to be set to 1 and -1 for the cation and anion, respectively.

What changes, if any, do you observe with increasing number of valence electrons? What is the origin of these changes?

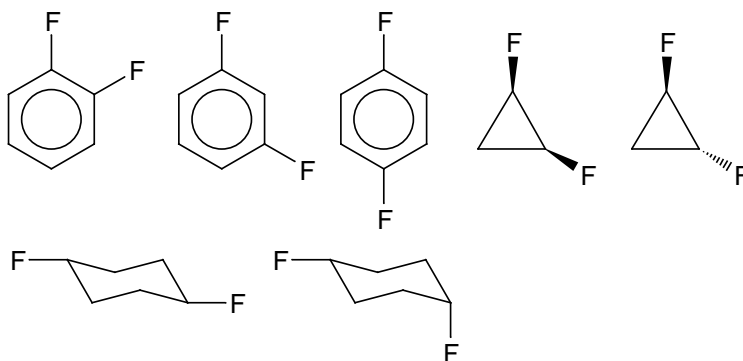
4. The dipole moment is related to the charge distribution in a molecule. Chemists often think about the dipole moment in terms of bond dipoles, that is, local dipoles directed along bonds. For example, a bond between carbon and fluorine will possess a bond dipole with the fluorine at the negative end.



The dipole moment arises from a vector sum of the individual bond dipoles. It depends not only on the magnitude of the individual bond dipoles but also on how they are oriented relative to each other. For example, CF bond dipoles reinforce in *cis*-1,2-difluoroethylene, leading to a finite dipole moment, but cancel in *trans*-1,2-difluoroethylene, leading to a zero dipole moment.



- a. Which molecules will have a non-zero dipole moment?



- b. Explain why 1,2-dichloroethane has a finite dipole moment.  
Hint: review *Molecular Shape* in **Chapter 3**.
5. Examine the direction of the dipole moment in the six heteronuclear diatomics X-Y, where X, Y are halogens (F, Cl, Br, I). Given that the more electronegative element will be at the negative end of the dipole, order the electronegativities of the halogens. Is the ordering you obtain the same as usually given, i.e.,  $F > Cl > Br > I$ ?
  6. Examine the direction of dipole moment in compounds  $X-C\equiv C-Y$  where X, Y are (different) halogens. Do you reach the same conclusions as in the previous problem with regard to the ordering of electronegativities of the halogens?
  7. Examine the direction of the dipole moment in compounds  $X-CN$ , where X is halogen (F, Cl, Br, I). Given that the more electronegative “group” (CN or X) will be at the negative end of the dipole, what can you say about the electronegativity of the cyanide group?
  8. Examine the direction of the dipole moment in  $X-NO_2$  compounds ( $X = F, Cl, Br, I$ ). What can you say about the electronegativity of the nitro group?
  9. What is the charge on hydrogen in a molecule? We think of hydrogen as “neutral” or nearly so in hydrocarbons, give it a positive charge in a molecule like hydrogen fluoride and a negative charge in a molecule like sodium hydride. This is conveyed in the underlying chemical nomenclature “sodium hydride”, meaning like  $H^-$ .
    - a. Measure the charge on hydrogen in lithium hydride (LiH), beryllium hydride ( $BeH_2$ ; linear), borane ( $BH_3$ ; trigonal planar), methane, ammonia, water and hydrogen fluoride. For which molecule does the hydrogen most closely approach a proton (charge = 1)? How close does it get? For which molecule does hydrogen most closely approach hydride (charge = -1)? How close does it get? For which molecule is the hydrogen closest to neutral (charge = 0)? Is there a rough correlation between the calculated charges on hydrogen in

the first-row hydrides and the difference in electronegativity between hydrogen and the first-row element?

H	2.2	B	2.0	O	3.4
Li	1.0	C	2.6	F	4.0
Be	1.6	N	3.0		

- b. Examine the electrostatic potential map for each of the molecules. This reflects the distribution of charge, the color red indicating excess negative charge and the color blue indicating excess positive charge. “Measure” the maximum (or minimum) value of the electrostatic potential at hydrogen in each of the compounds.

Select **Properties** from the **Display** menu. *Click* on the region of hydrogen that is most positive (or most negative). The value of the potential will be reported in the **Surface Properties** dialog.

Is there a correlation between maximum (or minimum) potential at hydrogen and difference in electronegativity between the two atoms which make up the bond?

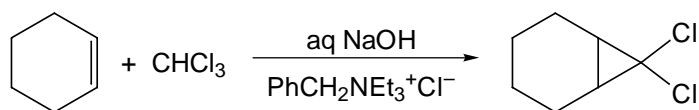
10. What is the charge on the methyl group in methyl fluoride? In methyl lithium? Are the charge distributions well represented by electrostatic potential maps for the two molecules? Which molecule more closely approaches its “ionic dissociation limit”? Is the difference in electronegativities between C and F/Li larger in this molecule than in the other?
11. Assign formal charges for dimethyl sulfide, dimethylsulfoxide and dimethylsulfone. Measure the charge at sulfur in each of the three compounds. Does it change from one molecule to another? If so, for which molecule is sulfur the least charged? The most charged? Do the measured charges differ from formal charges? Elaborate. Compare the three electrostatic potential maps recalling that colors near “red” indicate excess negative charge and that colors near “blue” indicate excess positive charge. On the basis of the measured charges and electrostatic potential maps, draw

appropriate Lewis structures (or sets of Lewis structures) for the three molecules.

12. Chromatography is a widely used technique for separating mixtures of organic compounds. While there are many different experimental procedures, all operate on the same principle. The mixture to be separated is passed over an immobile (or stationary) phase, typically rich in polar or charged groups. The more polar molecules in the mixture will tend to “stick” more strongly to this stationary phase than the less polar molecules, and, will therefore pass through the stationary phase more slowly.

Sulfides,  $\text{RSR}'$ , oxidize first to sulfoxides,  $\text{RSOR}'$ , and then to sulfones  $\text{RSO}_2\text{R}'$ . Using dipole moments as a measure of polarity, predict the order that the three components (including starting material) will elute. Do your conclusions vary as you move from small R groups, such as methyl, to larger groups, such as cyclohexyl, or from alkyl to aryl groups?

13. A phase transfer catalyst acts to assist transfer of molecules from a polar (“aqueous”) solvent to a non-polar (“organic”) solvent. For example, cyclohexene, chloroform and aqueous NaOH react only when combined with a phase-transfer catalyst, such as benzyltriethylammonium chloride. The organic reagents stay in the organic layer (chloroform), but hydroxide is able to migrate to the organic layer if accompanied by the catalyst. Deprotonation of chloroform by hydroxide leads to dichlorocarbene,  $\text{CCl}_2$ , which in turn adds to the double bond.



Examine the electrostatic potential map for benzyltriethylammonium ion. Which parts facilitate water solubility? Which parts facilitate solubility in chloroform?

14. Is “buckyball” (Buckminsterfullerene or  $\text{C}_{60}$ ) able to encapsulate molecules and act as an “inert” delivery system? Put another way,

how much “space” is available at its center? Examine the van der Waals surface to tell.

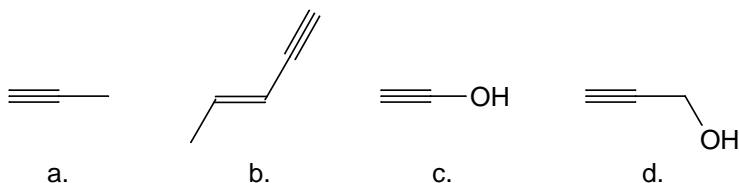
Turn on the electrostatic potential map, select **Properties** from the **Display** menu and *uncheck* “Property” inside the **Surface Properties** dialog. Switch to a **Mesh** surface. First, select (*click* on) the surface. On Windows, select **Mesh** from the **Style** menu at the bottom right of the screen. On Macintosh, position the cursor over the surface while holding down either the right or left button and select **Mesh** from the menu that appears. Notice that there are actually two van der Waals surfaces. Molecules are not only permitted to be “outside” the outer surface, but also “inside” the inner surface.

Build methane, ethane, propane, etc. and display as space-filling models. Drag each inside buckyball. Which is the largest that is able to fit comfortably inside?

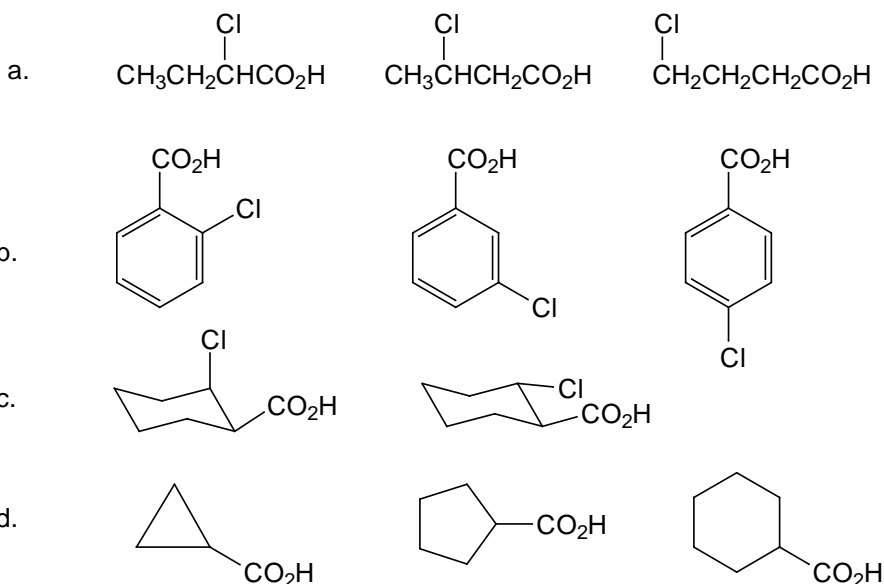
## Acids and Bases

1. Display electrostatic potential maps for ethane, ethylene and acetylene. For which are the hydrogens most positive? For which are they least positive? Is the ordering what you expected based on the known acidities of hydrocarbons: alkanes < alkenes < alkynes?
2. Display electrostatic potential maps for propane and cyclopropane. Are the hydrogens in cyclopropane more or less positive than the (most positive) hydrogen in propane? What does this result say about the acidity of cyclopropane relative to that of propane?
3. Display electrostatic potential maps for acetylene, propyne and 3,3,3-trifluoropropyne. For which is the hydrogen (on the alkyne) most positive? For which is it least positive? What does this say about the role of methyl and trifluoromethyl groups in affecting the acidity of acetylene? Which group has the stronger influence?
4. Is the energy required to deprotonate acetylene (leading to acetylide anion) less or greater than the energy required to deprotonate ethylene (leading to vinyl anion)? Which molecule (acetylene or ethylene) is the stronger acid?

5. What anion results from deprotonation of the following alkynes?



6. Use electrostatic potential maps to rank the compounds in each of the following sets in order of increasing acidity.

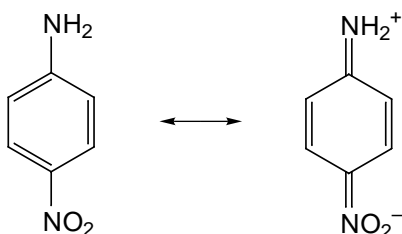


7. Molecules that are structurally quite similar often differ in acid strength by many orders of magnitude. For example, benzoic acid is moderately strong ( $\text{pK}_a = 4.2$ ), phenol is weak ( $\text{pK}_a = 9.9$ ) and cyclohexanol is very weak ( $\text{pK}_a = 18$ ). The difference is usually described in terms of the ability of the acid (the conjugate base) to delocalize charge.

Compare atomic charges and electrostatic potential maps for NH protonated imidazole and N protonated imidazole. In which ion is the positive charge more delocalized? Compare carbon-nitrogen bond distances in each ion to those in imidazole as a standard. Draw whatever Lewis structures are needed to describe each ion's geometry and charge distribution.

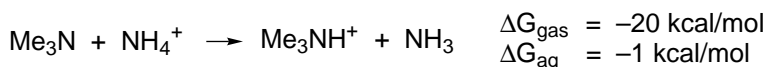


8. Aniline is known to be a significantly weaker base than the corresponding alkylamine, cyclohexylamine. Is aniline actually a nitrogen base or does protonation occur instead on the aromatic ring? Compare energies of both nitrogen and carbon (*para* to the amino group) protonated aniline. Which is more stable? Does your result change from gas phase to water?
9. The fact that *p*-nitroaniline is a weaker base than aniline is usually explained by invoking “push-pull” resonance structures.



Compare the structure of *p*-nitroaniline with those of aniline and nitrobenzene. Is there evidence for the involvement of push-pull resonance structures? Does *m*-nitroaniline show similar geometrical changes?

10. Trimethylamine is much more basic than ammonia in the gas phase, whereas in water, the two are of roughly equal strength.



Examine ammonium and trimethylammonium ions. How many acidic hydrogens are there in each ion to coordinate with solvent? Compare hydrogen (NH) charges and electrostatic potential maps for the two ions. For which are the hydrogens more acidic? Based on number and strength of acidic sites, rationalize the change in basicity from the gas phase into water.

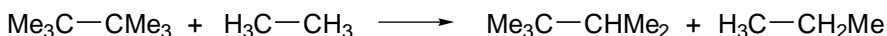
**Alkanes and Cycloalkanes (1 and 2 require you to access files from the activities directory.)**

1. *n*-butane (*activities* directory) shows the variation in the central CC bond length and the total energy for rotation around the central bond. Does the variation in bond length follow the change in energy throughout the rotation? Rationalize your observation. Is the bond length nearly identical or significantly different ( $>0.02\text{\AA}$ ) for the two equilibrium forms of *n*-butane? Is the bond length nearly identical or significantly different between the *anti* form and either or both of the transition states? Elaborate. Is the variation in bond length similar to the variation in CCC bond angle (see *Molecular Shape* in **Chapter 3**)? If not, why not?
2. Compare rotational energy profiles for ethane and 2,2,3,3-tetramethylbutane (*activities* directory). How are they similar and how are they different? Do both systems prefer geometries in which all single bonds are staggered?
3. Build isomers of formula  $\text{C}_7\text{H}_{16}$  and minimize their energies using molecular mechanics. Is there significant variation in the exposed surface area (of a space-filling model) between the different isomers?

Surface area is available from the **Molecule Properties** dialog (select **Properties** from the **Display** menu).

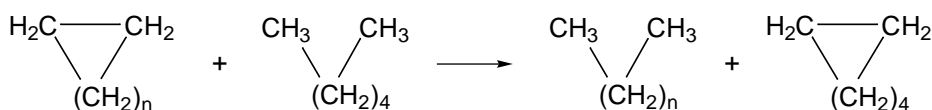
If so, what is the relationship between exposed surface area and extent of branching? Are the more branched isomers smaller or larger than the less branched isomers?

4. The (central) CC bond in 2,2,3,3-tetramethylbutane is known to be significantly ( $\sim 75\text{ kJ/mol}$ ) weaker than the CC bond in ethane. One explanation is that bond cleavage relieves the strain due to crowding of the six methyl groups. A measure of “strain relief” should be provided by the energy of the reaction:



Is the reaction *exothermic* as written? If it is, is the reaction energy large enough to explain the difference in bond strengths between the 2,2,3,3-tetramethylbutane and ethane? If the reaction is *endothermic* or if the energy change is too small, suggest an alternative reason for the difference in bond strengths.

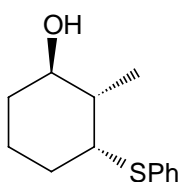
- Small-ring cycloalkanes are less stable than the corresponding *n*-alkanes. This is due to a variety of factors, most notably distortion of CCC bond angles away from idealized tetrahedral values, and eclipsing interactions between CH bonds in cycloalkanes that are unable to assume fully staggered arrangements. The destabilization of small-ring cycloalkanes, relative to *n*-alkanes, referred to as “ring strain”, is provided by the energy of a hypothetical reaction in which one equivalent of hydrogen is added leading to the analogous *n*-alkane, relative to the corresponding hydrogenation of cyclohexane (an unstrained molecule).



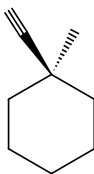
Use this reaction to obtain strain energies for cyclopropane, cyclobutane and cyclopentane. Which is the most strained cycloalkane? Are any of the alkanes less strained than cyclohexane? If so, why?

Obtain the strain energy for cycloheptane. Is it significantly less or greater than the strain energy of cyclohexane? If so, suggest why.

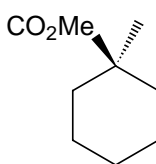
- Use molecular mechanics to assign the preferred conformation of *cis*-1-iodo-4-*tert*-butylcyclohexane. Is the iodine or the *tert*-butyl group *equatorial*? What does this imply about the relative sizes of the two substituents?
- Substituents on cyclohexane generally prefer *equatorial* over *axial* positions, and the conformation of rings with two or more different substituents will be dictated by which substituent exhibits the greatest preference. Use molecular mechanics to assign the preferred conformation of the following substituted cyclohexanes.



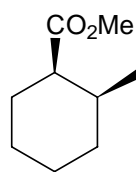
a.



b.



c.

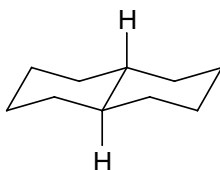


d.

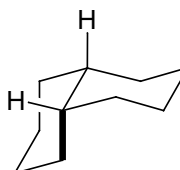
8. The principal component of peppermint oil is an isomer of 2-isopropyl-5-methylcyclohexanol. Assuming that this is the most stable isomer, use molecular mechanics to identify its structure.
9. Which (if any) isomers of dimethylcyclohexane have non-zero dipole moments?
10. Which of the possible bicyclic heptanes with the formula  $C_7H_{12}$  is the most stable? Why are the other isomers less stable? Be certain to examine both *cis* and *trans* stereoisomers, although some may be “impossible” to build.

Repeat for bicyclic octanes with the formula  $C_8H_{14}$ .

11. *Trans* decalin is more stable than *cis* decalin. The reason given is that all CC bonds in the former are *equatorial* while the latter incorporates one *axial* CC bond (drawn in bold).



*trans*-decalin




*cis*-decalin

- a. What is the energy difference between *trans* and *cis*-decalin? Is it similar to that between *trans* and *cis*-1,2-dimethylcyclohexane? If not, why not?
- b. Can you reverse the “native preference” by replacing one or both hydrogens at  $C_9$  and  $C_{10}$  (the ring junctions) by methyl groups? Examine energy differences between *cis* and *trans* isomers for 9-methyldecalin and 9,10-dimethyldecalin.


## Saturated Compounds with Heteroatoms

1. Water incorporates an equal number of electron pairs (hydrogen-bond acceptors) and “acidic hydrogens” (hydrogen-bond donors). It uses these complementary resources fully, to form a network of hydrogen bonds (with each water molecule participating in up to four hydrogen bonds).
  - a. Build a cluster of water molecules and display hydrogen bonds.

Select  $\text{sp}^3$  oxygen () in the organic model kit, hold down the **Insert** key (**option** key on Macintosh) and *click* repeatedly at different locations on the screen. Turn the cluster every few molecules to obtain a three-dimensional structure. Continue until the cluster has at least 30-40 water molecules in it. Minimize.


Examine the water molecules in “the middle” of the cluster. Are these involved in the “maximum” number of hydrogen bonds? Display the water cluster as a space-filling model. Is there much empty space in liquid water?

- b. Add a molecule of ammonia into the center of the water cluster and minimize the energy.

Enter the builder with the water cluster (**Add Fragment** from the **Build** menu), select  $\text{sp}^3$  nitrogen () , hold down the **Insert** key (**option** key on Macintosh) and *click* in the middle of the cluster.

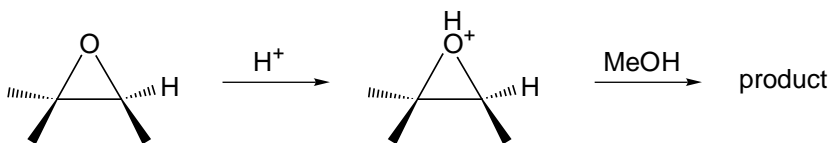
How many hydrogen bonds are there to the ammonia molecule that you added? On average, how many hydrogen bonds are there to the water molecules immediately surrounding the ammonia? Does the situation appear to be similar or different from that for the “pure” water cluster? Has the cluster noticeably expanded or contracted in the vicinity of ammonia? (Look at a space-filling model.) Would you expect water to dissolve ammonia? Elaborate.

- c. Replace ammonia by methane and minimize the energy.

Enter the builder with the cluster-ammonia system, select  $sp^3$  carbon () and *double click* on the nitrogen of ammonia.

Has the cluster noticeably expanded or contracted in the vicinity of methane? Rationalize your result in terms of changes in hydrogen bonding (relative to the “pure” water cluster). Would you expect water to dissolve methane? Elaborate.

- Examine the electrostatic potential map of water. In very rough terms, what percentage of the surface is “negative” (red color), what percentage is “positive” (blue color) and what percentage is neutral (green color)? Next, examine electrostatic potential maps for methanol, ethanol, propanol, 1-pentanol, 1-heptanol and 1-decanol. Divide the surface for each into negative, positive and neutral regions. Predict which of the alcohols is likely to be most water soluble and which is likely to be least water soluble.
- Explain the difference in boiling points of ethylamine ( $17^\circ\text{C}$ ) and ethanol ( $79^\circ\text{C}$ ) in terms of hydrogen bonding. (Examine hydrogen-bonded dimers and compare hydrogen-bond energies.)
- Examine space-filling models of 12-crown-4, 15-crown-5 and 18-crown-6. Which alkali metal cation ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ) fits most snugly in each?
- Trimethyloxirane undergoes acid-catalyzed nucleophilic addition of methanol leading to a ring-opened product. An intermediate “oxonium ion” is assumed to be involved.



What is the product? What aspects of the structure and charge distribution of the intermediate ion would lead to this product?

- Does the preferred conformation of piperidine place the  $\text{NH}$  bond *equatorial* or *axial*? What does this tell you about the relative “size” of an  $\text{NH}$  bond and a nitrogen lone pair?

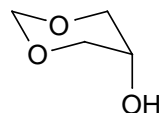
7. Both 5-fluoro-1,3-dioxane and 5-chloro-1,3-dioxane prefer a conformation in which the halogen occupies an *equatorial* position, whereas 1,3-dioxan-5-ol prefers a conformation in which the hydroxy group is *axial*. Speculate on the reason for the reversal.



5-fluoro-1,3-dioxane

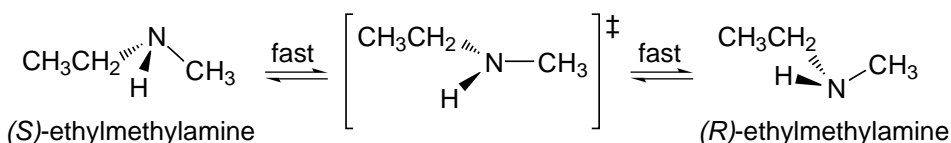


5-chloro-1,3-dioxane



1,3-dioxan-5-ol

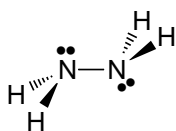
8. Amines in which nitrogen is bonded to three different groups (for example, ethylmethylamine) can exist in different enantiomers. These cannot be separated for most amines, however, because they rapidly interconvert via a planar transition state.



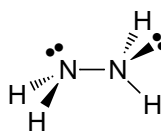
In order for the individual enantiomers to be isolated, the barrier to inversion needs to be 80-100 kJ/mol, or larger. Compare the energy of 2,2,3-trimethylaziridine with that of its inversion transition state in which the nitrogen is planar, and calculate the barrier separating enantiomers. Is the barrier large enough such that it should be possible to separate the enantiomers?

Repeat for 2,2,4-trimethylazetidine and 2,2,5-trimethylpyrrolidine. Rationalize the change in barrier height in going from the three-membered ring to four and five-membered rings.

9. Two conformers of hydrazine stagger NH bonds, one with the nitrogen lone pairs *anti* and the other with the lone pairs *gauche*.

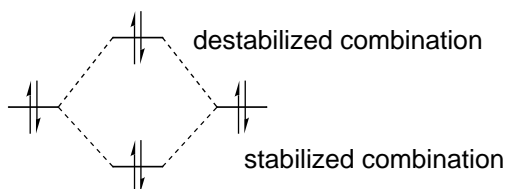


lone pairs *anti*



lone pairs *gauche*

VSEPR (Valence State Electron Pair Repulsion) theory presumes that lone pairs “take up more space” than bonds. This suggests that the *anti* conformer should be favored. In fact, the *gauche* conformer is preferred. To understand why, recognize that the lone pairs on the two nitrogens interact with each other to form combinations. One combination is “stabilized” (relative to non-interacting lone pairs) and the other combination (the highest-occupied molecular orbital or HOMO) is “destabilized”. The magnitude of the destabilization is greater than that of stabilization, meaning that the favored conformer is that for which the lone pairs interact the least.

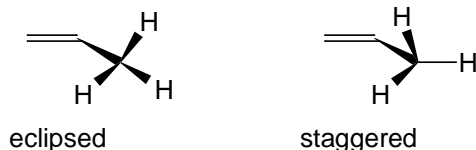


Obtain the HOMO energies for the *anti* and *gauche* conformers of hydrazine. For which is it lower? Is this also the favored conformer? Is the difference in HOMO energies comparable to the difference in conformer energies?



**Alkenes and Alkynes (17 requires you to access files from the activities directory.)**

1. Propene adopts a conformation in which one of the CH bonds on the methyl group eclipses the CC double bond.



The barrier to rotation through the unstable staggered conformation is about 8 kJ/mol, comparable in magnitude to barriers for single bond rotation in ethane (12 kJ/mol).

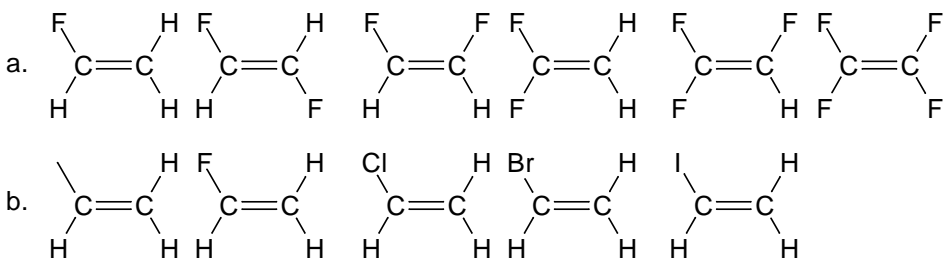
- a. What is the preferred conformation of *cis*-2-butene? Do CH bonds on both methyl groups eclipse the double bond, or do one or both “twist” to relieve the unfavorable non-bonded HH interaction?
- b. Examine the structure of cycloheptene. Does it fully satisfy the requirement that all single bonds stagger and that single bonds eclipse double bonds or are some “compromises” made? If the latter, which of the two factors appears to be the more important?

Repeat your analysis for cyclooctene and cyclononene.

2. Determine the sign of the dipole moment in propene. Is the methyl group acting as an electron donor or electron acceptor?

Repeat for propyne. Is the conclusion the same?

3. Order dipole moments in the following sets of compounds:



4. Which  $C_4H_6$  isomer is more stable, 1-butyne or 2-butyne? Is this the same preference seen for the analogous alkenes, 1-butene vs. *trans*-2-butene? Is the difference in alkyne isomer energies smaller, greater or about the same as that for the alkene?

Repeat for 1-pentyne vs. 2-pentyne (compare with 1-pentene and *trans*-2-pentene) and for 1-hexyne vs. 2-hexyne (compare with 1-hexene vs. *trans*-2-hexene). Do the conclusions reached for the four-carbon system remain essentially the same?

5. Obtain energy differences for the following sets of isomers:

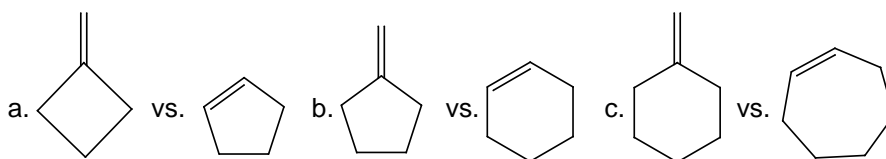
cyclobutene vs. 2-butyne  
cyclopentene vs. 2-pentyne  
cyclohexene vs. 3-hexyne  
cycloheptene vs. 3-heptyne

Assuming that cyclohexene is unstrained and that analogous CH and CC bonds in all molecules are of equal strength, calculate strain energies for cyclobutene, cyclopentene and cycloheptene.

6. Is 2-pentyne or 1,4-pentadiene more stable? Given that CH bonds involving  $sp^2$  hybridized carbon are stronger than CH bonds involving  $sp^3$  carbon, what does this tell you about the strength of a carbon-carbon triple bonds vs. two carbon-carbon double bonds?

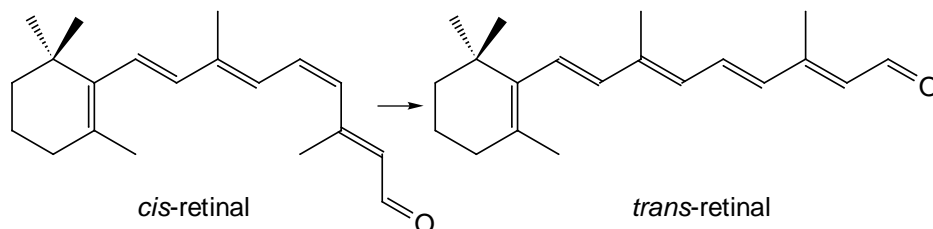
Repeat for  $C_6H_{10}$  isomers 3-hexyne and 1,5-hexadiene and  $C_7H_{12}$  isomers, 3-heptyne and 1,6-heptadiene. Do the conclusions reached for the five carbon system remain essentially the same?

7. Identify the more stable isomer for each of the following sets of compounds.



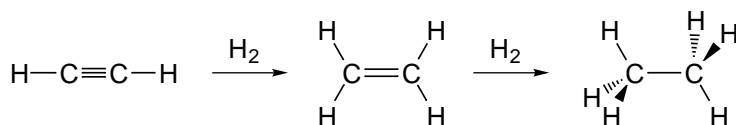
For each, is it also the isomer that incorporates the stronger  $\pi$  bond? (Use hydrogenation energies to assess  $\pi$  bond strength.) Rationalize your observations.

8. *Cis-trans* isomerization is an important step in the chemistry of vision, for example, the light-initiated, enzyme-catalyzed isomerization of *cis* to *trans*-retinal.



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

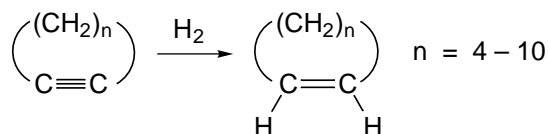
9. Which step in the hydrogenation of acetylene to ethane is the more *exothermic*?



Is a triple bond as strong as two double bonds?

10. Examine structures for cycloalkynes from cyclohexyne ( $\text{C}_6\text{H}_8$ ) to cyclododecyne ( $\text{C}_{12}\text{H}_{20}$ ). What is the minimum ring size needed to allow a nearly linear geometry (within  $10^\circ$ ) of the incorporated  $\text{C}-\text{C}\equiv\text{C}-\text{C}$  structural unit?

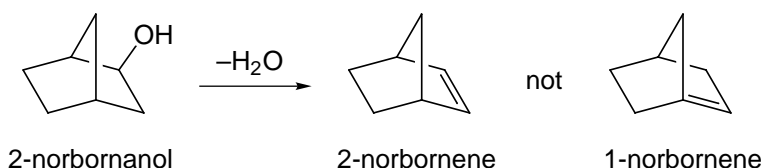
Calculate energies for addition of one equivalent of hydrogen to the cycloalkynes (leading to the analogous *cis*-cycloalkenes).



Is there a relationship between energy and  $\text{C}-\text{C}\equiv\text{C}$  bond angle?

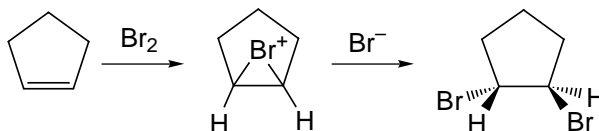
11. *Trans* alkenes are generally more stable than the corresponding *cis* alkenes. On the other hand, *trans* cycloalkenes are uniformly less stable than *cis* cycloalkenes.

- a. Compare energies for *cis* and *trans* cycloheptene, cyclooctene, cyclononene and cyclodecene. Which (*cis* or *trans*) is more stable for each? For which molecule is the energy difference the greatest? For which is it the smallest?
  - b. Compare geometries of *cis* and *trans* isomers of one or more of these cycloalkenes. Are the incorporated double bonds noticeably different? If they are, how are they different?
  - c. Compare electrostatic potential maps of *cis* and *trans* isomers of one or more of these cycloalkenes. Is the double bond in one likely to be significantly more susceptible to attack by electrophiles than that in the other? If so, is the *trans* or *cis* isomer likely to be the more reactive?
12. Elimination of water for 2-norbornanol leads preferentially to 2-norbornene and not 1-norbornene.

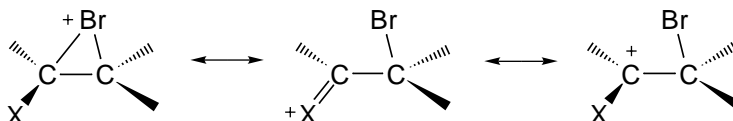


- Is 2-norbornene the thermodynamic (lower energy) product? Compare geometries of 1 and 2-norbornene. Are the incorporated double bonds noticeably different? If they are, how are they different? Compare electrostatic potential maps for the two isomers. Is one isomer likely to be more susceptible to attack by electrophiles than the other? If so, which one?
13. Which molecule, *trans*-2-butene or 2-butyne, is more susceptible to electrophilic attack? Use electrostatic potential maps to decide.
  14. Display electrostatic potential maps for substituted alkenes,  $\text{H}_2\text{C}=\text{CHX}$ : propene ( $\text{X}=\text{Me}$ ), vinyl chloride ( $\text{X}=\text{Cl}$ ), acrylonitrile ( $\text{X}=\text{CN}$ ) and 3,3,3-trifluoropropene ( $\text{X}=\text{CF}_3$ ). Which would be expected to be more susceptible to electrophilic attack than ethylene? For these molecules, which carbon is more likely to be attacked? Which would be expected to be less susceptible to electrophilic attack than ethylene?

15.  $\text{Br}_2$  adds to alkenes in a stepwise fashion. The first step involves formation of a cyclic bromonium ion that then undergoes backside attack by  $\text{Br}^-$  to give *trans* products.



While there is strong support for the existence of symmetrical cyclic bromonium ions formed from symmetrical alkenes, the fact that unsymmetrical alkenes give rise to selective formation of one regioisomer suggests that bromine can also bridge the two alkene carbons unsymmetrically, or not bridge at all.



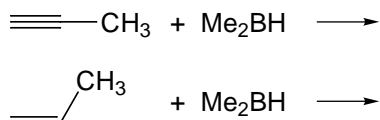
In these cases X and Br “compete” and the structure of the ion depends on their relative abilities to delocalize the positive charge.

Compare structures of bromonium ions derived from ethylene, propene, styrene and 2-methylpropene. Which ions are symmetrically bridged and which are unsymmetrically bridged? Are any ions unbridged? Predict the addition product for each.

16. Examine the electrostatic potential map of singlet dichlorocarbene. Where is the “electrophilic site”, in the  $\text{ClCCl}$  plane or out of the plane? How would you expect dichlorocarbene to approach an alkene? Is your expectation in line with the transition state for (dichlorocarbene) addition to ethylene?
17. Borane ( $\text{BH}_3$ ) does not exist as a monomer but rather as a dimer known as diborane. While diborane shares the same number of “heavy atoms” and the same number of hydrogens as ethane, its structure is quite different. In fact, its structure is instead closely related to that of ethylene, a molecule which shares the same number of valence electrons. Associate each of the six valence molecular orbitals of diborane with the corresponding orbital of

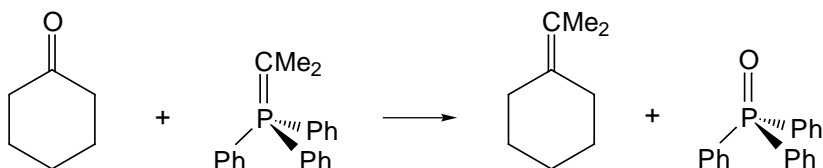
ethylene (*activities* directory). Point out any significant differences in orbital shapes. Is the energy of the orbitals the same in two molecules or are there differences? Elaborate.

18. Which hydroboration reaction is faster? Calculate activation energies to decide.



Rationalize your result based on the mechanism of hydroboration and “electronic” differences between alkynes and alkenes.

19. The Wittig reaction of cyclohexanone and isopropylidene-triphenylphosphorane to isopropylidenecyclohexane and triphenylphosphine oxide involves an intermediate and a transition state connecting the intermediate to the products, but there is no barrier to formation of the intermediate from reactants.



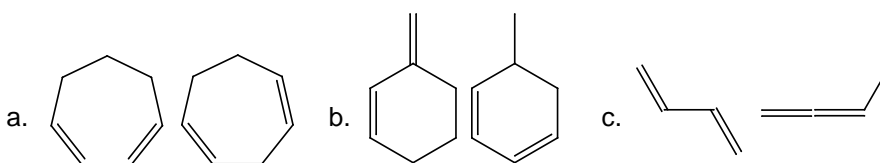
Why is there no barrier to formation of the intermediate? Hint: Consider the Hammond Postulate in light of the *exothermicity* of intermediate formation. Why does the reaction not stop at the intermediate? Hint: Examine the structure of the intermediate and the thermochemistry of product formation from the intermediate. Does the transition state (intermediate to products) more closely resemble the intermediate or the products? Rationalize your results. (The intermediate and transition state may be found in SpartanModel’s database under the names “Wittig intermediate” and “Wittig transition state”, respectively.)

**Dienes (2 requires you to access files from the activities directory.)**

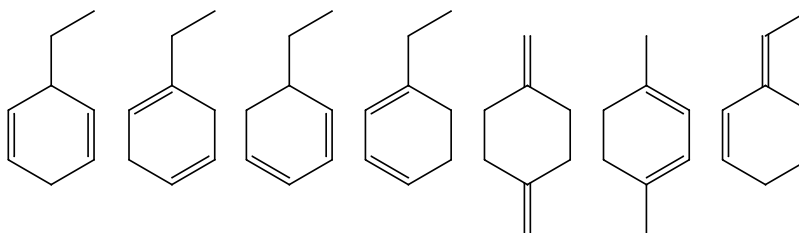
1. It is not always the lowest-energy conformer of a molecule that is “important”. For example, Diels-Alder cycloaddition of 1,3-butadiene and acrylonitrile requires that the diene be in a *syn* (or nearly *syn*) conformation, and not in a *anti* conformation.

What is the lowest-energy conformer of 1,3-butadiene? If it is not *syn* like, is there a second (higher-energy) conformer properly disposed for Diels-Alder cycloaddition? What “energy price” needs to be paid to bring 1,3-butadiene into this conformation?

2. Does substitution of 1,3-butadiene affect its conformation? Examine plots of the energy vs.  $\text{C}\equiv\text{C}-\text{C}=\text{C}$  dihedral angle for 1,3-butadiene, 2-methyl-1,3-butadiene and 2-*tert*-butyl-1,3-butadiene (*activities* directory; ignore the plot of HOMO/LUMO gap). Is the lowest-energy conformer the same in all three dienes? If not, why not? Do dihedral angles of stable conformers change significantly among the dienes? If so, why?
3. Which compound in each set is the more stable? Why?

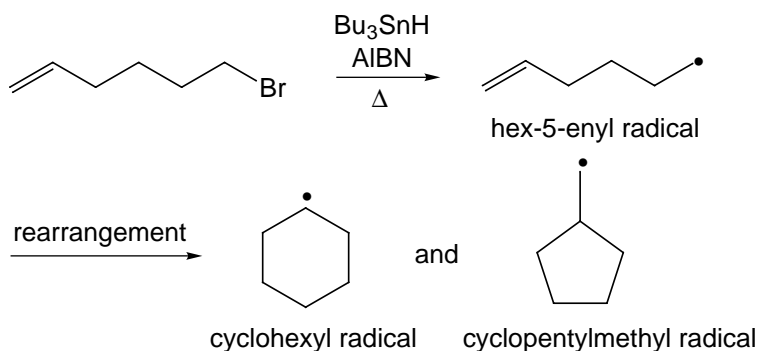


4. Is 1,3,5-heptatriene or 3-vinyl-1,3-pentadiene more stable? Why?
5. Calculate the HOMO/LUMO gap for the following  $\text{C}_8\text{H}_{12}$  isomers.



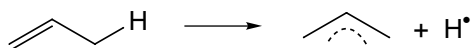
Is there a significant difference in gap between conjugated and non-conjugated systems? If so, for which is the gap smaller? Suggest an experiment that might be used to test your results.

6. Loss of bromine from 6-bromohexene first leads to hex-5-enyl radical which then undergoes ring closure to both cyclohexyl and cyclopentylmethyl radicals.

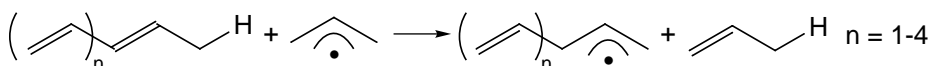


80% of the product is methylcyclopentane (and only 2% is cyclohexane). Is the reaction thermodynamically controlled, meaning that cyclopentylmethyl radical is more stable than cyclohexyl radical, or is the reaction kinetically controlled?

- Compare energies of cyclohexyl and cyclopentylmethyl radicals. Which is more stable? Is the energy difference large enough such that only one is likely to be observed were the reaction thermodynamically controlled? (See *Energy and Thermodynamics* in Chapter 3.)
  - Compare energies of the transition states leading to cyclohexyl and cyclopentylmethyl radicals. Which is more easily formed? What would be the ratio of cyclohexane and methylcyclopentane were the reaction kinetically controlled?
7. The (methyl) CH bond strength in propene is abnormally small, and may be attributed to the high stability of allyl radical.



Calculate (methyl) CH bond dissociation energies for 1,3-pentadiene, 1,3,5-heptatriene, 1,3,5,7-nonatetraene and 1,3,5,7,9-undecapentaene relative to the bond energy in propene.

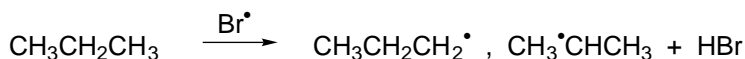




Does the fact that the  $\pi$  system is “extended” lead to a significant change in CH bond energy? Rationalize your result.

8. Draw resonance structures for the cation resulting from loss of chloride from 1-chloro-*trans*-2-butene. Based on the geometry and atomic charges for the cation, which is likely to be the principal contributor? What should be the product of hydrolysis of 1-chloro-*trans*-2-butene? Is this also the most stable product?
9. The knowledge that the transition state of an *endothermic* reaction more closely resembles products than reactants (Hammond Postulate), can be used to predict selectivity for competing reactions. The lowest-energy product should form most rapidly because it is connected to the reactants for the closest (and therefore lowest-energy) transition state.

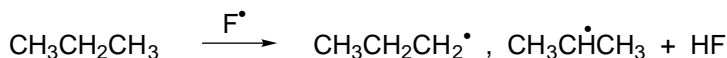
Calculate energies for hydrogen atom abstraction from propane by bromine atom, leading to either 1-propyl or 2-propyl radical.



Are these reactions *endothermic*? If they are, which radical will be formed most rapidly?

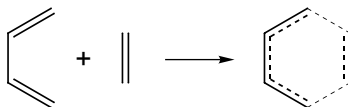
10. According to the Hammond Postulate, the transition state for an *exothermic* reaction more closely resembles reactants than products. Energy barriers for highly *exothermic* reactions are likely to be small and similar even if one product is favored.

Abstraction of hydrogen atom from propane can occur from either C<sub>1</sub> or C<sub>2</sub> and lead either to 1-propyl or 2-propyl radical.



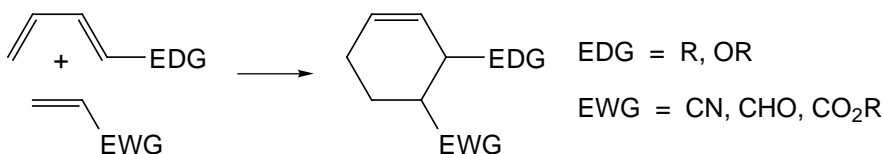
Are the reactions *exothermic* or *endothermic*? Which radical is favored? Use the Boltzmann equation to obtain the room temperature distribution of the two radicals. (See ***Energy and Thermodynamics*** in **Chapter 3**.) Which radical is most easily formed? Is this also the favored radical? Use the Boltzmann equation (with transition state energies instead of the energies of the stable radicals) to determine the kinetic product distribution.

11. The transition state for Diels-Alder reaction of 1,3-butadiene and ethylene is commonly viewed as a six-membered ring incorporating six  $\pi$  electrons. Benzene also accommodates six  $\pi$  electrons in a six-membered ring.

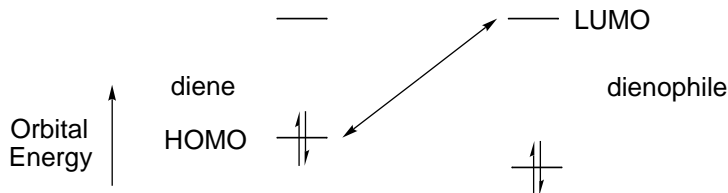


Compare structures of the Diels-Alder transition state and benzene. In what respects are they similar? Different?

12. The rate of Diels-Alder reactions generally increases with the  $\pi$ -donor ability of an electron-donor group (EDG) on the diene, and with the  $\pi$ -acceptor ability of an electron-withdrawing group (EWG) on the dienophile.



Electron donor groups “push up” the energy of the HOMO on the diene and electron acceptor groups “push down” the energy of the LUMO on the dienophile. The resulting decrease in “HOMO/LUMO gap” leads to stronger interaction between diene and dienophile and to a decrease in barrier.



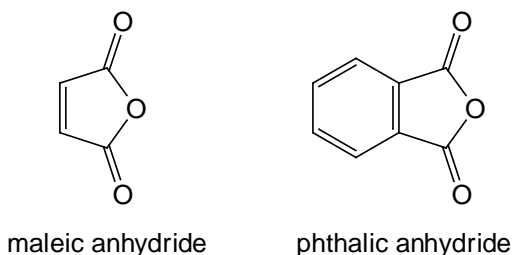
- a. Plot the LUMO energy of acrylonitrile, 1,1-dicyanoethylene, *cis* and *trans*-1,2-dicyanoethylene, tricyanoethylene and tetracyanoethylene vs. the log of the relative rate for Diels-Alder addition to cyclopentadiene (given on the next page).

acrylonitrile	0	1,1-dicyanoethylene	4.64
<i>trans</i> -1,2-dicyanoethylene	1.89	tricyanoethylene	5.66
<i>cis</i> -1,2-dicyanoethylene	1.94	tetracyanoethylene	7.61

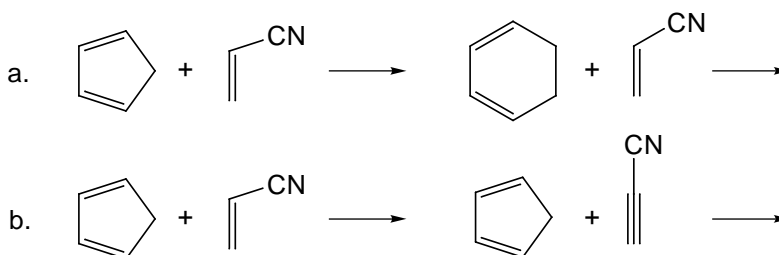
Which dienophile has the smallest LUMO energy and therefore leads to the smallest HOMO/LUMO gap? Is this the dienophile that reacts most rapidly with cyclopentadiene? Which has the largest LUMO energy? Is this the compound that reacts most slowly? Does the HOMO/LUMO gap correlate with relative reaction rate?

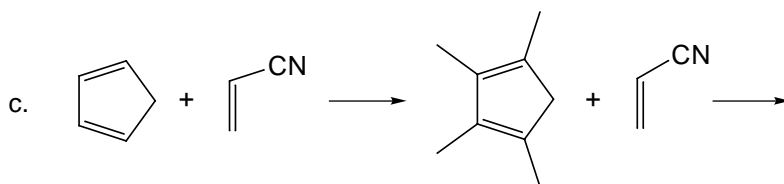
- b. Display electrostatic potential maps for the six dienophiles. For which is the double bond most electron-rich? For which is it most electron-poor? Is there a correlation between reaction rate and electron deficiency of the double bond of the dienophile, that is, does a large difference between the electron-rich diene and electron-poor dienophile translate into a large reaction rate? Elaborate.

13. Which dienophile would you expect to react more rapidly with cyclopentadiene, maleic anhydride or phthalic anhydride? Why?



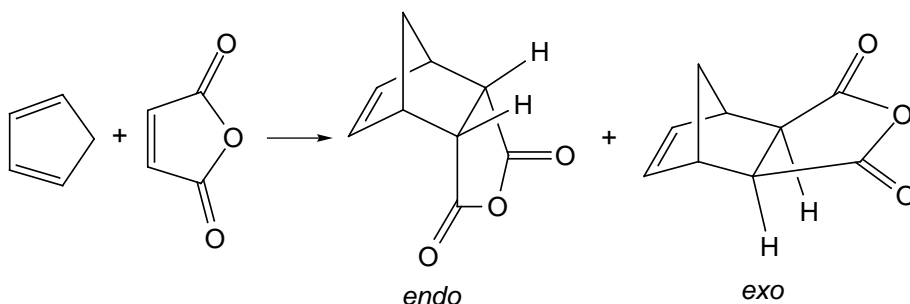
14. Identify the faster reaction from each set.





Rationalize your results in terms of electronic and/or steric effects.

15. Diels-Alder cycloaddition of cyclopentadiene and maleic anhydride can give rise to either *endo* or *exo* products.

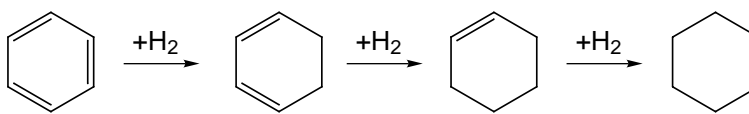


- Compare energies of *endo* and *exo* Diels-Alder adducts. What is the thermodynamic product? What is the thermodynamic distribution of *endo* and *exo* products at room temperature (see ***Energy and Thermodynamics*** in **Chapter 3**)?
  - Compare energies of transition states leading to *endo* and *exo* products. What is the kinetic product? What is the kinetic distribution of *endo* and *exo* products at room temperature? Given that *endo* products are usually favored, is the Diels-Alder reaction under thermodynamic or kinetic control?
16. Compare electrostatic potential maps for the following Diels-Alder transition states: cyclopentadiene+ethylene, cyclopentadiene+acrylonitrile and cyclopentadiene+tetracyanoethylene, with those of reactants: cyclopentadiene, ethylene, acrylonitrile and tetracyanoethylene. Are electrons transferred from diene to dienophile in the transition states (relative to reactants) or vice versa? For which reaction is the transfer the greatest? The least? Quantify your conclusion by measuring the total charge on the diene and dienophile components in the three transition states.

Calculate activation energies for the three Diels-Alder reactions (energy of transition state - sum of energies of reactants). Does this correlate with the magnitude of charge transfer between diene and dienophile components in the transition state?

## Aromatics

1. Compare the energy of the hypothetical molecule, 1,3,5-cyclohexatriene, with alternating single and double bonds, with that of benzene. (You need to retrieve 1,3,5-cyclohexatriene from the database using its name.) Is the difference in energy roughly the same as the aromatic stabilization afforded benzene (see activity 2), or is it significantly smaller? Does your result suggest that there is more to aromaticity than structure?
2. Consider the steps in the complete hydrogenation of benzene:

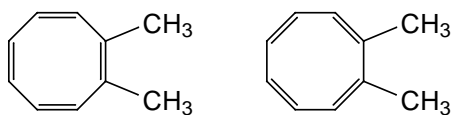


All three steps lead to the destruction of one  $\pi$  bond, but only the first leads to loss of aromaticity. Therefore, comparison of the energy of the first step with that of either of the other two provides an estimate of the aromatic stabilization afforded benzene.

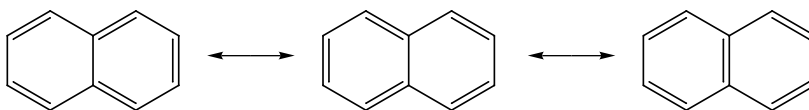
- a. What is difference in energy between the first hydrogenation step (benzene +  $\text{H}_2 \rightarrow$  1,3-cyclohexadiene) and the last hydrogenation step (cyclohexene +  $\text{H}_2 \rightarrow$  cyclohexane)?
  - b. Is there a difference in energy between the second hydrogenation step (1,3-cyclohexadiene +  $\text{H}_2 \rightarrow$  cyclohexene) and the last hydrogenation step (cyclohexene +  $\text{H}_2 \rightarrow$  cyclohexane)? If there is, which step is more difficult and by how much? Rationalize your result.
3. Consider molecules with the formula  $(\text{CH})_6$ , that is, isomers of benzene with each carbon bonded to one hydrogen. Rank the isomers according to energy, relative to that of benzene. Are any

likely to be observed in an hypothetical equilibrium with benzene? (See *Energy and Thermodynamics* in **Chapter 3**.)

4. Cyclooctatetraene incorporates four double bonds and might be expected to be a highly unstable (“antiaromatic”) molecule.
  - a. Calculate the energy of adding one equivalent of hydrogen to cyclooctatetraene (leading to 1,3,5-cyclooctatriene). Is it significantly different from the energy of adding hydrogen to cyclooctene (leading to cyclooctane)? How does your result compare with the analogous (first and last step hydrogenation energies for benzene (see activity 2)? Do you conclude that cyclooctatetraene is especially stable or especially unstable?
  - b. Identify any aspects of the structure of cyclooctatetraene that are significantly different from those of benzene.
5. Are the two structures below for dimethylcyclooctatetraene merely alternative representations or do they correspond to different molecules? If the latter, which is the more stable and why?

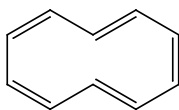


6. Naphthalene is depicted in terms of three resonance structures.

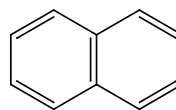


Assuming that each resonance structure contributes equally, which, if any of naphthalene’s carbon-carbon bonds would you expect to be shorter than the others? Explain. Is your conclusion in accord with the actual structure of naphthalene? If it is not, suggest which resonance structure is “more important” than the others.

7. (1Z, 3E, 5Z, 7E, 9Z)-cyclodeca-1,3,5,7,9-pentaene might be expected to be aromatic as is its analogue, naphthalene.



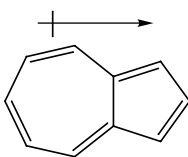
(1Z, 3E, 5Z, 7E, 9Z)-cyclodeca-1,3,5,7,9-pentane



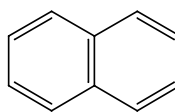
naphthalene

Identify aspects of the structure of the molecule that are evidence *for or against* it being aromatic like naphthalene.

8. Azulene has a sizeable dipole moment whereas its isomer naphthalene does not.



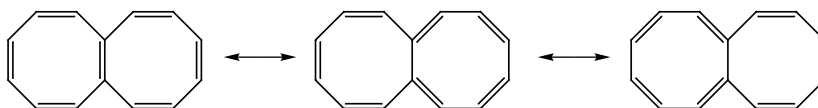
azulene



naphthalene

Compare electrostatic potential maps for the two molecules. Does the map for azulene suggest an overall polarity that is consistent with the observed direction of the dipole moment? Draw resonance structures for azulene to account for your result.

9. Octalene,  $C_{14}H_{12}$ , is the 8-membered ring analogue of naphthalene. Seven lines are observed in its  $^{13}C$  NMR spectrum at room temperature, but these resolve into fourteen lines at  $-150^{\circ}C$ . The  $^{13}C$  NMR spectrum of naphthalene exhibits three lines irrespective of temperature. Three resonance structures may be drawn for octalene, the first of which is unique and the second and third of which are equivalent.

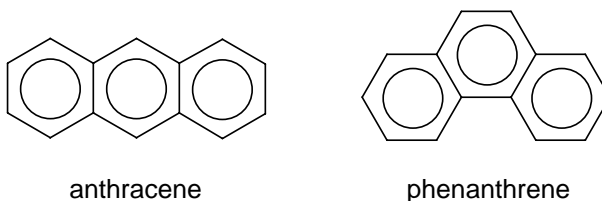


- a. How many  $^{13}C$  lines would be expected were octalene to be represented by the unique resonance structure? How many would be expected were octalene to be represented by a combination of the two equivalent resonance structures? How many would be expected were all three resonance structures

involved? Would any of your assignments change with change in temperature? Elaborate.

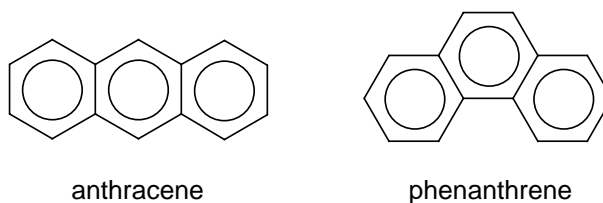
- b. Examine the structure of octalene, and show that it is consistent with a seven line  $^{13}\text{C}$  spectrum. Speculate what happens at low temperature to give rise to a fourteen line spectrum.

10. Draw all Lewis structures for anthracene and phenanthrene.



Assuming that each Lewis structure contributes equally, guess which of the carbon-carbon bonds in each of these molecules should be especially “short” or especially “long”. Are assignments based on the assumption of “equal” Lewis structures consistent with the actual structures? If not, suggest which Lewis structures need to be weighed more heavily (or which need to be weighed less heavily) in order to bring the two sets of data into accord.

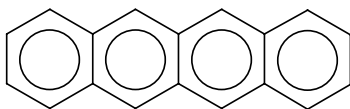
11. Which  $\text{C}_{14}\text{H}_{10}$  isomer is more stable, anthracene or phenanthrene?



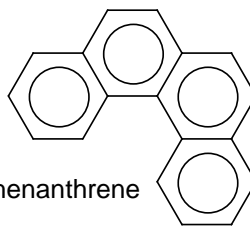
Justify your result by drawing the complete set of resonance structures for the two isomers.

Compare stabilities of anthracene and phenanthrene analogues comprising four (naphthalene and benzophenanthrene), five (pentacene and dibenzophenanthrene) and six (hexacene and hexahelicene) benzene rings, for example, naphthalene and benzophenanthrene.





naphthalene



benzophenanthrene

Does the preference seen for anthracene and phenanthrene maintain? What is surprising about your result?

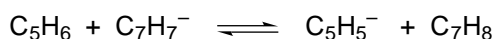
12. Examine the geometries of cycloheptatrienyl (tropylium) and cyclopentadienyl cations. Are all of the carbon-carbon bond distances equal in each ion, or do long and short bonds alternate? If the latter, are the CC distances like those of a typical single bond ( $\sim 1.54 \text{ \AA}$ ), a double bond ( $\sim 1.32 \text{ \AA}$ ), or a partial double bond ( $\sim 1.4 \text{ \AA}$ ) like that found in benzene? Examine electrostatic potential maps of the two ions. Do the maps show a symmetric distribution of the positive charge, or do they display alternating regions of high and low charge? Which ion, if either, appears to be resonance stabilized?

Which molecule, 7-bromo-1,3,5-cycloheptatriene or 5-bromo-1,3-cyclopentadiene, would you expect to dissociate into ions when dissolved in water?

13. Chromium tricarbonyl complexes onto the  $\pi$  face of benzene. Does it act to donate or accept electrons from the ring? Compare electrostatic potential maps for benzene chromium tricarbonyl and benzene. Is the  $\pi$  face of the metal complex more or less susceptible to electrophilic attack than the  $\pi$  face? If metal complexation makes the benzene ring more susceptible, is the effect comparable to that of a strong  $\pi$  donor, for example, a methoxy group? If metal complexation makes the ring less susceptible, is the effect comparable to that of a strong  $\pi$  acceptor, for example, a nitro group? Compare electrostatic potential maps with the appropriate substituted benzene to tell.
14. Examine the geometries of cyclopentadienyl and cycloheptatrienyl anions. Are the CC bond distances in each ion all equal,

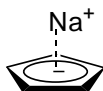
or do long and short bonds alternate? If the latter, are the CC distances like those of a typical single bond ( $\sim 1.54 \text{ \AA}$ ), a double bond ( $\sim 1.32 \text{ \AA}$ ), or a partial double bond ( $\sim 1.4 \text{ \AA}$ ) like that in benzene? Examine atomic charges and electrostatic potential maps for the two ions. Do they show a symmetric distribution of negative charge, or do they display alternating regions of high and low charge? Based on these results, which ion, if either, appears to be resonance stabilized?

Calculate the energy for the reaction, comparing the energy of deprotonation of cyclopentadiene to that of cycloheptatriene.



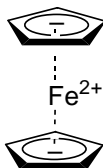
Is the reaction energy consistent with the other data? Explain.

15. Examine the charge on sodium in cyclopentadienyl sodium. is it consistent with representation of the system as a complex between sodium cation and cyclopentadienyl anion?

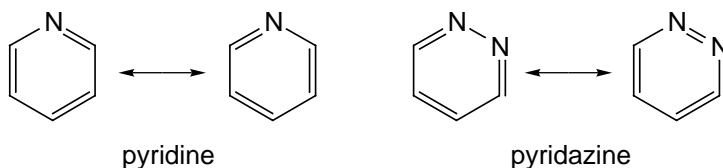


Does the geometry of the incorporated cyclopentadienyl fragment also fit such a description? (Compare with cyclopentadienyl anion.)

Repeat your analysis for ferrocene.

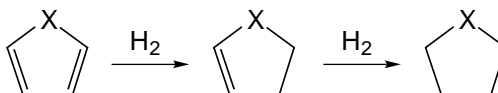


16. Pyridine and pyridazine are each represented by two Lewis structures.



While the two structures are the same for pyridine, they are different for pyridazine. Compare carbon-nitrogen bond distances in pyrazine (using those in pyridine as a “reference”). Should its two Lewis structures be given equal weight? If not, which structure is the more important? Elaborate.

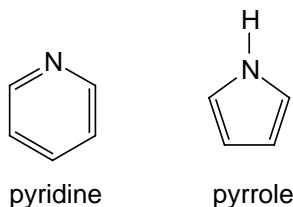
17. What is the difference in reaction energy for the first and second steps in the overall hydrogenation of thiophene ( $X=S$ )?



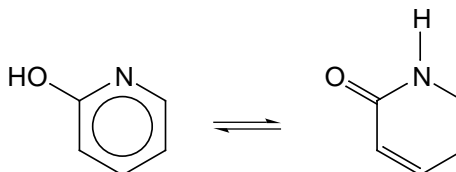
Do you conclude that thiophene possesses a similar degree of aromatic stabilization to benzene, or a significantly lesser or greater amount (see activity 2)?

Repeat for pyrrole ( $X=NH$ ) and furan ( $X=O$ ).

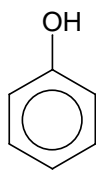
18. Rationalize the direction of the dipole moment in both pyridine and pyrrole.



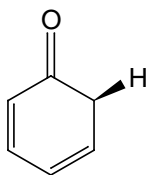
19. Calculate the equilibrium abundance of 2-hydroxypyridine and its “keto form” (2-pyridone) at room temperature (see ***Energy and Thermodynamics*** in **Chapter 3**). Is this system different from the phenol/cyclohexadienone equilibrium (see activity 20)?



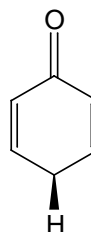
20. Phenol is in equilibrium with two enol forms, 2,4-cyclohexadieneone and 2,5-cyclohexadieneone.



phenol



2,4-cyclohexadieneone



2,5-cyclohexadieneone

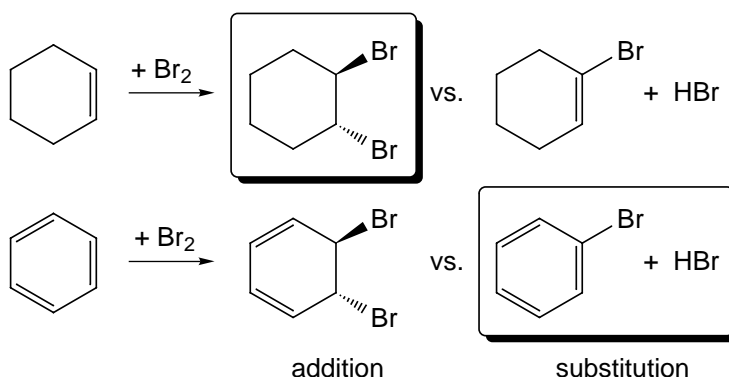
Use the Boltzmann equation (see *Energy and Thermodynamics* in **Chapter 3**) to calculate the room temperature distribution of the three forms. Is your result similar or different from that of the corresponding equilibrium between acetone and its enol (see activity 8 in **Carbonyl Compounds** later in this chapter)?

## Electrophilic Aromatic Substitution

1. Nitronium cation,  $\text{NO}_2^+$ , is the active reagent in aromatic electrophilic nitration. Is it linear or bent? What common neutral organic molecule has the same number of electrons as  $\text{NO}_2^+$ ? Is this molecule linear or bent? Examine the charges on the nitrogen and oxygen atoms in  $\text{NO}_2^+$ . Is nitrogen or oxygen more positive? Is your result consistent with the usual Lewis structure for the ion? Display an electrostatic potential map for  $\text{NO}_2^+$ . What atom (nitrogen or oxygen) would you expect to add to an arene in electrophilic nitration?
2. Acyl cation,  $\text{CH}_3\text{CO}^+$ , is the active reagent in Friedel-Crafts acylation. Which atom is the most positively charged? Draw the Lewis structure for acyl cation that is most consistent with its charge distribution. Is the calculated geometry of acyl cation consistent with its Lewis structure? Which atom (carbon or oxygen) would you expect to add to an arene in electrophilic acylation?
3. The mixture of antimony pentafluoride ( $\text{SbF}_5$ ) and hydrogen fluoride ( $\text{HF}$ ) turns out to be a very strong acid (a “superacid”). Examine the structure of the  $\text{SbF}_5/\text{HF}$  system. Is it better described as a complex between neutral antimony pentafluoride and neutral hydrogen fluoride or between  $\text{SbF}_6^-$  anion and a proton? (Compare with geometries of  $\text{SbF}_5$ ,  $\text{SbF}_6^-$  and  $\text{HF}$ .) Compare charges at

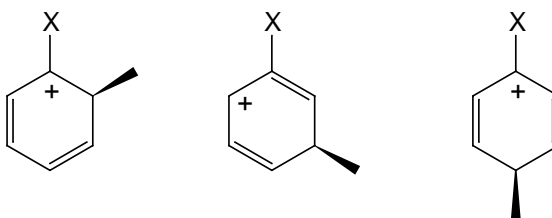
hydrogen and electrostatic potential maps for the  $\text{SbF}_5/\text{HF}$  system and for “free” HF. Is the hydrogen (in HF) “more positive” because of its association with  $\text{SbF}_5$ ?

4. Alkenes typically undergo (*trans*) addition reactions whereas aromatics typically undergo substitution reactions, for example.



Compare the energies of the products of both (*trans*) addition and substitution for reaction of both cyclohexene and benzene with  $\text{Br}_2$ . Are the noted preferences the thermodynamic preferences? Provide a rationale.

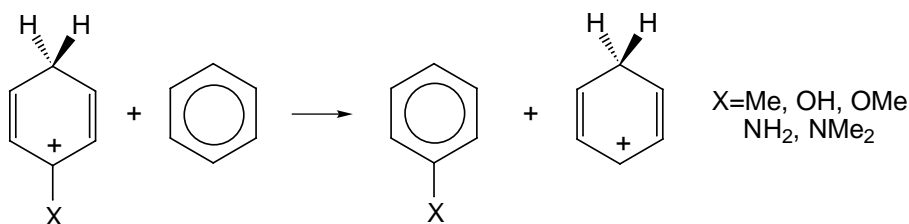
5. Compare total energies of *ortho*, *meta* and *para* methyl cation adducts of toluene ( $\text{X}=\text{CH}_3$ ).



Assuming their role as reactive intermediates, use the Boltzmann equation (see **Energy and Thermodynamics** in **Chapter 3**) to predict the ratio of *ortho*, *meta* and *para*-xylene products.

Repeat for *ortho*, *meta* and *para* adducts of anisole ( $\text{X}=\text{OCH}_3$ ) and trifluorotoluene ( $\text{X}=\text{CF}_3$ ).

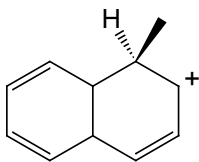
6. Obtain energies for benzenium ion and benzenium ion substituted in the *para* position by methyl, hydroxy, methoxy, amino and dimethylamino groups, and calculate energies for the (protonation) reactions (you will also need energies for the corresponding neutral benzenes):



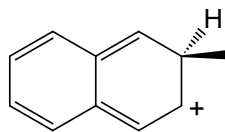
Which group is most effective in increasing the proton affinity of benzene? Least effective? Does the ordering of proton affinities parallel the order of electrophilic reactivities of these systems?

Repeat with benzenium ions substituted in the *meta* position by chloro, formyl, carboxylic acid, sulfonic acid, cyano and nitro groups. Which group is most effective in decreasing the proton affinity of benzene? Least effective? Does the ordering of proton affinities parallel the order of electrophilic reactivities in these systems?

7. Compare electrostatic potential maps for benzene, toluene, aniline, N,N-dimethylamine, phenol and anisole. Which substituents are most effective in activating benzene for electrophilic attack, that is, in increasing the negative potential on the ring? Which are least effective?
8. Compare electrostatic potential maps for benzene, chlorobenzene, benzaldehyde, benzoic acid, benzonitrile, benzene sulfonic acid and nitrobenzene. Which substituents are most effective in deactivating benzene for electrophilic attack, that is, in decreasing the negative potential on the ring? Which are least effective?
9. On which position, C<sub>1</sub> or C<sub>2</sub>, does naphthalene alkylate? Compare energies of methyl cation adducts to tell. Is the same preference noted for electrophilic bromination of naphthalene? Compare Br<sup>+</sup> adducts to tell.

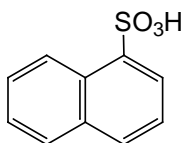


naphthalene methylated at C1

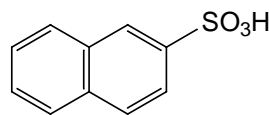
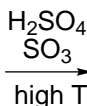
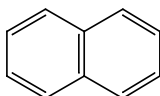
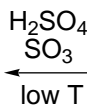


naphthalene methylated at C2

10. Sulfonation of naphthalene gives two different products, depending on reaction conditions. Lower temperatures favor formation of 1-naphthalenesulfonic acid, while higher temperatures favor formation of 2-naphthalenesulfonic acid.

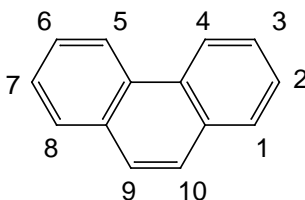


1-naphthalenesulfonic acid



2-naphthalenesulfonic acid

- Compare energies of 1 and 2-naphthalenesulfonic acids. Which is more stable? What is the equilibrium distribution of the two at room temperature? Is your result in line with the high temperature product distribution? Explain.
  - Compare energies of naphthalenium ion complexes leading to 1 and 2-naphthalenesulfonic acids. (See activity 9 for placement of the formal positive charge. The complexes are named “naphthalene sulfonated at C1”, etc.) Which is more stable? What is the equilibrium distribution of the two at room temperature? (See *Energy and Thermodynamics* in **Chapter 3**.) Is your result in line with the low temperature product distribution? Explain.
11. Phenanthrene undergoes nitration at C<sub>9</sub>, whereas sulfonation occurs primarily at C<sub>2</sub> and C<sub>3</sub>.



Compare energies of 2, 3 and 9-nitrophenanthrenes and 2, 3 and 9-phenanthrenesulfonic acids to establish the thermodynamic product distributions for the two reactions. (See ***Energy and Thermodynamics*** in **Chapter 3**.) Compare energies of phenanthrenium ion complexes leading to 2, 3 and 9-nitrophenanthrenes and to 2, 3 and 9-phenanthrenesulfonic acids to establish the kinetic product distributions for the two reactions. (To access by structure, place the formal positive charge at C<sub>1</sub>, C<sub>4</sub> and C<sub>10</sub> for complexes leading to C<sub>2</sub>, C<sub>3</sub> and C<sub>9</sub> products. The complexes are named “phenanthrene nitrated at C2”, etc.) Is nitration under thermodynamic or kinetic control? Is sulfonation under thermodynamic or kinetic control? Elaborate.

**Nucleophilic Additions (2 and 3 require you to access files from the activities directory)**

1. Compare the geometries of adamantane and adamantyl cation. Which (if any) bond lengths and angles are significantly different? Try to rationalize what you observe by examining the geometry of a “normal” carbocation such as *tert*-butyl cation.
2. The S<sub>N</sub>2 reaction involves transfer of a pair of electrons from the highest-occupied molecular orbital (the HOMO) on the nucleophile into the lowest-unoccupied molecular orbital (the LUMO) on the substrate.

Examine the LUMO of methyl iodide (***activities*** directory). Is it antibonding between carbon and iodine? Between carbon and hydrogen? What should happen if electrons are added to this orbital? Is this consistent with what actually happens?

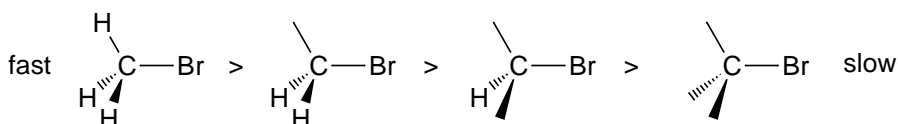
3. Cyanide anion acts as a “carbon nucleophile” in S<sub>N</sub>2 reactions leading to formation of a new carbon-carbon bond, for example, addition to methyl iodide leading to acetonitrile. Reconcile this with the fact that nitrogen is more electronegative than carbon and therefore would be expected to hold the excess electrons.

Examine the HOMO of cyanide anion (***activities*** directory). Is it concentrated on carbon, on nitrogen or on both? If both, is it

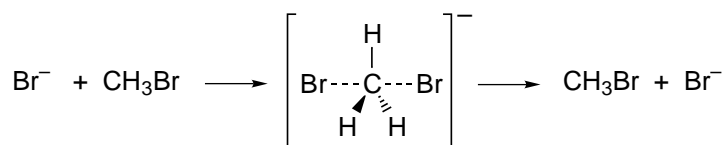


more concentrated on nitrogen or carbon? Given that the HOMO contains the most available (highest-energy) electron pair, does your result suggest that nucleophilic addition should occur from carbon or from nitrogen? Is this conclusion at odds with the notion that the more electronegative an atom, the more likely it is to hold on to its electrons? Elaborate.

4.  $S_N2$  reactions involving methyl halides are fast but slow down with each successive replacement of hydrogen by methyl, for example.



The usual explanation is that  $S_N2$  reactions involve transition states in which carbon has five “neighbors” instead of four, e.g., for reaction of bromide and methyl bromide,



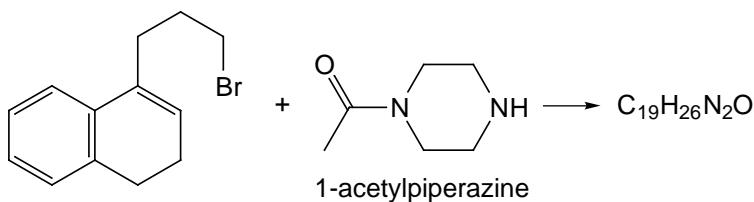
and steric effects will be “amplified” in the transition state. Therefore, reaction rates should decrease with increased substitution.

Examine space-filling for transition states for bromide addition to methyl bromide and to *tert*-butyl bromide. Is the transition state for addition to *tert*-butyl bromide actually more crowded than that for addition to methyl bromide? If not, why not? Hint: examine CBr bond distances in the two transition states.

Compare electrostatic potential maps for the two transition states. Is the extent of charge separation comparable or does it differ between the two transition states? If the latter, what is the relationship between CBr distance and charge separation?

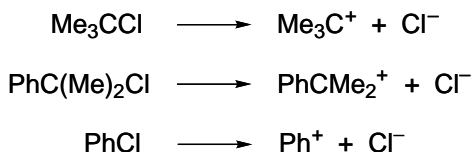
What is the origin of the change in rate of  $S_N2$  reactions with change in substitution at carbon?

5. The following  $S_N2$  reaction yields a single product.

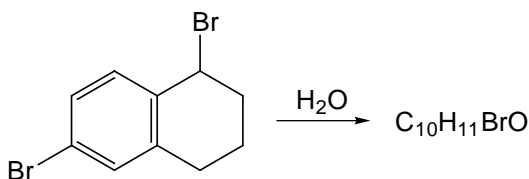


Which nitrogen in 1-acetylpiperazine is more negative? (Base your conclusion both on atomic charges and on the electrostatic potential map.) Assuming that the more negative nitrogen acts as the nucleophile, what is the product of the reaction? Do you conclude that amides or amines are better nucleophiles?

6. Phenyl rings greatly affect  $S_N1$  reaction rates, depending on the position of the ring relative to the leaving group. Consider the following reactions:

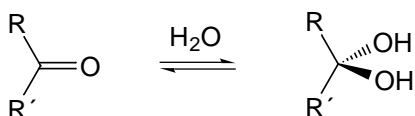


- a. Calculate energies for these three reactions (don't worry that all will be highly *exothermic* in the absence of solvent). Assuming that the first reaction is "normal", would the other two reactions expected to be slower or faster? Compare the geometries of the three carbocations with each other and with their respective neutral precursors. If the structural charges in the first reaction are "normal", then what unusual changes, if any, occur in the other two reactions? Compare atomic charges and electrostatic potential maps for the three cations. For each, is the charge localized or delocalized? Does charge localization/delocalization correlate with reaction energy?
- b. Based on your results, what would you expect to be the product of the following reaction?



## Carbonyl Compounds

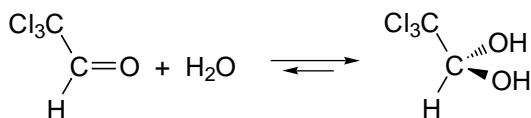
1. Rank the reactivity toward nucleophilic addition of carbonyl compounds  $\text{CH}_3\text{COX}$  for  $\text{X} = \text{NH}_2$  (acetamide),  $\text{OH}$  (acetic acid),  $\text{OCH}_3$  (methyl acetate),  $\text{Cl}$  (acetyl chloride) and  $\text{OCOCH}_3$  (acetic anhydride) based on the availability of the LUMO, that is, the lower the LUMO energy, the more reactive.
2. Is there a relation between the reactivity toward nucleophilic addition of the carbonyl compounds in the previous problem and the energies of protonation of these compounds? (Assume that protonation occurs on the (carbonyl) oxygen and that the formal charge is on the carbonyl carbon.)
3. Why is phenyl acetate more reactive toward nucleophilic addition than cyclohexyl acetate?
4. What effect (if any) does protonation have on the energy of the lowest-energy unoccupied molecular orbital of acetone? Would you expect the protonated compound to be more or less susceptible to nucleophilic attack than acetone itself?
5. Aldehydes and ketones add water to form carbonyl hydrates.



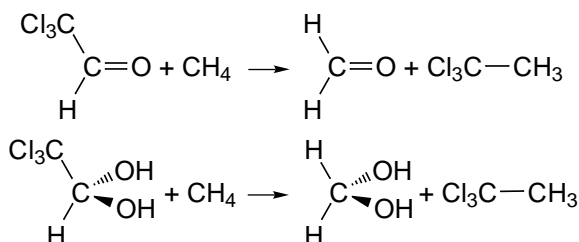
Equilibrium constants for dilute solutions vary over an enormous range and some compounds exist solely as the hydrate.

Calculate reaction energies for addition of water to acetaldehyde, acetone and hexafluoroacetone. Which is the least likely to exist as a hydrate? Which is the most likely? Explain your results in terms of your knowledge of electron donating/accepting effects of methyl and trifluoromethyl substituents.

6. Carbonyl compounds in water coexist in equilibrium with their respective hydrates. Whereas equilibrium normally favors the carbonyl compound, for trichloroacetaldehyde (chloral), it lies almost entirely in favor of the hydrate, chloral hydrate.

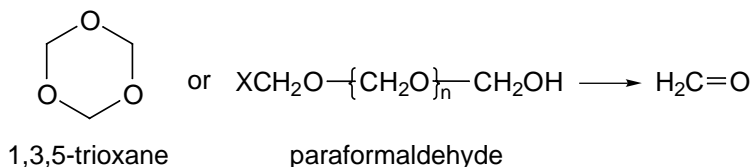


Is this because the trichloromethyl group destabilizes the carbonyl, stabilizes the hydrate or a combination of both? To tell, calculate energies for the two reactions:



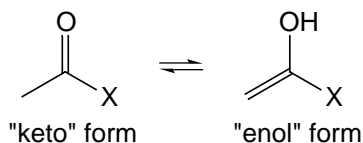
These compare the effect of a trichloromethyl group relative to that of hydrogen on both the carbonyl and the hydrate.

7. Formaldehyde cannot be purchased as a pure substance. When formaldehyde is needed, it is common to purchase either 1,3,5-trioxane or paraformaldehyde, and then “crack” these substances into formaldehyde *in situ*.



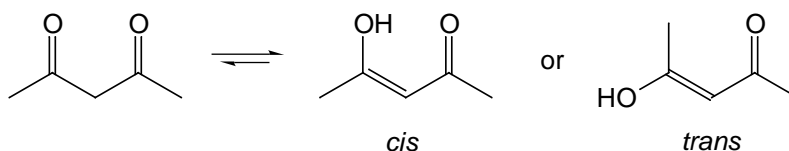
Is “cracking” 1,3,5-trioxane *endothermic* or *exothermic*? Is the entropy change for the cracking reaction likely to be positive or negative? Explain. Given the direction of the change in entropy, should one “crack” trioxane at higher or lower temperatures? Explain. (Recall that  $\Delta G = \Delta H - T\Delta S$ .)

8. Use the Boltzmann equation to calculate the room temperature equilibrium distribution between acetone and its enol, propen-2-ol ( $\text{X}=\text{CH}_3$ ). (See *Energy and Thermodynamics* in **Chapter 3**.)



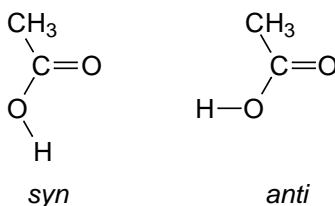
Repeat your calculations for 1,1,1-trifluoroacetone ( $\text{X}=\text{CF}_3$ ) and methyl acetate ( $\text{X}=\text{OCH}_3$ ) and their respective enol forms. For which system is the equilibrium abundance of the enol form the highest? For which is it the lowest? Rationalize your result.

9. Two reasons are usually given to explain why the equilibrium involving 2,4-pentanedione and its enol, 4-hydroxy-3-penten-2-one, lies in favor of the enol: i) Conjugation involving the CC and CO double bonds, and ii) intramolecular hydrogen-bonding.



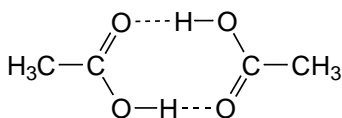
What is the strength of the intramolecular hydrogen bond? Compare energies of *cis* and *trans*-4-hydroxy-3-penten-2-one to tell. (You need to assume that the conjugation energy is the same in the two isomers.) Is hydrogen bonding by itself sufficient to account for the direction of the equilibrium? Explain.

10. What is the preferred conformation of acetic acid, with the OH bond *syn* or *anti* to the CO bond?



Is the difference small enough that the minor conformer might be observable at room temperature ( $> 1\%$ )? (See ***Energy and Thermodynamics in Chapter 3.***) Rationalize your result. Hint: look at the dipole moments of both conformers.

11. Acetic acid forms a symmetrical hydrogen-bonded dimer.

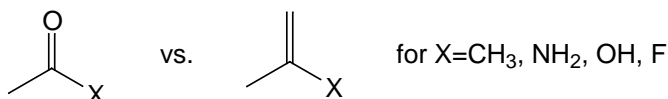


Compare its structure with that of free acetic acid. Point out any significant changes in bond lengths and angles. Have the hydrogens involved in the hydrogen bonds moved to positions halfway between the oxygens or have they remained with one oxygen (as in acetic acid)? Do the structural changes (or lack of structural changes) suggest that hydrogen bonds are comparable to normal (covalent) bonds or are weaker? Elaborate.

12. Examine the electrostatic potential map for sodium stearate. Explain why it, or the corresponding carboxylate anion, is able to function as a soap.

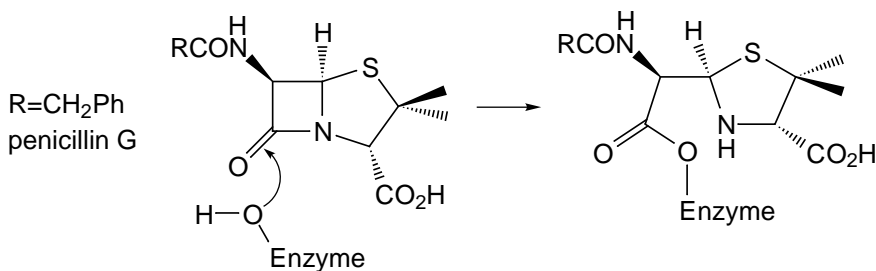
Repeat for sodium dodecyl sulfate, a molecule that is a component in common detergents. What is the “chemical” difference between soaps and detergents?

13. Compare CX bond distances in the following pairs of compounds.



For which X group is the difference the greatest? For which is it the smallest? Rationalize your observations.

14. The mode of action of penicillin is believed to involve nucleophilic attack by a bacterial enzyme.



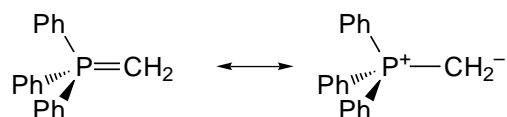
Amides are generally poor candidates for nucleophilic attack, but penicillin is apparently an exception.

Examine the structure of penicillin G. What (if anything) distinguishes it from N,N-dimethylacetamide, a typical amide? What is responsible for the differences? Compare electrostatic potential maps for penicillin G and dimethylacetamide. Which compound is more likely to undergo nucleophilic attack? Explain.

15. Examine the geometry, atomic charges and electrostatic potential map for lithium aluminum hydride,  $\text{LiAlH}_4$ . Is it better described as an ion pair, that is, a “loose complex” between lithium cation and aluminum hydride anion or as a molecule where the two components are covalently bonded? Compare its structure and atomic charges with aluminum hydride anion.

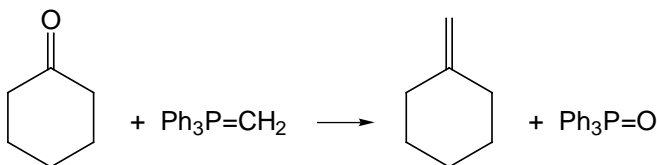
Repeat your analysis for sodium borohydride,  $\text{NaBH}_4$ .

16. Grignard reagents such as methyl magnesium bromide commonly exist only in the presence of ethers, for example, tetrahydrofuran (THF). Compare the geometries, atomic charges and electrostatic potential maps for methyl magnesium bromide both as a “free molecule” and as complexed to two THF molecules. Has THF altered the structure and/or charge distribution of the Grignard in a significant way? Elaborate. What role do you think THF plays in stabilizing the Grignard?
17. Ylides such as trimethylphosphine ylide are commonly written in terms of both “neutral” and zwitterionic resonance structures.



Examine the geometry, atomic charges and electrostatic potential map for triphenylphosphine ylide. Is the distance between phosphorous and the (methylene) carbon consistent with a single bond (as in trimethylphosphine) or is it significantly shorter? Does the phosphorous carry a nearly full positive charge? Does the methylene group carry a nearly full negative charge? Suggest which, if either, resonance structure is more appropriate.

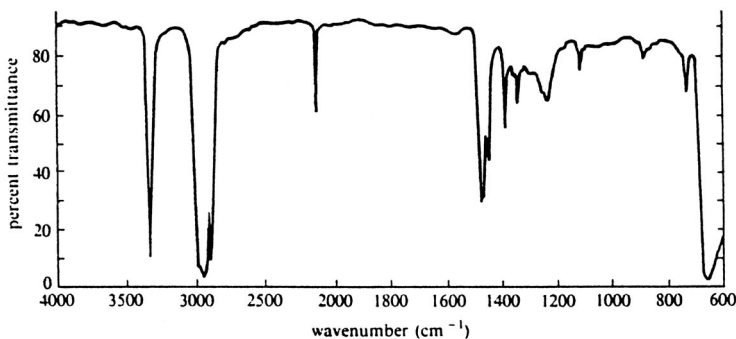
18. Reaction of cyclohexanone with triphenylphosphine ylide yields methylenecyclohexane and triphenylphosphine oxide.



Calculate the energetics of reaction. Is it *exothermic*? If it is, suggest why. (Hint: consider the properties of the phosphine oxide in light of those of the corresponding ylide; see activity 18).

**IR/UV Spectra** (*1 to 12 require frequencies from SpartanModel's database. These are typically 10-12% larger than experimental frequencies. 13 to 15 require you to access files from the activities directory.*)

1. Examine the infrared spectrum of ethanol in the range 500 - 4000  $\text{cm}^{-1}$ . How many lines in the spectrum that involve stretching of CH bonds? Does each involve only one CH bond or several CH bonds? Is the line in the spectrum that involves stretching of the OH bond of lower or higher frequency than the lines that involve the CH stretches? Given that the mass of oxygen is greater than that of carbon, what (if anything) does this tell you about the "stiffness" of an OH bond relative to a CH bond? How does this relate to the relative strengths of OH and CH bonds?
2. The experimental infrared spectrum of 1-octyne is given below.





Assign each of the major bands ( $>1400\text{ cm}^{-1}$ ) to specific vibrational motions, for example, CH, CC and  $\text{C}\equiv\text{C}$  stretches and HCH and CCC bends.

3. The infrared spectrum of a dilute solution of 1-butanol in carbon tetrachloride contains two bands attributed to OH stretching. The more intense band is centered at  $3350\text{ cm}^{-1}$ . This has been taken as evidence that 1-butanol forms hydrogen-bonded dimers (or larger hydrogen-bonded clusters).

Examine the infrared spectrum of a hydrogen-bonded dimer of 1-butanol, and identify any lines corresponding to OH stretches. Is what you find consistent with the experimental spectrum with regard to both line placement and intensity? Which (if either) line is associated with the hydrogen bond? Rationalize why it is higher or lower in frequency than the line not associated with the hydrogen bond.

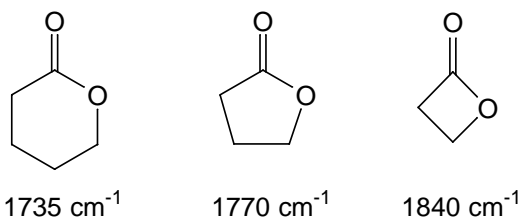
4. The infrared spectra of alcohols change markedly with increasing concentration. For example, at very low concentration, the infrared spectrum of 2-methyl-2-propanol in carbon tetrachloride contains a single sharp band at approximately  $3600\text{ cm}^{-1}$  corresponding to the OH stretching motion. As the alcohol's concentration increases (by adding more alcohol to the sample), a second broad OH stretch band grows in at approximately  $3400\text{ cm}^{-1}$  and eventually replaces the other band.

Examine the infrared spectrum of 2,3-dimethyl-2,3-butanediol (commonly known as pinacol). Is it closer to what is expected of a dilute solution or to a more concentrated sample? Rationalize what you observe in terms of the molecule's geometry.

5. Compare infrared spectra of acetic acid and its dimer. (Focus on the two "characteristic frequencies" of the acid, the  $\text{C}=\text{O}$  stretch and the OH stretch.) Do the changes that you observe parallel changes in geometry? (See activity 12 in *Carbonyl Compounds*.)
6. Examine the infrared spectrum of acetone and locate the line corresponding to CO stretch. Repeat for one or two more related ketones. Based on your observation, why do you think that IR

spectroscopy provides a reliable diagnostic for the presence of carbonyl functionality?

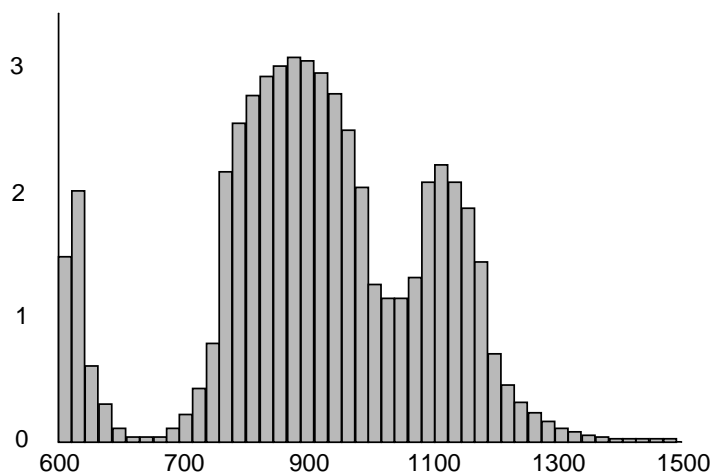
7. Examine the infrared spectra of compounds  $\text{MeCOX}$ : acetone ( $\text{X} = \text{Me}$ ), acetyl chloride ( $\text{X} = \text{Cl}$ ), methyl acetate ( $\text{X} = \text{OMe}$ ) and  $\text{N,N}$ -dimethylacetamide ( $\text{X} = \text{NMe}_2$ ). For each, locate the line corresponding to the  $\text{C}=\text{O}$  stretch. Are the frequencies noticeably different among the compounds? If they are, which molecule provides the smallest frequency? Which provides the largest? Is there a correlation between stretching frequency and  $\text{C}=\text{O}$  bond length?
8. The (experimental)  $\text{CO}$  stretching frequencies in lactones vary significantly with ring size.



Is the change in frequencies paralleled by a change in the  $\text{CO}$  bond distances? Is this unique to lactones or is the same trend also noted for the analogous lactones and ketones? Speculate on the origin of the change.

9. Which (if any) of the following molecules has one or more vibrational modes that are infrared inactive: water, carbon dioxide, acetone, 2-butyne? Describe each infrared inactive mode.
10. The earth acts as a blackbody that radiates into the universe. This provides a means to dissipate the energy that falls on it from the sun. Because of the earth's low ambient temperature, so-called blackbody radiation occurs primarily in the infrared. The earth is actually warmer than such a picture would predict, due to the fact that some of the blackbody radiation is absorbed by its atmosphere. This is known as the "greenhouse effect". The magnitude of the effect, "greenhouse warming", depends on both the extent and chemical makeup of the atmosphere. To be effective, a "greenhouse gas" must absorb in the infrared. Neither

nitrogen nor oxygen, which together make up the majority of earth's atmosphere, satisfy this requirement. Several "minor" atmospheric components, including carbon dioxide, water and ozone, absorb in the infrared and contribute directly to greenhouse warming. These "subtract" from the earth's blackbody radiation leaving a profile (in the range of 600 to 1500  $\text{cm}^{-1}$ ), meaning that, to be an effective greenhouse gas, a molecule must absorb in a region where blackbody radiation is intense.



Methane and nitrous oxide ( $\text{N}_2\text{O}$ ) are both released into the atmosphere from agriculture. Methane is also released as a result of oil recovery and fuel production. 1,1,1,2-tetrafluoroethane is now widely used in automobile air conditioners and is likely also released into the atmosphere in significant quantities. Which (if any) would you expect to be an effective greenhouse gas?

11. The infrared spectrum of a  $\text{C}_4\text{H}_4$  isomer shows strong absorptions at 215, 854, 1608, 2994 and 3080  $\text{cm}^{-1}$ . "Reasonable"  $\text{C}_4\text{H}_4$  structures include but-1-yne-3-ene, butatriene, singlet and triplet electronic states of cyclobutadiene, methylenecyclopropene and tetrahedrane. Examine the vibrational frequencies of each. Are all of these structures actually energy minima, or can you eliminate one or more? Which structure best fits the experimental infrared spectrum? Is it the lowest-energy  $\text{C}_4\text{H}_4$  isomer? Assign

the vibrational frequencies in the experimental spectrum using the data from the structure you selected.

12. While benzyne has long been implicated as an intermediate in nucleophilic aromatic substitution, it has never been isolated. However, the infrared spectrum of a molecule purported to be benzyne has been recorded and a line in the spectrum at  $2085\text{ cm}^{-1}$  assigned to the  $\text{C}\equiv\text{C}$  stretch.
- a. Compare the geometries of benzyne, 2-butyne and benzene. Does benzyne incorporate a “real” triple bond (as does 2-butyne) or is the length closer to that in benzene? Based on a comparison of structures among the three molecules, draw what you feel is an appropriate bonding arrangement for benzyne. Draw a Lewis structure (or set of Lewis structures).

To build benzyne, start with benzene and delete two adjacent free valences.

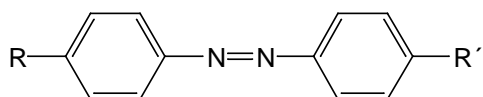
- b. Display the infrared spectrum of benzyne and locate the line corresponding to the “ $\text{C}\equiv\text{C}$ ” stretch. Is the predicted stretching frequency for benzyne in reasonable accord with the reported experimental value of  $2085\text{ cm}^{-1}$ ? Is the  $\text{C}\equiv\text{C}$  stretch “weak” or “intense” relative to the other lines in the benzyne spectrum? Would you expect that the  $\text{C}\equiv\text{C}$  stretch in benzyne to be easy or difficult to observe? Do you think that the infrared spectrum of benzyne has actually been recorded? Elaborate.
13. Examine the HOMO and LUMO of nitrogen (*activities* directory). Is the lowest-energy (longest-wavelength) electronic transition  $n \rightarrow \pi^*$  or  $\pi \rightarrow \pi^*$ ?
14. Examine the HOMO and LUMO of acetone (*activities* directory). Is the lowest-energy (longest-wavelength) electronic transition  $n \rightarrow \pi^*$  or  $\pi \rightarrow \pi^*$ ?
15. Does conformation affect  $\lambda_{\text{max}}$  for a diene? Examine 1,3-butadiene, 2-methyl-1,3-butadiene and 2-tert-butyl-1,3-butadiene (*activities* directory). Each file contains two plots, the first showing change

in total energy and the second change in the energy gap between HOMO and LUMO as a function of C=C–C=C dihedral angle. To first approximation, the HOMO/LUMO gap should mirror  $\lambda_{\text{max}}$ .

For each diene: At what dihedral angle is the HOMO/LUMO gap the largest? At what dihedral angle is it the smallest? Is there much difference in the HOMO/LUMO gap between *cis* and *trans*-planar diene conformers? Is there much difference among the three dienes? For each diene: Does the variation in total energy closely follow the HOMO/LUMO gap or are the two uncorrelated? What (if anything) does your result say about the importance of conjugation (double bonds coplanar) on diene conformation?

16. Light absorption causes an electron in a molecule to “jump” from the highest-occupied to the lowest-unoccupied molecular orbital (HOMO to LUMO). Therefore, the HOMO/LUMO energy gap can be used to estimate the color of light required for excitation.

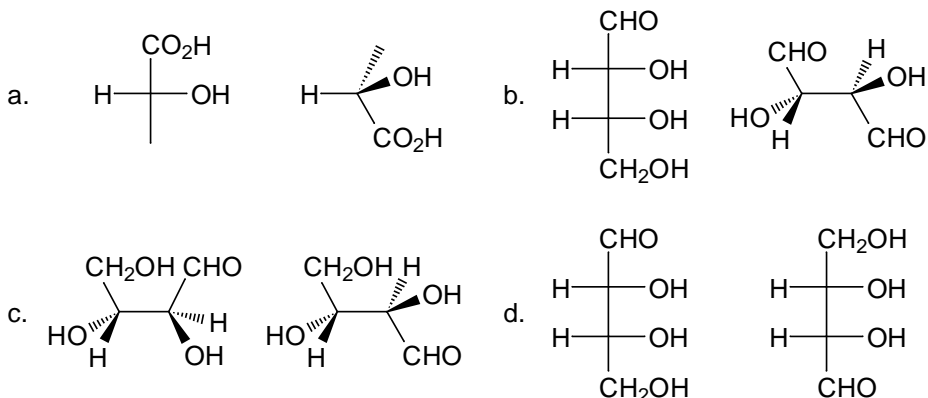
Compare HOMO/LUMO gaps for azobenzene ( $R=R'=H$ ), 4-hydroxyazobenzene ( $R=OH$ ,  $R'=H$ ) and 4-amino-4'-nitroazobenzene ( $R=NH_2$ ,  $R'=NO_2$ ).



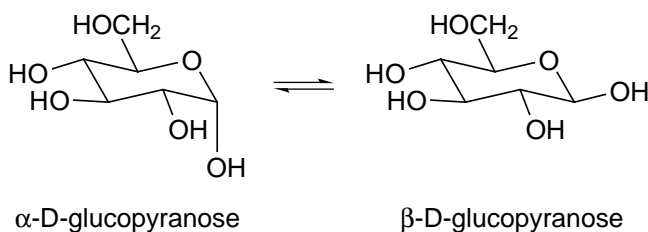
Azobenzene is orange. Predict the color of each of the other molecules, that is, shifted toward the red or blue end of the spectrum.

## Biomolecules

- Indicate the relationship between molecules in each pair: same molecule, enantiomers or diastereomers. Molecular mechanics calculations may prove of value in assisting you.

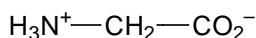


- The cyclic (pyranose) form of D-glucose can be crystallized in two different forms, “ $\alpha$ -D-glucopyranose” and “ $\beta$ -D-glucopyranose”.

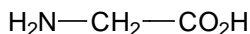


The forms have different melting points, and different specific rotations when dissolved in water. However, they eventually equilibrate via a process termed mutarotation. How are  $\alpha$ -D-glucopyranose and  $\beta$ -D-glucopyranose related? Are they constitutional isomers? Conformers? Enantiomers? Diastereomers? Is mutarotation a chemical reaction or an internal rotation?

- Glycine and other amino acids are usually drawn as zwitterions, with nitrogen positively charged and oxygen negatively charged.

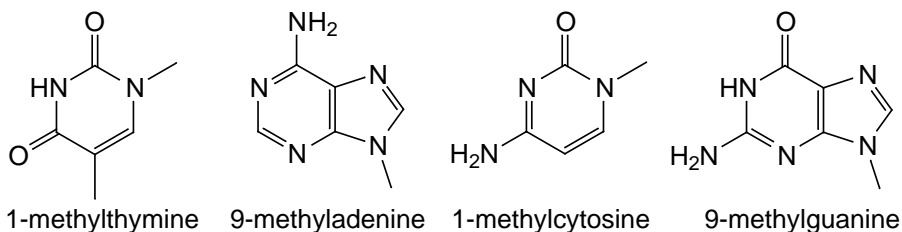


An alternative structure (tautomer) involves uncharged amino and carboxylic acid groups.



Compare atomic charges in the zwitterionic and non-zwitterionic forms of glycine. What is the total charge on  $-\text{NH}_3$  in the zwitterionic form? What is the total charge on  $-\text{CO}_2^-$ ? Are these charges much greater than those on  $-\text{NH}_2$  and  $-\text{CO}_2\text{H}$ , respectively, in the non-zwitterionic form of glycine? Is the dipole moment for zwitterionic glycine greater than that for the non-zwitterionic tautomer? Display electrostatic potential maps for both zwitterionic and non-zwitterionic glycine. Which form shows the greater charge separation?

- Examine the hydrogen-bonded complex of 9-methylguanine and 1-methylcytosine (as a mimic of the GC base pair in DNA).



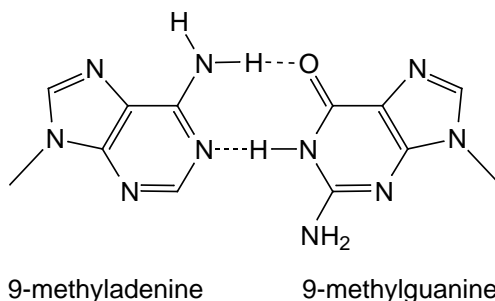
How many hydrogen bonds are there? Is the strength of an individual hydrogen bond comparable to that of a typical covalent bond or is it significantly smaller?

Repeat for the complex of 9-methyladenine and 1-methylthymine. Is the hydrogen bond strength (per hydrogen bond) comparable to that in the guanine-cytosine complex?

- Build a “strand” of DNA containing one AT base pair and one GC base pair. What is the distance between the carbon on the tetrahydropyran ring connected to adenine and the corresponding carbon connected to thymine? How does this compare with the corresponding distance for the G–C pair?

Examine the structure of an “alternative” base pair, that between adenine and guanine (use a methyl group at the 9 position in

adenine and at the 9 position in guanine to mimic the tetrahydropyran ring).



What is the distance between the (methyl group) attachment points? Would this base pair fit into DNA?

6. A potentially important case of tautomeric equilibrium involves the four nucleotide bases found in DNA: adenine, thymine, cytosine and guanine. Each may give rise to two or more tautomers. The structure of DNA assumes the predominance of only one tautomer for each base (the one drawn in textbooks), which in turn hydrogen bonds to its “complementary base”. Were any “alternative” tautomers present in significant amounts, the consequences could be catastrophic.

First, obtain the energy of a methyl derivative of one of the nucleotide bases in its usual tautomeric form (to mimic the connection to the sugar-phosphate backbone in DNA). See activity 4 for structures.

Next, obtain energies for all alternative tautomers for your chosen nucleotide base. Are any actually lower than that for the principal tautomer? According to the Boltzmann equation (see *Energy and Thermodynamics* in **Chapter 3**), would you expect the room temperature equilibrium abundance of the “best” of the alternative tautomers to be large enough to seriously affect DNA replication?

Repeat your analysis with the other nucleotide bases.



# Appendix





## SpartanModel Overview

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### A. Menus

#### **File**

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<u>N</u> ew (  )	Brings up a model kit for molecule building
<u>O</u> pen... (  )	Opens a molecule (or set of molecules)
<u>R</u> etrieve (  )	Retrieves a molecule by name from SpartanModel's database
<u>C</u> lose (  )	Closes a molecule
<u>P</u> rint...	Prints on-screen display
<u>P</u> rint Setup...	Setup for printing
<u>E</u> xit	Exits SpartanModel

#### **Edit**

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<u>U</u> ndo	Undoes previous operations
Cu <u>t</u> / <u>C</u> opy	Moves/copies the current molecule or contents of the selection box to the clipboard
<u>P</u> aste	Pastes contents of the clipboard to the screen
Center <u>u</u>	Centers the molecule on screen
C <u>l</u> ear	Clears the screen (build mode only)

#### **Model**

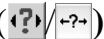


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<u>W</u> ire	Displays structure as wire-frame model
B <u>a</u> ll and Wire	Displays structure as ball-and-wire model
<u>T</u> ube	Displays structure as tube model
B <u>a</u> ll and Sp <u>o</u> ke	Displays structure as ball-and-spoke model
S <u>p</u> ace Filling	Displays structure as space-filling model
<u>H</u> ide	Hides structure model from view
H <u>y</u> drogens	Toggles hydrogens “on/off”
L <u>a</u> bel <u>s</u>	Toggles labels “on/off”

R <b>ibbons</b>	Toggles ribbons “on/off”
H <b>ydrogen B</b> onds	Toggles hydrogen bonds “on/off”
C <b>onfigure...</b>	Specifies labels for atoms, etc., and specifies ribbon displays







## **Geometry**

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M <b>ea</b> sure <b>D</b> istance (  )	Displays and/or sets bond distance
M <b>ea</b> sure <b>A</b> ngle (  )	Displays and/or sets bond angle
M <b>ea</b> sure <b>D</b> ihedral (  )	Displays and/or sets dihedral angle
D <b>efine P</b> oint	Defines a point as a geometric mean of a set of atoms
D <b>efine P</b> lane	Defines a plane made by three atoms

## **Build**

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V <b>iew</b> (  )	Removes the model kit
A <b>dd F</b> ragment (  )	Adds atomic fragment, group, etc.
D <b>el</b> ete (  )	Deletes atoms, points, planes, etc.
M <b>ake B</b> ond (  )	Makes a bond between atoms or free valences
B <b>reak B</b> ond (  )	Breaks a bond
M <b>inimize</b> (  )	Performs molecular mechanics energy minimization

## **Display**

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P <b>ro</b> perties	Displays molecule, atom, graphical surface and spectra properties
S <b>ur</b> faces	Displays graphical surfaces
S <b>pec</b> tra	Displays infrared spectra

## **Options**

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A <b>bo</b> ut...	Provides SpartanModel information
P <b>re</b> ferences...	Sets run-time preferences
C <b>ol</b> ors	Sets screen and model colors
F <b>on</b> ts...	Sets fonts for labels and plots

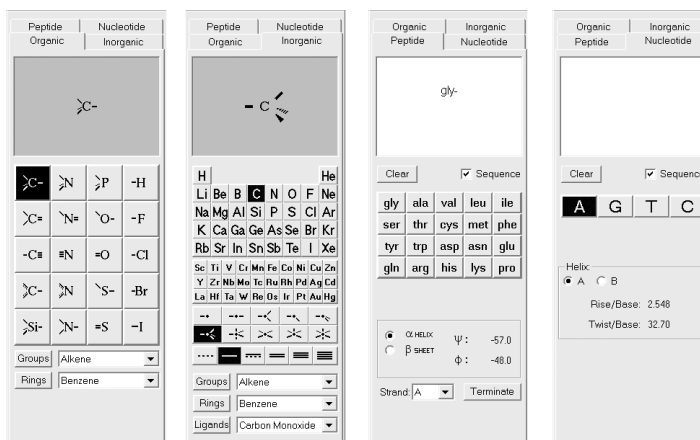
## Help

On-Line Help (?)

Provides on-line help

### B. Model Kits and Builder Functions

The **organic model kit** contains a suite of molecule building/editing tools specifically designed to construct organic molecules.



The model kit provides a selection of “atomic fragments” displayed as icons, and menus that provide access to common organic functional groups and hydrocarbon rings. Building initiates by selecting either an atomic fragment or an entry from the **Groups** or **Rings** menu and then *clicking* on screen. To add alongside of an existing structure, *press* the **Insert** key (**option** key for Macintosh), and then *click* anywhere on screen. To bond to an existing fragment, *click* on a free valence. Selection of bond type, i.e., single, double, triple or aromatic, in the case of atomic fragments with multiple bond types, e.g.,  $sp^2$  carbon, depends on the nature of the free valence selected.

The amide and carboxylic acid groups and cyclohexane, naphthalene, anthracene and phenanthrene rings have more than one free valence, and the free valence that will actually be used to connect to the molecule under construction is marked with a “•” (in the icon at the top of the model kit). The marked position circulates among the possible positions with repeated *clicking* on the icon. Selection of an *axial* or *equatorial* free valence in the cyclohexane ring is indicated

by the label “*ax*” or “*eq*” appearing alongside the icon. All rings in this menu are hydrocarbons. Heteroatoms may be substituted for the ring carbons using the atom replacement feature (see **Atom/Fragment Replacement** following).

The **inorganic model kit** provides tools for construction of inorganic and organometallic compounds as well as molecules that violate conventional bonding rules. The inorganic model kit is reached by *clicking* on the **Inorganic** tab at the top of the model kit.

At the top of the model kit is a *Periodic Table*\*. Below is a selection of atomic hybrids and a selection of bond types. Near the bottom of the model kit are menus of **Groups**, **Rings** and **Ligands**. Selection of element is effected by *clicking* on the appropriate entry in the *Periodic Table*, which will then be highlighted. Selection of an atomic hybrid follows by *clicking* on the appropriate icon which will then be highlighted. Once fully specified, the “atom” (element + atomic hybrid) can be used to initiate building, to add alongside of an existing structure or to add to an existing molecular fragment.

Two of the hybrids (trigonal bipyramidal and square-based pyramidal) may bond either *axially* or *equatorially*. Selection of the appropriate bonding point, marked by a “•”, is effected by repeatedly *clicking* on the icon at the top of the model kit.

All atoms are initially connected with single bonds. Bond types (partial single, single, aromatic, double, triple or quadruple) may be changed by first selecting the appropriate bond type from those available, then *clicking* on the bond to be changed, and then *clicking* again to institute the change, i.e., *double clicking* on the bond.

No valence checking is performed in the inorganic model kit.

The **peptide model kit** provides for construction of polypeptides. It is reached by *clicking* on the **Peptide** tab located at the top of the model kit.

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\* SpartanModel on Macintosh brings up a separate window containing a *Periodic Table* upon *clicking* inside the box to the left of “Element”. An element is selected from the *Periodic Table* by *clicking* on it.

At the middle of the peptide model kit are icons designating the amino acids (specified by three-letter codes). An amino acid is selected by *clicking* on its code, following which, either the code is appended to the sequence of codes in the box or an icon of the amino acid is displayed in the box at the top of the model kit, depending on whether the box to the left of **Sequence** is or is not *checked*. Peptide construction (**Sequence checked**) is accomplished in three steps:

- (i) Specification of an amino acid sequence. This is accomplished by *clicking* in the desired order on the amino acid codes. Building occurs from the “N” end to the “C” end of the peptide.
- (ii) Specification of macroscopic structure. Once sequencing is complete, macroscopic structure ( $\psi$  and  $\phi$  angles), is specified by *clicking* on one of  **$\alpha$  Helix** or  **$\beta$  Sheet**. In response, preset angle values are displayed on the right.
- (iii) Termination. *Clicking* on the terminate button replaces the “C end” with  $\text{CO}_2^-$  and the “N end” with  $\text{NH}_3^+$ . Note that, following termination, hydrogens occupy all free valences.

The peptide may now be used to initiate building, to add alongside of an existing structure, or to add to an existing structure.

The **nucleotide model kit** provides for construction of strands of DNA. It is reached by *clicking* on the **Nucleotide** tab located at the top of the model kit.

A nucleotide base is selected by *clicking* on its letter code: A = adenine, G = guanine, T = thymine, C = cytosine. Following this, either the letter for the base is appended to the sequence of letters in the box or an icon of the base is displayed in the box at the top of the model kit depending on whether the box to the left of **Sequence** is or is not *checked*. Polynucleotide construction (**Sequence checked**) is accomplished in two steps:

- i) Specification of base sequence. This is accomplished by *clicking* in order on the base codes. The sequence can be altered or cleared, (by *clicking* on **Clear**).

- ii) Specification of helical structure. These “Standard” A and B helices may be specified by *clicking* on **A** or **B**, respectively. Rise (in Å) per base (**Rise/Base**) and twist (in degrees) per base (**Twist/Base**) are reported.

The polynucleotide may now be used to initiate building, to add alongside of an existing structure, or to join onto an existing structure. In the latter case, attachment is made from the “phosphate” end.

### Bond Rotation/Bond Stretching

To rotate about and stretch bonds not incorporated into rings:

- (i) *Click* on the desired bond which will then be marked by a red cylinder. (The bond connecting the last “atom” added to the molecule is automatically selected.)
- (ii) Simultaneously *press* the **Alt** key (**spacebar** on Macintosh) and the left button and *drag* the mouse, for bond rotation, or the **Alt** key (**spacebar** on Macintosh) and the right button for bond stretching.

### Atom/Fragment Replacement

*Double clicking* on an atom (not a free valence) with an atomic fragment (organic model kit) or an atom icon (inorganic model kit) highlighted, replaces this atom by the selected atomic fragment or atom icon. In the organic model kit, free valences are adjusted to accommodate the replacement, e.g., replacement of  $sp^3$  carbon by  $sp^3$  oxygen results in two free valences being removed. Atom replacements that violate valence rules or which would disrupt substituents are not permitted. In the inorganic model kit, atom replacement merely changes the atomic number. No changes in the number or arrangement of free valences is made, and no checking is done.

### Chirality Inversion

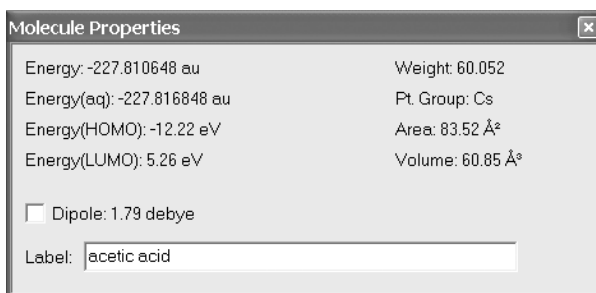
*Press* the **Ctrl** key and *double click* on an atom to invert its chirality.

## C. Properties Dialogs

SpartanModel provides dialogs for reporting the properties of molecules, atoms and graphical surfaces. Only one **Properties** dialog is permitted on screen, and this dialog refers either to the selected molecule (**Molecule Properties**), or to the selected atom (**Atom Properties**) or graphical surface (**Surface Properties**). Selection of a different molecule (with a **Properties** dialog on screen) leads to the **Molecule Properties** dialog for the newly selected molecule.

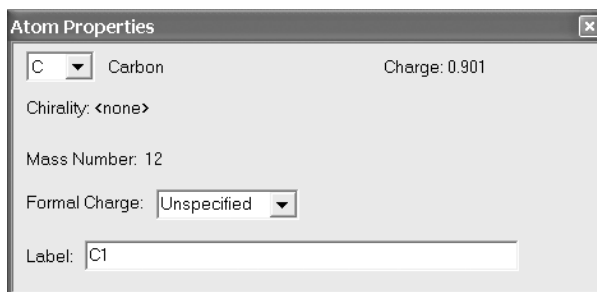
Dialog selection operates in “toggle” mode, with the **Molecule Properties** dialog being in “neutral”. With the **Molecule Properties** dialog on screen, *clicking* on an atom brings up the **Atom Properties** dialog. *Clicking* on a different atom or on a graphical surface brings up the appropriate **Properties** dialog. On Windows, *clicking* a second time on the same component reverts back to the **Molecule Properties** dialog. On Macintosh, *clicking* on the background leads to the **Molecule Properties** dialog.

### (i) Molecule Properties



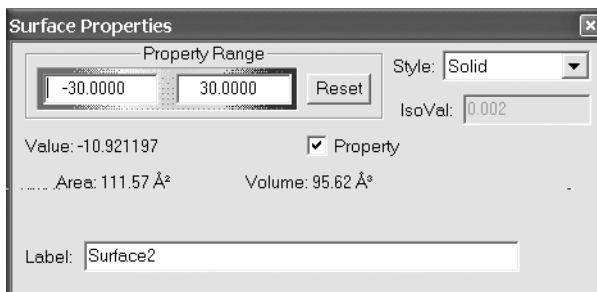
Displays the total energy (in au), or strain energy (in kJ/mol) in the case of a molecular mechanics calculation, HOMO and LUMO energies (in eV), dipole moment (in debyes), molecular weight (in amu), surface area and volume (in Å<sup>2</sup> and Å<sup>3</sup>, respectively) and symmetry point group. Permits turning “on” and “off” the dipole moment vector.

## (ii) Atom Properties



Displays the element name, mass number, R/S chirality, and charges (in electrons), and allows for setting formal charge.

## (iii) Surface Properties



Displays the area (in Å<sup>2</sup>) and volume (in Å<sup>3</sup>) of the surface. Allows for turning “on” and “off” and setting the range of a **Property** map and the display **Style**. Reports the “value” of the property at the cursor position on a property map. To obtain the property value at another position, move the cursor and *click* (*double click* on Windows).

## (iv) Other Properties

SpartanModel provides dialogs for other “properties”, for example, dialogs for bond properties and to query and adjust plots. Note that, except for IR Spectra, plots cannot be generated from SpartanModel, although plots read in as Spartan files may be displayed.