Introduction to molecular modeling

Molecular modeling is a multi-disciplinary activity combining chemistry, physics, mathematics, and computer software. Although its use is rapidly growing, it is still, in my opinion, underappreciated and underutilized.

Modeling’s current status probably owes its roots to the low quality models that were available until just a few years ago. Most working chemists learned their science without using models, or occasionally making a plastic model. Years of model-free thinking has taught them that models do not play an important part in intellectual pursuits.

Another problem holding back wider model use is the interdisciplinary nature of molecular modeling. Modern modeling tools depend in vital ways on chemistry, quantum mechanics, statistical mechanics, mathematics, and computer software. Hardly any chemist (including yours truly) feels comfortable at the nexus of these intellectually demanding fields.

Fortunately, useful models can be produced by anyone with even a modest understanding of computer software, physics and mathematics. Far more important is a good understanding of chemistry. Molecular modeling is fundamentally a tool for generating information about molecules. Therefore, you need to have some idea what information will prove useful, and you need to have some idea how to extract this information from a model. The key to successful modeling is to begin with a positive mindset that says, "Looking at a molecule and some of its properties can show me things that I might not think about otherwise, so let's take a look!" You will quickly discover that molecular modeling is easier, and often more rewarding, than you think.

Goals

The goal of this homework assignment is to (re)introduce you to our main modeling tool, the Spartan molecular modeling program. Three skills are emphasized in this assignment:

1. Building a trial model and refining its geometry
2. Locating data output
3. Creating and working with graphical data, e.g., potential maps.

Additional modeling skills will be developed during in-class modeling sessions and future homework assignments.

This homework assignment is divided into two parts: a “practice” section in which you can practice each of the skills listed above, and an “assignment” section in which I ask you to make some specific models and tell me about their properties. The practice section should be completed before class on Friday, Feb. 3 (there is nothing to hand in for this section). The assignment section is due at the end of the following Monday, Feb. 6.

STUG ALERT. STUG is my abbreviation for the Spartan '04 Windows Tutorial & User's Guide. This book contains detailed step-by-step instructions for the use of Spartan. Please refer to this book (several copies can be found in the chemistry computer lab) if you need more detailed help. It contains a tutorial, a user’s guide, a table of contents, and an index.

STUG On-Line ALERT. If you can’t find a copy of STUG in the lab, you can access an electronic version from your computer. Simply start Spartan '04, click Help: On-line help and follow the link at the bottom of the window (it helps to maximize the window). The electronic version of STUG does not contain an index, but the table of contents is hyperlinked to the appropriate pages.

Spartan Model ALERT. The chemistry lab computers contain two “Spartan” programs: Spartan '04 and Spartan Model. These programs are similar in many respects, but this course will only use Spartan '04. Make sure you are using the correct program during your modeling sessions.
Handling models: New, View, Modify, Open, Close, Save, Delete

To create a new model, click (or select File: New).

**Reading ALERT:** menu commands are specified here as a series of menu labels separated by colons. File: New means click New on the File menu.

**Mouse ALERT:** all “select” and “click” operations are performed using the left mouse button.

This opens a Modify window and moves Spartan into Modify mode ( is pressed). The Modify window is divided into a model area on the left and a palette of small model pieces on the right.

After you build a model, switch to View mode by clicking .

You can switch back and forth between Modify and View modes by clicking and (or by selecting Build: Add fragment and Build: View).

You can open, close, or save a model, at any time by clicking , , or (or by selecting commands from the File menu). To delete a model, you must close the model, find the model file in the My Documents folder, and throw it away.

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**Practice Handling and Moving Models**

Start a new model. Select Rings: Benzene from the palette and click inside the model area on the left. Switch to View mode.

**Dangling bond = Hydrogen ALERT:** When you switch between Modify and View modes, dangling yellow bonds are replaced by white hydrogen atoms, and vice versa.

Save your model (name it benzene).

**My Documents folder ALERT:** Files must be stored in the My Documents folder or in a subfolder. This limitation applies to the chemistry computers only.

Switch back to Modify mode. Click on the tip of a dangling bond. This replaces the dangling bond (hydrogen) with a second benzene ring. Save your model (name it biphenyl).

**Moving models (Rotate, Translate, Resize) ALERT:** Different mouse keys initiate different model movements. Try each of the following operations until you feel like you can anticipate what each operation will do:

- **Rotate around x/y axis.** Press left mouse button + move mouse.
- **Rotate around z axis.** Press left mouse button + SHIFT key + move mouse.
- **Translate along x/y axis.** Press right mouse button + move mouse.
- **Translate along z axis (RESIZE).** Press right mouse button + SHIFT key + move mouse.

Switch to View mode and open benzene. Although both models are visible, only one model is active. The name of the active model is given at the top of the Spartan window. Mouse operations affect only the active model. You can make any visible model active by clicking on it. Practice switching between models and moving the active model. Also practice switching back and forth between View and Modify modes. All models are displayed in View mode, but only the active model is displayed in Modify mode.
Building models: Entry builder

Models are mainly built by combining small pieces: atoms, functional groups, and rings. Spartan provides several palettes of small pieces called the Entry builder, the Expert builder, the Peptide builder, and the Nucleotide builder. These palettes are abbreviated Ent, Exp, Pep, and Nuc, and you access each palette by clicking on the appropriate label at the top of the palette. The Entry builder can be used to build most "normal" organic molecules.

Universal building rules:

1. **Start with one piece:** Select a piece (atom, functional group, or ring) from the palette and click anywhere in the model area.
2. **Add pieces to your model:** Select a piece that you want to add and click on the tip of a dangling bond (yellow).
3. **Match bond types:** When adding a piece, the bond type of a dangling bond in the piece being added must match the bond type of the dangling bond that you click on.
4. **Don't add hydrogens:** Dangling bonds turn into hydrogen atoms when you switch from Modify mode to View mode.
5. **Don't worry about formal charges or radicals:** The location of charges and unpaired electrons in a molecular model is governed by its electron distribution. This part of the model is created later.

**Trial model ALERT:** Spartan connects your pieces together assuming standard distances and angles for all bonds. This produces a trial geometry that does not reflect the individual characteristics of your molecule, e.g., the bond angles around tetrahedral atoms are exactly 109.47° in a trial geometry regardless of the neighboring atoms and their spatial requirements. I will tell you how to refine the geometry (and obtain other model properties) in a later section.

**Practice building trial models (Entry builder)**

**Full window ALERT:** The Spartan window opens incorrectly on our computers. Always maximize the window (click on maximize button in upper right corner) so you can see the full window.

Build a trial model of benzoic acid, PhCO2H, using each of these methods (when you finish one model, clear it from the model area by selecting Edit: Clear before you begin the next model):

- Start with a benzene ring (Rings: Benzene) then attach, in order: \(\text{C} = \text{O} - = \text{O}\). Notice that Spartan will complain if you try to mismatch bond types, e.g., by connecting divalent O to a dangling double bond on C. Do not attach hydrogens (see above); to see hydrogen locations, switch to View mode.

- Start with a benzene ring. Attach a carbonyl group (Groups: Carbonyl) and

- Start with a benzene ring. Attach a carboxyl group (Groups: Carboxylic Acid).

Some functional groups and rings have multiple attachment points, e.g., a carboxyl group can be attached via C or O. The attachment point is shown as a yellow dot on the formula (top of palette window). You can change the attachment point by clicking on the formula. Try this with the carboxyl group, then try building phenyl formate, PhOCH(=O).

**Delete tool**. Anions are often obtained by deprotonating neutral molecules. We can build a model of this kind of ion by building a model of the neutral molecule and removing the dangling bond that represents the acidic proton. Try this out by building benzoate anion, PhCO2-. First,
build benzoic acid, \( \text{PhCO}_2\text{H} \). Then click \( \text{X} \) and click the dangling bond on O. Notice that this removes an atom (switch to View mode to verify this), but it does not adjust bond types, distances, or angles. Your trial geometry must be refined by a modeling calculation (described later) before it can be considered realistic.

**Rotate around active bond (internal rotation).** Press left mouse button + ALT key + move mouse. When you build a model, the most recently formed bond has a small red arrow girdling it. This is the active bond (to make another bond active, click on it). You can rotate the model around this bond (either the entire model or half of the model) by pressing the ALT key and using the mouse. Try this out by adding a chain of several atoms to the current model. First, change the active bond by clicking on different bonds. Next, try rotating around each bond (ALT key). Notice that rotation about active terminal bonds or active ring bonds moves the entire model and leaves its geometry intact, but rotation about “chain” bonds moves half of the model (internal rotation) and changes the model’s geometry.

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### Building models: Expert builder

The Expert palette contains many more options than the Entry palette. Some common reasons for using the Expert palette include:

- Your model contains atoms not found on the Entry palette, e.g., transition metals
- Your model contains an atom with a nonstandard geometry, e.g., linear \(-\text{O}–\)
- Your model contains an atom that is bonded to *more* than the usual number of neighbors, e.g., \(\text{ROH}_2^+\) or \(\text{R}_3\text{NH}^+\)
- You want to adjust the bond type to a nonstandard type, e.g., a partial single bond

You might think that the Expert palette, because of its flexibility, is the preferred building tool in all situations, but this is definitely not the case. The Expert palette is powerful, but inconvenient to use. Every atom in the Expert palette must be built in two steps before it can be used. Likewise, bonds other than single bonds must be built in two steps.

**Expert-only building rules:**

1. **Atom + coordination environment.** Atom pieces are defined by choosing an atom from the pseudo-Periodic Table palette and a coordinaton environment from the next palette. The formula of the atom piece is shown above the Periodic Table. Try selecting different atoms and coordination environments so that you understand this feature.

2. **Dangling single bonds only.** The dangling bonds on an Expert atom are always single and can only be attached to dangling single bonds in your model. If you need to attach an Expert atom to a dangling multiple bond, you will need to modify the dangling bond so that it is a dangling single bond (see below), make the bond, and then modify the bond again so that it is of the appropriate type.

3. **Modifying bonds.** Bond types of dangling and completed bonds can be modified by clicking on the bond type palette (just below the coordination environment palette) and double-clicking on the bond of interest (note: a single click makes the bond active, but does not change its type).

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### Practice building trial models (Expert builder)

**Glycine zwitterion, \(\text{H}_3\text{N}^+\text{CH}_2\text{CO}_2^-\).** Start with a tetrahedral C for the alpha C. Add tetrahedral N and a carboxyl group (Groups: Carboxylic Acid). Delete the dangling bond on O. The most plausible geometry for this model contains an intramolecular hydrogen bond, \(\text{N}^+\cdot\cdot\cdot\text{H} \leftrightarrow \text{O}^-\). If necessary, rotate around the CN and CC bonds (ALT key) to bring these atoms near each other.
Iminium ion, H$_2$C=N$^+$ (CH$_3$)$_2$. This cation can be formed experimentally by combining formaldehyde, CH$_2$=O, and dimethylamine, HN(CH$_3$)$_2$. Build a trial model by starting with trigonal C. Add trigonal N and change the CN bond from single to double. Finally, attach two tetrahedral C:

![Model of Iminium ion](image)

**Phosphoric acid, (HO)$_3$PO.** The formula for phosphoric acid is usually written H$_3$PO$_4$, but this hides the fact that there are four PO bonds. Start with tetrahedral P. Add one terminal O and three bent O. Depending on your personal tastes, you can leave the unique PO bond as a single bond or change it to partial double, or even double. None of these choices will affect subsequent calculations.

**Sulfur tetrafluoride, SF$_4$.** This molecule looks like a trigonal bipyramid with a missing atom in an equatorial position. Start with trigonal bipyramidal S. Add four terminal F and delete the dangling equatorial bond on S:

![Model of Sulfur tetrafluoride](image)

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**Building models: Extra skills**

This section completes your introduction (review) of basic model building skills. The material covered in this section includes an assortment of skills:

- Replacing one atom with another
- Connecting dangling bonds together to make rings and multiple bonds with **Make bond**
- Cleaning up trial geometries with **Minimize**

**Atom replacement.** Atom replacement allows you to change an atom in your model from one element into another. To accomplish this, simply select the atom you want from the palette and double-click on the atom that you want to replace.

**Entry builder atom replacement ALERT:** Replacements in the Entry builder are allowed only if replacement does not change existing bonds. The dangling bonds, however, do not have to match and are adjusted to fit the new atom.
The following steps show how to build the epoxypyridine shown above from an all-carbon model:

- **Construct phenylcyclopropane (Rings: Benzene + Rings: Cyclopropane)**

- **Select (Entry builder) and double-click on the appropriate benzene C. Notice that N’s bond pattern matches the bonds that C has already made, and that C’s dangling bond is removed.**

- **Select (Entry builder) and double-click on the appropriate cyclopropane C. As before, notice that O’s bond pattern matches the bonds that C has already made, and that C’s dangling bonds are removed.**

**Expert builder atom replacement ALERT:** Replacements are always allowed. No bond changes occur and the new atom inherits all of the original bonds (and the original geometry).

This atom replacement provides an efficient tool for producing a model in which one atom has made an unusual number of bonds. Simply build a model using an atom for which this bond pattern is normal and then use atom replacement to insert the desired atom.

For example, the N in dimethyliminium ion, \( \text{H}_2\text{C} = \text{N}^+\text{(CH}_3\text{)}_2 \), makes four bonds, the number normally made by C. Therefore, we can build this ion from an all-carbon model as follows:

- Start with an alkene (Groups: Alkene)
- Add two tetrahedral C to one alkene C
- Select N (Expert builder) and double-click on the substituted alkene C. Notice that N inherits the C’s bond pattern and geometry.

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**Practice building trial models by atom replacement**

Start by building the molecule in box. Then replace atoms as needed (figure out whether the Entry or Expert builder gives the results you need).

<table>
<thead>
<tr>
<th><strong>2,2'-bipyridine (bipy)</strong></th>
<th>![bipy]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N,N-dimethylaminopyridinium ion (DMAP-H(^+))</strong></td>
<td>![DMAP-H(^+)]</td>
</tr>
<tr>
<td><strong>trimethyloxonium ions</strong></td>
<td>![oxonium]</td>
</tr>
<tr>
<td><strong>pyridine N-oxide</strong></td>
<td>![pyridine-N-oxide]</td>
</tr>
</tbody>
</table>
**Make bond** and **Minimize** tools. Any pair of dangling bonds can be connected together to form a new bond. Click **Make bond** and then click the tips of the dangling bonds that you want to connect. The result is a multiple bond or ring with the same geometry as the original model.

**Make bond** changes a model's bond pattern, but not its geometry. After you use **Make bond**, you should always click **Minimize** so that the model geometry will reflect the new bond pattern.

**Minimize ALERT:** **Minimize** revises your model's geometry on the basis of a molecular mechanics calculation. I am going to deliberately avoid a discussion of this calculation for now. All you need to know right now is this: 1) the calculation proceeds by trial-and-error, so you may see your model twitching around on the screen as various geometries are considered, and 2) the resulting geometry, although improved, must still be considered a trial geometry.

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**Practice building trial models by making bonds and minimizing**

**Dihydropyran.** Dihydropyran is commonly used to protect alcohols. The diagrams show just two ways to build a trial model of molecule. You can start with cyclohexane (**Rings: Cyclohexane**) and connect vicinal dangling bonds to make a double bond in the ring. Or, you can start with ethylene (**Groups: Alkene**), add O to one alkene carbon and 3 tetrahedral C’s to the other alkene C (**note:** substituents must be added *cis*), and connect O and C together to make a ring. Don’t forget to **Minimize** the model after you use **Make bond**.

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**Prismane.** Polycyclic models must be built using **Make bond** whenever any atom is shared by two or more rings. This is the case in prismane; every C in this strained molecule belongs to three different rings!

As the diagram shows, prismane can be constructed easily from cyclopropylcyclopropane. First rotate about the indicated bond (**ALT** key) to make the eclipsed conformer, and then use **Make bond** to form two additional CC single bonds. Don’t forget to **Minimize**, or your model will look quite silly.

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**Calculating an equilibrium geometry and molecular energy**

The geometry that defines a molecule’s characteristic properties is its equilibrium geometry, or geometry of lowest potential energy. The theory behind potential energy calculations and equilibrium geometry calculations will be discussed in class. This section simply shows you how to setup and perform these calculations using a particular electron/energy model: Hartree-Fock/3-21G(*).
First, build a model of methanol, CH₃OH. Next, switch to View mode.

To setup and perform an equilibrium geometry calculation, do the following:

- Click Setup: Calculations. This opens the Calculations window. You can read the entries in this window almost as if they formed a sentence. Set the menu entries so that the window reads:

  
  Calculate Equilibrium Geometry at Ground state with Hartree-Fock 3-21G(*). Start from Initial geometry, Subject to Symmetry.

- Next, tell Spartan the overall charge and number of unpaired electrons for your model by setting the Total Charge and Multiplicity to read:

  
  Total Charge: Neutral, Multiplicity: Singlet.

- Finally, click Submit. You will be asked to save your model. After you save it, the calculation will begin automatically and two message windows will inform you that the calculation has started and completed, respectively. Once the calculation has completed (a matter of just a few minutes for a small molecule like methanol), your model’s geometry and data files will be updated automatically.

Troubleshooting ALERT: The equilibrium geometry/energy calculation is a sophisticated and sensitive procedure. If there is a chance of something going wrong, it is here. I have listed some of the most common “unpleasant” outcomes below:

- **Calculation never seems to end. No “job completed” message ever appears.**
  o In most cases, this message appears because you forgot to click Submit. Check Setup: Calculations to see if Submit is active (black) or in use (gray).
  o Another explanation is that you set up a more time-consuming calculation than the one I suggested. Compare your Setup entries to mine (see above). If you chose something more demanding, it may be necessary to kill your calculation. See STUG, p. 244, for instructions on killing calculations.
  o Yet another explanation is that some other process, e.g., a virus scan, is running on the computer and hindering your calculation. See me if you think this is a possibility.

- **“Error” or “Failed” message appears.** Most errors and failures fall into two categories: improper setup and incomplete optimization.

  o Improper setup occurs when there is a mismatch between your model and the entries in your setup. For example, Multiplicity: Singlet means all electrons are paired, i.e., the model contains an even number of electrons. However, setting methanol’s Total Charge to Cation (or Anion) implies an odd number of electrons. Spartan can’t resolve this conflict, so you need to check your setup all over again. Did you build your model correctly? Did you specify the Total Charge and Multiplicity correctly?

  o Incomplete optimization is not really an error or failure at all. It is triggered by a safety procedure that is built into Spartan. Equilibrium geometry calculations proceed by trial-and-error, and it is possible (though rather unlikely) that a calculation will never reach an equilibrium geometry. To prevent this situation from locking the computer into an endless loop, Spartan decides how many trials it is willing to risk on a trial-and-error process and stops when this number is reached. Spartan reports this as a failed calculation, but you should regard this as a partial calculation. All you need to do is click Setup: Submit and the calculation should proceed to a satisfactory conclusion.

Molecular energy. At this point, we are most interested in the molecular energy and geometry. To see the results of the energy calculation, click Display: Properties. The potential energy
should be displayed as **Energy: -114.398019 au.** (Any energy that reads -114.3980… is acceptable.)

**Atomic units ALERT:** Certain results are reported in atomic units or **au**. The atomic unit of energy is called the **Hartree**. 1 Hartree (or 1 au) = 627.5 kcal/mol = 2625.5 kJ/mol.

**Equilibrium geometry tools**. Clicking on any of these icons will give you information about molecular geometry. The three tools provide information about distances, bond angles, and dihedral angles, respectively. To use them, click on an icon, click on the required number of atoms (a gold sphere shows a selected atom), and read the resulting value from the lower right corner. Check your results for methanol against the ones listed below.

<table>
<thead>
<tr>
<th>Equilibrium bond distance (in Å)</th>
<th>OH = 0.966</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH = 1.079, 1.085</td>
</tr>
<tr>
<td></td>
<td>CO = 1.441</td>
</tr>
<tr>
<td>Equilibrium bond angle (in °)</td>
<td>HOC = 110.34</td>
</tr>
<tr>
<td></td>
<td>HCO = 106.28, 112.23</td>
</tr>
<tr>
<td>Equilibrium dihedral angle (in °)</td>
<td>HCOH = ±61.41, 180.00</td>
</tr>
</tbody>
</table>

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**Calculating and displaying a potential map**

*Spartan* can display information about the electron distribution using a variety of surfaces and maps. The distinction between a surface and a map is subtle.

- **Surface.** Also called **isosurface.** Surfaces are parts of a three-dimensional contour graph. Each surface passes through all of the points in space where some designated variable (HOMO, LUMO, electron density, electrostatic potential, etc.) has a particular value.

- **Map.** A map shows variations in the value of a designated variable (HOMO, LUMO, electron density, electrostatic potential, etc.) across a set of points. *Spartan* maps can be drawn on isosurfaces or "slices" (a horizontal plane).

You have seen potential maps used in other courses. A potential map shows variations in the value of electrostatic potential across an isodensity surface, usually the 0.002 au surface. The variations in potential are color-coded so that red regions represent the most negative potentials and dark blue regions represent the most positive potentials.

- Red < Yellow < Green (median value) < light Blue < dark Blue

**Setup and display.** Setup a potential map calculation by clicking **Setup: Surfaces.** Click **Add.** Then set **surface: density, property: potential, and resolution: medium** (or **intermediate**). Click **OK** (this adds your map to the list in the window) and click **Setup: Submit.**

After the map has been calculated, you can display it and adjust its appearance.

To display a map, click **Display: Surfaces** and click in the map’s yellow box.

To adjust a map’s appearance, click **Display: Properties** and click on the map until you see a window titled **Surface Properties.** This window is loaded with information, so I’ll just focus on a few items:

- **Style.** You can switch between Solid, Transparent, Mesh, and Dots.
• Property Range. The extreme values of the map potentials in kcal/mol are listed in the two boxes: red = most negative and blue = most positive. You can change these values by typing new values in the boxes and pressing Enter on the keyboard, and you can reset to the default values by clicking Reset. My methanol map shows potentials ranging from -60.4 to +55.0 kcal/mol. If I change -60.4 to -20.4, more of the map is colored red. The red zone on the revised map shows where the potential is -20.4 or less. Changing the values in the range boxes does not change the potentials on the map, just the way colors are assigned to different regions.

Assignment #2

The following assignment is due on Monday, Feb. 6, at the end of the day. I’m allowing a little extra time for this part so that you can ask me questions.

Build trial models of the four molecules shown below. Calculate the Hartree-Fock/3-21G(*) equilibrium geometry, molecular energy, and potential map of each model (note: these molecules are fairly large, so it could take anywhere from 5-50 minutes for each calculation to finish).

• Report the Hartree-Fock/3-21G(*) potential energy of each model.
• Use the energies to calculate the potential energy change (in kcal/mol) for each reaction.
• Briefly explain why one side of each equilibrium is preferred. Back up your answer by referring to specific features of the potential maps and equilibrium geometries that you find significant.

Reaction #1

\[
\begin{align*}
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{H}
\end{align*}
\quad \leftrightarrow \quad 
\begin{align*}
\text{H} & \quad \text{N} \\
\text{N} & \quad \text{H}
\end{align*}
\]

Reaction #2

\[
\begin{align*}
\text{NC} & \quad \text{H} \\
\text{N} & \quad \text{H}
\end{align*}
\quad \leftrightarrow \quad 
\begin{align*}
\text{NC} & \quad \text{H} \\
\text{N} & \quad \text{H}
\end{align*}
\]