Chem 322 - Organic Chemistry II
Laboratory Exercise – Molecular Modeling – Part 1

The term "molecular modeling" implies building a model of a molecule. This is usually done with the idea that, if the model is a good one, it will reveal something about the properties of the substance being modeled.

Two types of molecular models have been in use for over 100 years; they are structural formulas and physical molecular models. Today, chemists regularly employ Lewis structures to explain and predict properties like electron distribution and reactivity. Physical models, ranging from inexpensive plastic "ball and tube" kits to carefully crafted space-filling models, are employed to help us visualize chemistry in three dimensions.

A third type of molecular model is of more recent origin; it is the computer generated molecular model. This type of molecular modeling is about 50 years old, but was the province of specialists until about 10 years ago. At that time desktop computers became powerful enough to do the necessary calculations. Consequently, programs like Titan and Cache have been developed to enable chemists, without a lot of specialized training, to produce models of compounds that are of interest to them. Computer generated models can provide information that is not available from the more classical types – accurate bond angles and (perhaps not quite so accurate) bond energies, for example. On the other hand, even today, a computer is a lot more expensive than pencil and paper or plastic tubing. More importantly, if you treat the model generating program as a "black box" or are clueless about real-world chemistry, the results you obtain can be misleading.

Computer generated molecular models are based either on *molecular mechanics* calculations or *molecular orbital* calculations. Molecular mechanics treats a molecule using classical physics. Basically, the molecule is considered to be an assembly of masses (the atomic nuclei) held together by springs (the bonds). A molecular mechanics program is likely to be aware of bond angles, steric repulsions, vander Waals attractions, repulsion between charges of like sign and attraction between charges of unlike sign. Since quantum mechanics is not involved in these calculations, electrons are not specifically taken into account. These calculations are usually successful in calculating conformations and frequently produce a reasonable geometry for a molecule as a whole. Since quantum mechanics is not involved, these calculations are fast. This means they can be applied to large molecules containing hundreds of atoms – proteins, for example.

In molecular orbital calculations the electrons are explicitly considered. Computationally this is much more difficult than molecular mechanics and takes much longer, as you shall see! Molecular orbital calculations come in different degrees of sophistication. The simplest, fastest, and usually least accurate are called semi-empirical. These methods use adjustable parameters (sometimes derisively referred to as fudge factors) in the calculations. *Ab initio* methods do not use adjustable parameters and give better results for some molecular properties than the semi-empirical methods. There are a number of ab initio methods of varying sophistication (Hartree-Fock, Møller-Plesset, etc.). The more sophisticated the method the longer the calculation takes. Calculation
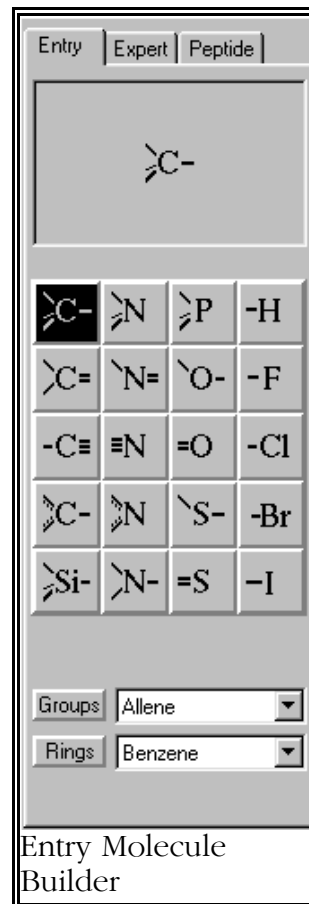
times scale roughly as the cube of the number of atoms in the molecule. Consequently, the highly sophisticated models are limited to relatively small molecules. Molecular orbital calculations do, naturally, calculate the energies and shapes of molecular orbitals; molecular mechanics calculations do not do this.

Let's play with the Titan program.

Click on Titan in the Start menu. When it boots, click on the [□] icon in the upper right corner to make the window full-screen.

Click on the New [ ] icon (or File|New *via* menu). The Entry Molecule Builder will appear on the right. If you click on an atom type shown on the builder and then click on the green work area, an atom of that type will appear.

Click on the tetrahedral carbon in the Builder Menu which should then look as shown to the right. Then click on the green work area and a tetrahedral carbon will appear in wire form. Note that the bonds are tipped in yellow. This means that they are free valences – places where other atoms can be attached. Click on one of the free valences and a second tetrahedral carbon is joined to the first. Do this once more to make propane. Click on the tetrahedral oxygen [`O-] in the Builder Menu and then click on one of the free valences on one of the terminal carbon atoms of the propane. You now have 1-propanol minus its hydrogens.

Entry	Expert	Peptide

>C-

>C-	>N	>P	-H
>C=	`N=	`O-	-F
-C≡	≡N	=O	-Cl
>C-	>N	`S-	-Br
>Si-	>N-	=S	-I

Groups | Allene ▼
Rings | Benzene ▼

Entry Molecule Builder

Click on the Minimize icon ⬇E which will cause hydrogens to become attached at the yellow free valences and will do a molecular mechanics calculation (using an algorithm based on the "MMFF94" force field) to find an energy minimized conformation for the molecule. (This is similar to the "beautify" function in Cache.)

Click on the View icon V . Then rotate the molecule so you are looking at carbon-3 with carbon-2 directly behind it – a Newman projection. This is done using the left mouse button. Click anywhere in the green work area, hold the button down and drag the mouse. This provides rotations around the X- and Y-axes. Holding down the Shift key and dragging causes rotation around the Z-axis. For reference, a summary of mouse actions appears below.

Keyboard	Left Mouse Button	Right Mouse Button
Nothing	picking, X/Y rotate	X/Y translate
Shift	Z rotate	scaling[1]
Control	global X/Y rotate[2]	global X/Y translate
Control + Shift	global Z rotate[2]	scaling[1]
Control (build mode)	fragment X/Y rotate	fragment X/Y translate
Control + Shift (build mode)	fragment Z rotate	scaling[1]
Alt	rotation around active bond	active bond stretching

[1] Scaling is always applied to all open molecules and all fragments.
[2] Global rotations can be either molecule or screen centered. This is controlled by Global Rotate in the Preferences dialog of the Options menu.

Is the energy minimized conformation staggered or eclipsed? (check one)

☑✓ staggered ☐ eclipsed ☐ neither

Let's determine some angles and bond lengths in the MMFF94 minimized structure.

Click on the bond length icon ![icon] . To determine the H-O bond length, click first on one atom, then the other. Each will be highlighted, in turn, in yellow and the bond length will appear in the lower right of the screen in the format: Distance (H#,O#) = xÅ. (Note that the numbers that are associated with each atom in this format relate to the order in which the atoms were deposited in the workspace. They are *not* IUPAC nomenclature numbers, which we will use to identify various atoms below.) Do the same for the C-O bond, the C2-C3 bond, and a C3-H bond. Enter the results in the table below. When you are finished, again click on the view icon ![icon] to turn off this feature.

Bond	H-O	C-O	C2-C3	C3-H
Bond Length	0.972Å	1.421Å	1.518Å	1.095Å

To see the different ways Titan can present 1-propanol, and other molecules, click on the following menu items, in turn: Model|Wire, Model|Ball and Wire, Model|Tube, Model|Ball and Spoke, and Model|Space Filling. The last of these, Space Filling, places a vander Waals surface around each atom. In other words, as molecules approach each other, they will attract each other through vander Waals attractions. However, as the molecules get close to each other steric interactions cause them to repel each other. When the vander Waals surface of one molecule just touches that of the other the attractive and repulsive forces are in balance and the energy involved is at a minimum. Certain features and properties of molecules – multiple bonds, for example – can only be shown in the Wire and Ball and Wire modes. A multiple bond will look the same as a single bond in the other modes.

Let's measure some angles. Click on the bond angle icon ![icon] . Then click on the OH hydrogen, the oxygen, and carbon-1, in that order. Each will be highlighted in yellow as you click it. On the lower right of the screen you will see: Angle (H#,O#,C#) = x°. In the same manner, measure the O, C-1, C-2 bond angle, the C-1, C-2, C-3 bond angle, and one of the H, C-3, H bond angles. Enter these values in the table below. A word of caution. If you click on *any* three atoms in the structure, Titan will return an angle. It will be the angle between the line defined by the first and second click and the line defined by the second and third click. Thus, if you want a meaningful angle, the order of clicking is important. To see this, instead of clicking in the order H, O, C-1 to get the H, O, C-1 bond angle, try clicking in this order: H, C-1, O. Is this the H, O, C-1 bond angle?

Angle	H,O,C-1	O,C-1,C-2	C-1,C-2,C-3	H,C-3,H
Size	107.05^o	108.86^o	111.84^o	108.08^o

Before we leave 1-propanol, let's calculate a couple of dihedral angles in this energy-minimized conformation.

Click on the Dihedral Angle icon ⌐?⌐ . Then click on the OH hydrogen, oxygen, carbon-1, and carbon-2, in that order. Titan will return a result in the lower right corner that has the format: Dihedral (H#,O#,C#,C#) = x^o. This is the angle between the plane defined by the hydrogen/oxygen/carbon-1 atoms and that defined by the oxygen/carbon-1/carbon-2 atoms. Also, determine the dihedral angle of the OH hydrogen, oxygen, carbon-1, and one of the hydrogens on carbon-1. Enter these results in the table.

| Dihedral Angle	H,O,C-1,C-2	H,O,C-1,H
Size	179.99^o	±59.17^o

Click on the Close icon 🗁 .

Now we're going to make acetone. Click on the New icon 🗋 .

Click on the Tetrahedral Carbon icon in the Entry Molecule Builder and then somewhere in the green workspace to generate a tetrahedral carbon with four yellow free valences.

Next, select the Trigonal Carbon with the double free valence ⟩C= , and click on one of the free valences of the tetrahedral carbon. When you use the Entry page of the Molecule Builder, Titan matches single free valences with single free valences to form a single bond and double free valences with double free valences to form a double bond, *etc*. So, the trigonal carbon fragment has been joined to the tetrahedral carbon fragment through a single bond. At this point it may be necessary for you to rotate the molecule to see the single and double free valences on the trigonal carbon (one may be eclipsing the other).

Click on the Tetrahedral Carbon icon in the Entry Molecule Builder and then click on the single free valence of the trigonal carbon in the green workspace.

Click on the Trigonal Oxygen icon ☐=O in the Entry Molecule Builder and then on the double free valence of the trigonal carbon in the workspace. Click on the Minimize icon ☐E to add hydrogens and generate a low energy conformation of acetone.

Click on Setup|Calculations.... In the resulting dialog box the top line should have appropriate selections made so it reads, Calculate: Equilibrium Geometry with Semi-Empirical AM1. You can leave the other items in their default state except you should check the box next to Frequencies in the Compute line. Click on OK.

Click on Setup|Surfaces. A dialog box will appear. Click on Add..., then select density for Surface and potential for Property. Click on OK.
Repeat this process selecting the following pairs of items for Surface and Property:

Surface	Property	Surface	Property
HOMO -2 (*via* HOMO{-})	none	density	|HOMO|
HOMO -1 (*via* HOMO{-})	none	density	|LUMO|
HOMO	none		
LUMO	none		

Click on Setup|Submit. A dialog box will ask you for a file name for this molecule. Call it acetone_semi-empirical_am1.spartan. Then click on OK. You will be informed that Titan has started the calculation. Click on OK and wait until Titan has told you it has finished. Then again click OK. In the Surfaces dialog box click to place a check mark in the yellow box next to density/potential. If all has gone well you should have a image similar to the one on the right. The colored surface is a potential map (the colors) superimposed on an approximate vander Waals surface of the molecule. This is how a point positive charge "sees" acetone. The red regions are attractive because they are regions of negative charge. The blue regions are repulsive because they are regions of positive charge. This is also pretty much how a positively charged ion, or the positive end of a polar molecule, or an electrophile, or a Lewis acid sees acetone.
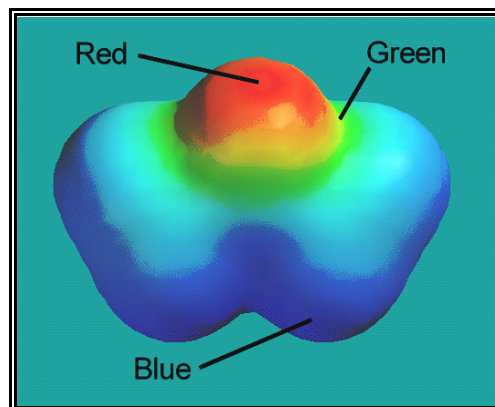
Electrostatic Potential Map of Acetone

On the other hand, a point negative charge "sees" the red regions as repulsive and the blue regions as attractive. This would also be true for negatively charged ions, the negative ends of polar molecules, nucleophiles, and Lewis bases.

"But wadeaminit, doc! Where's da molecule? All I see is a blob."

"Good point, Rooster." Click anywhere on the potential surface ... errr ... blob, and a

menu will open in the lower right of the screen allowing you to make the surface transparent or a mesh or a bunch of dots. Try it. Now you can see the molecule and the potential surface.

Click on Display|Properties. A dialog box will open displaying the surface properties (since you clicked on the surface earlier). Change the IsoVal from 0.002 to 0.1, hit Enter, and click the Reset button to get a look at the potential map closer to the nuclei.
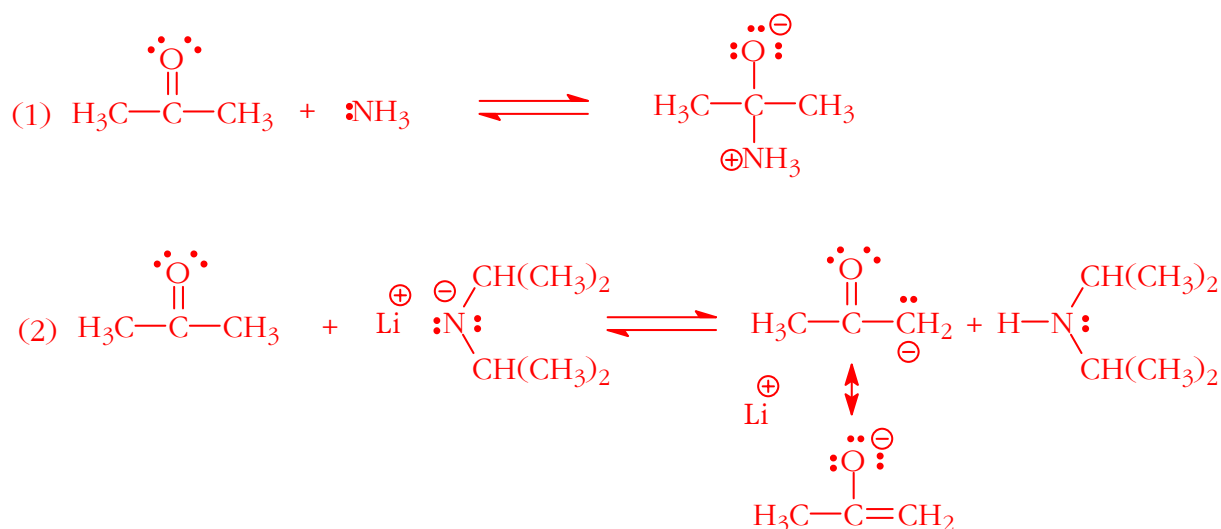
What do the two reddest regions at IsoVal = 0.1 correspond to?
The two unshared pairs of electrons on oxygen.

Based on both potential maps, which atoms appear to be most electrophilic *i.e.* which atoms are most likely to be attacked by a base or nucleophile?
carbonyl carbon (1) and methyl hydrogens (2)

Based on your extensive knowledge of ketone chemistry, show one reaction mechanism where this applies. (Do this at home.)

(1) $H_3C\!-\!\overset{\overset{\displaystyle O}{||}}{C}\!-\!CH_3$ + :NH$_3$ ⇌ $H_3C\!-\!\overset{\overset{\displaystyle \ominus}{\underset{}{:\ddot{O}:}}}{\underset{\oplus NH_3}{C}}\!-\!CH_3$

(2) $H_3C\!-\!\overset{\overset{\displaystyle O}{||}}{C}\!-\!CH_3$ + Li$^{\oplus}$ $^{\ominus}$:N$\overset{CH(CH_3)_2}{\underset{CH(CH_3)_2}{}}$ ⇌ $H_3C\!-\!\overset{\overset{\displaystyle O}{||}}{C}\!-\!\overset{\ominus}{CH_2}$ + H$-$N$\overset{CH(CH_3)_2}{\underset{CH(CH_3)_2}{}}$

$H_3C\!-\!\overset{\overset{\displaystyle :\ddot{O}:^{\ominus}}{|}}{C}\!=\!CH_2$

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Based on both potential maps which atoms appear to be most nucleophilic *i.e.* which atoms are most likely to be attacked by an acid or electrophile?
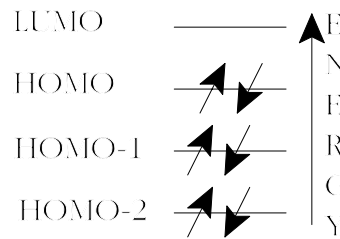oxygen

Based on your extensive knowledge of ketone chemistry, show one reaction mechanism where this applies. (Do this at home.)
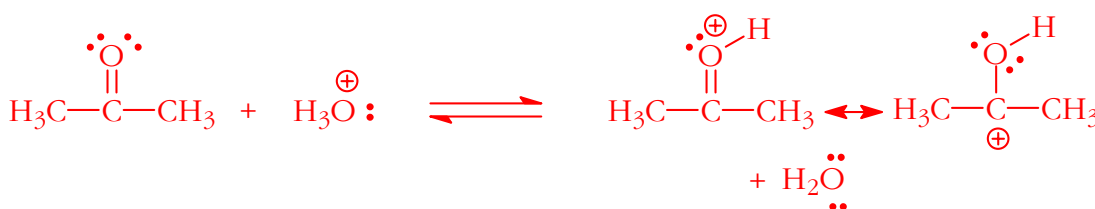
Change the IsoVal back to 0.002, click on Reset, and close the Properties dialog box.

If the Surfaces List dialog box is not open, click on Display|Surfaces.
Make sure the molecule is Ball and Wire mode (Model|Ball and Wire).

Click on the yellow box to the left of HOMO-2. The HOMO-2 molecular orbital will appear around the molecule. [HOMO stands for **h**ighest (energy) **o**ccupied (by electrons) **m**olecular **o**rbital. HOMO-1 is the next lower energy orbital and HOMO-2 is the one below that, *etc.* LUMO stands for **l**owest (energy) **u**noccupied (by electrons) **m**olecular **o**rbital. It is the next higher energy orbital above HOMO. LUMO+1 would be the next higher energy orbital *etc.*] Click on the surface of this orbital; then click on Display|Properties. A dialog box will appear. Look it over and copy the orbital Volume into the table below. Close the dialog box.

Click on the yellow box to the left of HOMO-2 to remove the check mark. Click on the yellow box to the left of HOMO-1. The HOMO-1 molecular orbital will appear around the molecule. Click on the orbital surface; then click on Display|Properties. A dialog box will appear. Look it over and copy the orbital Volume into the table below. Close the dialog box.

Repeat the above process for the HOMO and LUMO.

Orbital	Volume, Å^3
LUMO	10.11
HOMO	14.67
HOMO-1	20.41
HOMO-2	23.40

What conclusion can you draw, at least tentatively, about the relationship between orbital size and energy?
The larger the orbital size, the lower the energy.

What is the relationship between orbital size and the term *electron delocalization?*
The larger the orbital size the greater the delocalization of the electrons therein.

What is the relationship between energy and electron delocalization?
The greater the delocalization the lower the energy.

Click the yellow box next to LUMO in the Surfaces List box to place a check mark there and be sure all the other surfaces are unchecked. You are now looking at the LUMO.

The LUMO is the lowest energy orbital that does not contain electrons.

Question 1: If a nucleophile (an electron pair donor — :NH_2CH_3, for example) approaches acetone, which orbital in acetone is likely to accept these electrons?
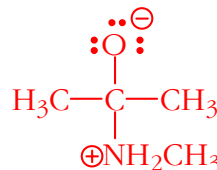LUMO

Question 2: At which atom of acetone is this attack most likely to occur?
carbonyl carbon

Click the yellow box next to LUMO in the Surfaces List box to remove the check mark. Check the yellow box next to: density — |LUMO|. This surface is the vander Waals surface and the colors are a map of the absolute value of the LUMO at this surface. Blue represents a large value and red represents a small value.

Does this map corroborate your answer to question #2, above? Draw the Lewis structure of the product that would form if :NH_2CH_3 attacked acetone.
Yes.

$$H_3C-\underset{\underset{\oplus NH_2CH_3}{|}}{\overset{\overset{\ominus}{:\ddot{O}:}}{C}}-CH_3$$

Click the yellow box next to HOMO in the Surfaces List box to place a check mark there and be sure all the other surfaces are unchecked. You are now looking at the HOMO.

The HOMO is the highest energy orbital that contains electrons.

Question 1: If an electrophile (an electron pair acceptor — H_3O^+, for example) approaches acetone which orbital in acetone is likely to relinquish electrons to the electrophile?
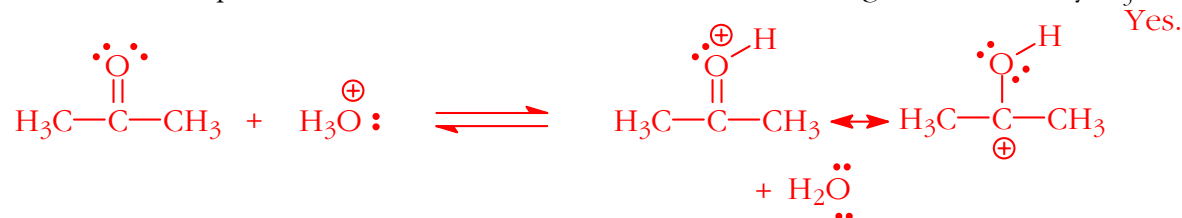HOMO

Questions 2&3: At which atom of acetone is this attack most likely to occur? Is this as clear as the case of the nucleophile and the LUMO?
oxygen, no

Click the yellow box next to HOMO in the Surfaces List box to remove the check mark. Check the yellow box next to: density — |HOMO|. This surface is the vander Waals surface and the colors are a map of the absolute value of the HOMO at this surface. Blue represents a large value and red represents a small value.

Does this map clarify the situation with regard to questions 2&3, above? Which atom will the electrophile attack? Draw the Lewis structure resulting from attack by H_3O^+.
Yes.

Uncheck the yellow box next to: density — |HOMO|. Close the Surfaces List box.

Click on Display|Vibrations. A dialog box will open in which a number of infrared vibrational frequencies are listed. Click on Model|Ball and Spoke. Click on the yellow check-boxes sequentially and observe the molecular vibrations. They will be of basically two types: bending and stretching. In bending bond angles change; in stretching bond lengths change.

Is there a relationship between the frequency of the vibration and whether it is a bend or stretch?
high frequency: stretch, low frequency: bend

Note: Calculated vibrational frequencies are typically something like 10% high. They are not particularly useful for compound identification.

The strength of an infrared absorption depends on the dipole moment of the molecule changing with the vibration. If the dipole moment does not change at all, there will be no absorption; conversely, if the dipole moment changes a lot with the vibration it will be a strong one. Remember: dipole moment = (amount of charge separation) x (distance of separation). Vibrations do not change the amount of charge separation, but they can change the distance.

Click on <u>M</u>odel|Ba<u>l</u>l and Wire. Click on <u>M</u>odel|<u>D</u>ipole. You asked Titan to calculate the dipole moment and now it is displayed as a yellow arrow. Run through the various frequencies again. Is it surprising that the C=O stretch (calculated frequency = 2063cm^{-1}) is the strongest absorption in the infrared spectrum of acetone?

Close down the program.