

Experiment 4 —

Molecular Modeling

Pre-lab preparation (1) This lab has intentionally been scheduled to happen before the associated material has been covered in lecture. So before lab, you should do just a little background reading and make some models. Text sections 6.3, 6.5, and 6.7 should be enough to familiarize you with the basics. (2) In a sentence or two, explain the types of calculations that you will be doing, i.e. what will the computer program be doing with the molecular structures that you give it? What information do you expect to get out? (3) Define torsional strain, angle strain, and steric strain, and illustrate each by drawing a structure. (4) Draw the following common substituents: methyl, ethyl, isopropyl, *tert*-butyl, vinyl, phenyl. (5) ***Bring your model kit to lab.*** (6) You will probably not need goggles.

Chemists often use molecular modeling calculations to gain insight into structures and energies of molecules, reaction pathways, spectroscopic properties, etc. The two most common types are quantum mechanical calculations, and molecular mechanics (also called empirical force field) calculations.

Quantum mechanical calculations can be performed at widely varying levels of sophistication — from a simple treatment of arrays of uniformly interacting p-orbitals, known as Hückel theory, to *ab initio* calculations that explicitly treat all the components of electrostatic attraction and repulsion and electron kinetic energy. The most sophisticated *ab initio* calculations can be extraordinary complex and require huge amounts of computer processing power. These types of calculations are especially useful for molecules with unusual electronic structures, for modeling reaction pathways that involve breaking and forming of bonds, for predicting structures and properties of electronically excited states, for predicting spectroscopic properties like wavelengths of light absorption, vibrational frequencies (IR spectra), and many other properties.

Molecular mechanics (MM) calculations, like the ones that we will be doing, in their most basic form, treat molecules like assemblies of high-tech balls and springs. No orbitals, no quantum mechanics of any kind. These calculations are relatively simple and fast, and can be used reliably for molecules that have no "unusual" structural features. They provide reasonable 3-dimensional geometries, and allow comparison of energies between different *conformations* or between geometrical isomers. Some MM programs have been parameterized to calculate enthalpies of formation, allowing comparison of energies of a wider range of structures as well as estimation of reaction energy changes.

Molecular mechanics calculations rely on parameters derived from experimental data to model the energy changes associated with bond stretching and compression, angle bending, bond rotations, and van der Waals repulsion (also called *steric* repulsion). Some MM programs also incorporate parameters to model electrostatic attractions or repulsions and some include subroutines that do a rudimentary quantum mechanical treatment of conjugated π -systems. These programs adjust the structure to minimize the total energy of the molecule.

Most structures that we build, whether with models or digitally, will have geometrical problems. For example, some angles might be too small or too large, some atoms may be too close together, etc. The energy of such a structure will be higher than it would be if all these structural parameters had their optimal values. The MM program's job is to simultaneously adjust all the bond lengths, angles, and spatial relationships of atoms to generate the best possible structure — meaning the structure with the lowest possible energy. But even the optimized structure may still have some structural problems.

The total MM energy for a particular structure, E_{MM} , is the sum of the contributions from the independently adjustable structural features mentioned above —

$$E_{\text{MM}} = \Sigma E_{\text{bond}} + \Sigma E_{\text{angle}} + \Sigma E_{\text{torsional}} + \Sigma E_{\text{vdW}} + \Sigma E_{\text{es}}$$

The first term, for example, might be a simple parabolic potential that mimics the effect of compression or stretching of a bond,

$$E_{\text{bond}} = \frac{1}{2} k_d (d - d_0)^2$$

where k_d is the force constant for the particular type of bond (derived from experimental data), d_0 is the natural bond distance (from experimental data), and d is the *actual* bond distance in the structure. (Most MM programs use a somewhat more complex function to better approximate the asymmetry of real bond stretching potentials.) Every bond in the structure that is stretched or compressed relative to its natural length increases the energy of the molecule; the sum of these contributions is the first term in the E_{MM} equation. The programs use a similar type of potential function for angle bending. A cosine function is used to model the energy change that accompanies rotation around bonds (the "torsional potential"), a suitable function is used to approximate van der Waals repulsion (and weak attraction at certain distances), and a term is included to account for electrostatic attractions or repulsions between charged or polar atoms. The programs optimize the structure by calculating the gradient of the energy with respect to all the adjustable structural parameters and then following the most direct route down the energy slope to the structure of lowest energy. This is called energy minimization.

This procedure has one obvious pitfall — the programs are not smart enough to do anything but fall downhill (in E) and then sit there. There may be another minimum of even *lower* energy just over the horizon, but the program is oblivious to that until someone comes along and gives it a push in the right direction. That is, an MM program will take whatever structure you give it and go straight to the *nearest* energy minimum — it won't rationally adjust the structure to find other reasonable geometries, no matter how obvious they may be. That's your job.

HyperChem — *nuts 'n' bolts*. In addition to a few quantum mechanics options, HyperChem includes several different MM routines. Three, BIO+, OPAL, and AMBER, were developed for large bio-molecules like proteins and DNA. The one we will be using is **MM+**. This is *HyperChem's* version of N.L. Allinger's wildly popular MM2 program, which has been tested extensively and shown to reliably predict physical data for small organic molecules.

You'll find the program under *start* — *All Programs* — *[upper]Course-related* — *HyperChem Pro* (*not* the Amateur version)

Menus and defaults. Various cosmetic aspects of the program can be customized. There should be no need to mess with colors, but you may want to check *File* — *Preferences...* bond

color should be "by element", and selection color should be anything different from the background so your structure doesn't become invisible. Make sure nothing is checked under the *Build* menu. Under *Display*, *Show Hydrogens* and *Show Multiple Bonds* should be checked. And while we're there, select *Rendering...* and note that the *Rendering Method* panel allows you to choose how the molecule is displayed. Once you have a structure, you may want to play with this. *Sticks* will be cleanest; you may prefer *Balls and Cylinders* (you can change the sizes); *Overlapping Spheres* will produce something that resembles an authentic space-filling model but isn't, because the atoms are too small (Grrrrr). Fortunately, your plastic model kit *does* have Hs of the proper relative diameter so you can see when steric effects are likely to be an issue.

Structure drawing tools — (assume "click" means left-click; right-clicks will be made explicit)



The Draw Tool. Double-click to bring up a periodic table. Select an atom and then click to plop it into the work space or click on an existing atom to change it. Dragging makes bonds. Right-click to delete. Try it. You'll like it. Build something. Something cyclic, perhaps. Throw in a double bond or two — you can make these by click-dragging over a single bond. No need to add Hs (see below).



The Selection Tool. Click to highlight atoms or groups of atoms. Clicking on the background highlights everything. Right-click deselects.

With everything deselected, double-clicking *on the tool button* will clean up even the ugliest drawing by using typical bond lengths and angles to create a nice 3-D structure. And it even adds the Hs for you. You can continue to add to the structure or change the conformation if you need to.

Selecting two bonded atoms (click-drag) or their bond will display the bond length, selecting three contiguous bonded atoms (click-drag along the bonds or straight from the first to the third) will give the bond angle, selecting four will display the torsional (dihedral) angle. Selecting more than that will confuse the program. Clicking on any two atoms will display the distance between them. Keep in mind that the program has far less common sense than you do when it comes to significant figures. Don't just copy down any silly string of digits you see.

Once you've selected a bond, an angle, or a dihedral angle, a *Set...* option will be activated near the bottom of the *Edit* menu. This will allow you to constrain this aspect of the structure during a calculation. For example, with a dihedral angle selected, you can choose *Set Bond Torsion....* then enter the desired torsional angle. This is useful for working with structures that are not energy minima. And under the *Build* menu a *Constrain...* option will be activated that will allow you to control the starting structure that the model builder generates. For example, you can use *Constrain bond torsion...* to specify the dihedral angle for your starting structure.



The Rotate In-Plane,



Rotate Out-of-Plane, and



Translate Tools.

Self-explanatory. Click-drag and see what happens. Try not to get dizzy. Now stop that and get back to work.



The Magnify and Shrink Tool. Also self-explanatory. Click-drag.

Other Tools are also provided for your amusement. The most useful may be the space bar, which will retrieve and center your molecule if it falls off the edge of the screen.



Important: You must deselect everything and double-click the select tool button before doing a calculation (unless instructed otherwise). *Double-clicking the tool button will prepare the structure for the MM routine.* What exactly it does is a



mystery, but experience has taught us that if you don't do this the program may appear to run normally but give spurious results (even worse, those numbers may not be obviously wrong), so be sure not to skip this step or you'll be very very confused.

Running a calculation. You will find the calculation controls under the *Setup* and *Compute* menus. Choose *Molecular Mechanics* and *MM+*. Under *Compute*, you'll see *Single Point* — this will take the structure displayed and determine its energy (E_{MM}) without changing the geometry. *Geometry Optimization...* will do exactly that. In the Optimization panel, select Block-diagonal Newton-Raphson minimization, and note the energy change criterion for termination. The RMS gradient defines how small an energy change per unit of structural

change we want to worry about in deciding whether we're close enough to a minimum. That should be 0.1 kcal/mol per Å. Clicking *OK* will start the calculation. When it's done, you'll see the energy in kcal/mol displayed at the bottom of the window. This is only meaningful in comparison to the energies of closely related structures — e.g., different conformations of one molecule, different geometrical isomers (i.e. stereoisomers), but not structural isomers.

Ethane. Ya gotta start somewhere, eh? CH_3CH_3 . Make an analog model with your plastic model kit (use the semi-space-filling Hs), and make a digital model with *HyperChem*. Don't forget to double-click that select button to get the program to add Hs and tidy up the structure. Spin it around so that you can see it clearly.

Is the computer's structure staggered or eclipsed? _____

OK, so that pre-minimization clean-up feature knows a little chemistry. Do a *Single Point calculation*. What's the energy? _____

The units are kcal/mol. (How hard would it have been for the program to display "kcal/mol"?) Please report all your energies with units. Now do a *Geometry Optimization* (check that N-R minimization is selected and 0.1 kcal/mol per Å for termination). Now what's the energy?

Make the eclipsed conformation. To do this you'll need to "freeze" one of the H-C-C-H dihedral angles at 0°. Special procedure for this: Select an H-C-C-H dihedral, then, under the *Edit* menu, *Set Bond Torsion* to 0°. Deselect by right-clicking in the background, but **do not** double-click the select button. Do a *geom opt*. What's the energy? _____

Which conformer is more stable and by how much? _____

Sig figs, please! MM results are generally reliable to about 0.1 kcal/mol. So please don't report more than one decimal place for a ΔE between two structures. You can carry an extra digit or two in the raw energies to avoid rounding errors, but once you subtract them to get an experimentally meaningful quantity there's no reason to report more than one decimal place.

Most textbooks (yours appears to be the only exception) claim that the eclipsed conformation is less stable than the staggered because of steric (van der Waals) repulsion between pairs of eclipsed Hs. These repulsions occur when two Hs are forced closer than about 2.35Å. So

finding Hs closer than this is a clear indication of a problem. Structures sometimes avoid a serious clash by stretching or rotating bonds or opening angles, but this also raises the energy. We normally say the structure is destabilized by a steric clash (vdW repulsion) whether the energy increase is entirely in the E_{vdW} term, or the structure has spread that energy among several terms by distorting to avoid a potential steric clash. We'll see clear evidence of this later.

While you still have the eclipsed structure on the screen, let's extract some geometrical info.

Report the requested structural parameters in the first column of the table below. The relevant non-bonded H - - - H distance is between a pair of eclipsed Hs (or the closest pair of Hs on different Cs in the staggered conformation)

(Note that the bond lengths are meaningful only to two decimal places, angles probably to one)

Ethane	Eclipsed	Staggered
C-C bond length		
C-C-H angle		
H - - - H distance		

Now deselect everything and double-click the select button to get back to the staggered conformation. Optimize the structure, and complete the second column of the table.

Is there any indication of a serious interaction between Hs in the eclipsed structure?

What does your plastic model imply about the presence or absence of "bumping" between eclipsed Hs?

Butane. Now here's an interesting molecule. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3$. Make a plastic model to start. Use the space-filling Hs on the methyl groups. Focus on rotation around the central C-C bond, and look at the three staggered conformers. We know that the eclipsed structures are energy

maxima, and they're typically about 3 - 5 kcal/mol higher in energy than the nearby staggered structures. What else do we really need to know about these? Nothing, that's what. From now on, we'll focus only on the *stable*, i.e. staggered conformers.

Draw Newman projections of the three stable conformers of butane in the space below (recall that these are views along the bond of interest, showing the front atom as a point and the rear atom as a circle).

Label the conformers *anti* or *gauche*, as appropriate.

Which of the staggered conformers do your models indicate should be more stable, and which should be less stable?

Why?

Of course the models can't tell us the relative energies. Do MM+ calculations to determine the difference in energies and to determine the structural reasons for the difference. Note that you may have to change the C-C-C-C dihedral angle to create the starting structures. Use the *Constrain* feature in the *Build* menu to do this, then deselect and double-click the select button. Once you have the correct starting structure, run the geometry optimization. Here's another one of those nifty tables... fill in the data for the stable conformers of butane.

Butane		
MM Energy		
C ₂ -C ₃ bond length		
C-C-C angle		
C-C-C-C dihedral angle		
Closest H - - - H dist b/w CH ₃ s		

Now let's summarize... What is the calculated energy difference? _____

Your models showed a potential steric clash between Hs. Is there evidence of Hs in your optimized higher-E structure interpenetrating (i.e. are they closer than 2.35 Å?) Is there evidence that the structure has distorted somehow to diminish the effects of a potential steric clash?

Let's briefly revisit the question of "why"? Many students say that "the methyls are farther apart" in the lower-E structure (maybe you said that — that's ok for the moment). Imagine a structure with two methyl groups whose separation could magically be varied (without distorting the rest of the structure in any way) so that the closest non-bonded H - - - H went from, say, 2 Å to 5 Å. How would the van der Waals repulsion energy change?

So is being "farther" apart the real issue? If you said that previously, here's your chance to revise your answer...

Cyclohexane. Now for some *real* fun. Build a chair cyclohexane with your analog model kit. The bond connectors are designed to be a bit "loose"; for a cyclohexane, you'll probably need to spin them to "lock" so that they don't pop apart as you wrestle with the structure. If you need help figuring out what the chair looks like, try building it with *HyperChem*.

Note that the chair has perfect staggering along every C–C bond, no distorted angles, no Hs clashing — it's very nearly "perfect" structurally.

Grab any two opposing ring Cs (C_1 and C_4) of your chair cyclohexane — notice that one is "up" and the other is "down". Without letting the ring twist, move the "down" C up and the "up" C down. You've just made the other chair conformer. Cool. Do it again. Let your partner try. (I've found that demonstrating this at parties is a good way to break the ice and get people talking.)

Attach a methyl group to the ring of your plastic model, and look at the two chair conformers. In one the methyl is *axial*, in the other it's *equatorial*. Which is which? Sketch and label them below. Drawing these is tough at first, so I've provided templates. You're welcome. Just stick on the methyls.



Note that each of these structures can be drawn with the methyl group on *any* ring C. Demonstrate this by turning your model of the axial-methyl conformer in different orientations; try sketching these on a sheet of scratch paper — note how the ring always looks like one or the other of the chair drawings above.

Which do you think is the more stable, and why? You may want to put a few space-filling Hs in certain strategic locations... Add the relevant Hs and indicate any key H - - - H interactions on your drawings above.

Use *HyperChem* to determine the energy difference between the axial and equatorial conformers and report your result here _____

Is there evidence of a steric clash in either or both structures? (Remember to look for both interpenetration of Hs and structural distortions that indicate the molecule is trying to minimize this clash.)

You may notice a similarity between one of your Newman projections for butane and the view along one of the ring CC bonds in your cyclohexane chairs. In particular, certain key interactions look very similar. Which interactions, and how is this structural feature reflected in the energy difference between the butane conformers as compared to the methylcyclohexane conformers?

Substituted cyclohexanes. Find the axial-equatorial energy differences for ethylcyclohexane, isopropylcyclohexane, and *tert*-butylcyclohexane. Don't spend time digitally examining all possible conformations — use your plastic models to find the most stable conformation of the substituent when it's equatorial and again when it's axial. If it's clear which way the substituent should be turned, all you need to do is feed the computer the best axial and the best equatorial conformer. Report their energy differences below.

Substituent	$E_{\text{axial}} - E_{\text{equatorial}}$
methyl	
ethyl	
isopropyl	
<i>tert</i> -butyl	

Students who don't like models and don't like to think about structures are often baffled by the fact that the energy difference in this series is not proportional to the number of Cs in the substituent. The reason should now be clear. What is it?

This is fast, so let's look at a few more substituents. — Bromo ($-\text{Br}$), cyano ($-\text{CN}$), vinyl (you have that structure in your pre-lab), and a double-bonded O (i.e., put a carbonyl group, $\text{C}=\text{O}$, into the ring). Report the ax-eq energy differences (except in the one case where that doesn't make sense).

Disubstituted cyclohexanes. With your plastic models, make *trans*-1,2-dimethylcyclohexane. *Trans* means that the substituents are on opposite faces of a *flattened* ring. Now pucker the model into one chair and then the other and look at the positions of the methyls. Use your data from previous calculations to *predict* the energy difference between the two. Show your work below.

Now test your prediction with *HyperChem*. What ΔE did you calculate? _____

Was your prediction close? If not, what did you do wrong?

Make *cis*-1,2-dimethylcyclohexane (substituents on *same* face of a flattened ring) and look at the two chairs. What do you expect for their energy difference?

What do you predict for the energy difference between the *trans* and the *cis* isomers? Essentially all the molecules will be in the more stable conformation of each, so those are the ones we need to compare.

Test your prediction with *HyperChem*. What's the *cis-trans* ΔE ? _____

Was your prediction close? If not, what went wrong?

Compounds containing halogens. Bromine is similar to methyl in size, or so it is often claimed. Do your results for bromocyclohexane support this notion?

Compared to butane, would you expect a larger or smaller gauche-anti energy difference in 1,2-dibromoethane ($\text{Br}-\text{CH}_2-\text{CH}_2-\text{Br}$)?

Based on your result for bromocyclohexane, predict the ΔE between the two conformers of *trans*-1,2-dibromocyclohexane. Which should be more stable and by how much?

Now do the calculations on both 1,2-dibromoethane and *trans*-1,2-dibromocyclohexane, and report your findings. If the ΔE s between conformers are very different from your predictions, explain why.

Turn in these completed pages and you're done for the week.