

Chapter 6: Molecular Mechanics

Key Notes:

Fundamental Aspects:

Molecular mechanics is the application of classical mechanics to molecules. Classical mechanics is used to describe the motion of macroscopic objects. In molecular mechanics, atoms are treated as spheres whose mass depends on the element. Chemical bonds are treated as springs whose stiffness depends on which elements are bound together, and whether the bond is single, double, or triple. Other types of springs are used to model changes in bond angles, dihedral angles, etc. Each of these various types of springs will have spring constants associated with them. Experimental and theoretical methods are used to determine these parameters. Additional equations from classical physics, such as Coulomb's Law, are used to handle any electrostatic interactions present within a molecule. The sum of all energy terms that apply to a particular molecule are added together to define what is called the "steric" energy, or total potential energy, of the molecule. These energies are not externally referenced (e.g. energies calculated for different molecules cannot be directly compared) and must be used with caution. All of the equations and associated parameters used to calculate each energy term are collectively called the "force field". Different force fields have been developed for different molecular types (e.g. small organic molecules vs. large biomolecules). Since molecular mechanics does not deal directly with electrons and orbitals, we cannot study chemical reactions or predict the reactivity of the molecules studied with this technique.

Applications:

In computational terms, molecular mechanics is the least expensive (fastest) method. It is especially well suited for providing excellent structural parameters in terms of bond distances, angles, etc., for the most stable conformation of a molecule. This so-called "geometry optimization" is often used as the first step before a calculation of another type is performed. This is done to insure that the molecule is in its' lowest energy state so that calculated results can be compared to those done experimentally. Since molecular mechanics is computationally inexpensive, it is often the only method available for use with large molecules, especially those of biochemical interest such as proteins.

Molecular Mechanics Methods:

Although a large number of different methods have been developed, this text will focus on three. For organic molecules with a variety of functional groups, there are two widely used methods known as MM2 and MM3. The MM2 method is a precursor of MM3. The parameters used in these methods were chosen to reproduce the experimental structure and conformational energy differences for individual molecules. The MM3 method has parameters for more atom types and addresses known problems with the MM2 method. The third method is known as OPLS-AA, an acronym for Optimized Potential for Liquid Simulations – All

Atom. This method can also be used with organic molecules but is more widely used in studies of proteins, focusing on reproducing liquid properties, such as heat of vaporization and density.

Molecular Mechanics Software Tools:

The molecular mechanics software program available on the North Carolina High School Computational Chemistry Server is known as Tinker. This program currently utilizes the MM2, MM3, and OPLS-AA molecular mechanics force fields as described above. The program also has the ability to use other, commercially available, force fields.

Advantages:

Perhaps the greatest advantage of molecular mechanics is its computational speed. As the fastest computational chemistry method, this method can be used to study large biomolecules (assuming the required hardware is in place!). For single processor systems like most desktop and laptop machines, calculations on a large biomolecule will still take a prohibitively long time. The main advantage of molecular mechanics with typical computer hardware is in the area of geometry optimization – finding the most stable conformer of a molecule. As long as a good force field is available for the molecule under study, structural results from a molecular mechanics calculation will more closely match experimentally determined structures than other computational chemistry techniques. The method is thus a good choice when studies of molecular geometry are undertaken.

Disadvantages:

The main disadvantage of molecular mechanics, and it is a serious one, is the lack of available parameters for many compound types. Approximately 80% of known compounds do not have parameters available. This severely limits the areas of applicability of the method. Also, since electrons and orbitals are not used in the method, we cannot study chemical reactions or predict reactivity of molecules. Other methods that involve more computational expense must be used to study these properties.

Fundamental Aspects:

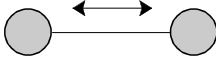
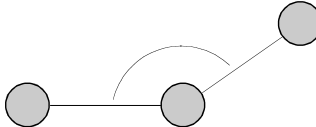
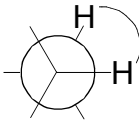
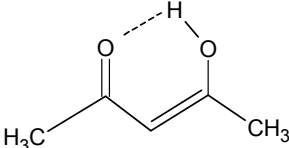
The molecular mechanics view of a molecule has spheres of different mass (atoms) connected together by a variety of springs (chemical bonds). If we can find the coordinates of all the atoms at the place where all the springs are at their equilibrium length, this should correspond to the lowest energy state of the molecule. Dynamic behavior of the molecule could also be calculated through application of the laws of classical mechanics.

In real molecules, there are other forces present than just those between bonded atoms. There may be charges present that can repel or attract. Repulsions between nonbonded atoms that are close together in space might also occur. These forces may act to change bond angles or cause

twisting around single bonds. To describe the energy of the system, we have to account for all of the different types of interactions that are applicable. The sum of the energy of all of these various components is the basis of a *force field*. A force field allows for calculation of all the forces on the system which in turn gives the energy of the system.

In order to create a force field, we need a mathematical equation for each energy term as well as any required parameters (constants) for these equations. For example, if we are using springs to represent chemical bonds between atoms, we will need to know the strength of each spring (called the spring constant), and the equilibrium distance between atoms, for each different type of bond present. A C-N bond will have a different spring constant and equilibrium distance than an O-H bond. So, these force fields contain a huge number of equations and parameters. The equations come from classical physics, and the parameters come from either experimental data, or from higher level quantum mechanics calculations, which will be discussed in subsequent chapters.

Some of the energy terms that need to be taken into account are:

- (1) Bond stretching (l): 
- (2) Bond angle bending (∠): 
- (3) Dihedral angle rotation (∠): 
- (4) van der Waals forces
- (5) Hydrogen bonding: 
- (6) Electrostatic interactions

Since molecular mechanics views chemical bonds as springs, we use an equation from physics called the harmonic oscillator approximation to describe this behavior:

$$E_{stretch} = \frac{k_s}{2} (l - l_0)^2$$

k_s = spring constant; l_0 = equilibrium bond length

Bond angle bending is treated with a similar equation:

$$E_{\theta} = \frac{k_{\theta}}{2}(\theta - \theta_0)^2$$

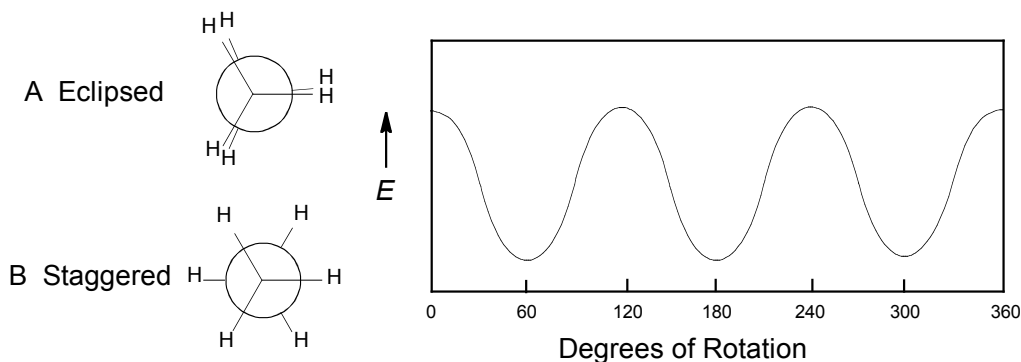
k_{θ} = spring force constant; θ_0 = equilibrium bond angle

Rotation about a single bond (torsion) changes the dihedral angle (ϕ) and involves a sum of periodic functions. As the dihedral angle changes from 0° to 360° , the energy profile will begin to repeat itself.

$$E_{torsion} = \frac{1}{2}V_1(1 + \cos\phi) + \frac{1}{2}V_2(1 + \cos 2\phi) + \frac{1}{2}V_3(1 + \cos 3\phi) + \dots?$$

V_n = dihedral force constant; n = periodicity; ϕ = dihedral angle

An example is shown below with rotation about the C-C bond in ethane. The eclipsed dihedral angle is taken as 0° , and the staggered form with its lowered steric crowding between H atoms, occurs at 60° :



Neutral atoms undergo a long range attractive van der Waals, or dispersion force. At shorter range, the electron clouds of atoms will begin to repel one another (Pauli repulsion). These two effects are modeled using the Lennard-Jones, or “6-12” potential:

$$E_{vdW} = \frac{A}{r^{12}} - \frac{B}{r^6}$$

A = repulsive term; B = attractive term

Hydrogen bonding is often handled in the van der Waals and electrostatic terms, but is sometimes placed in a separate term. This “10-12” potential decays more rapidly with distance:

$$E_{HB} = \frac{C}{r^{12}} - \frac{D}{r^{10}}$$

Electrostatic interactions are based on Coulomb’s Law:

$$E_{electro} = \frac{q_a q_b}{\epsilon_{ab} r_{ab}}$$

q_n = atomic partial charge; ϵ_{ab} = dielectric constant; r = interatomic distance

What is called the steric energy, or total potential energy, of the system is given by a summation of all the energy terms:

$$E_{total} = E_{stretch} + E_{\theta} + E_{torsion} + E_{vdW} + E_{HB} + E_{electro}$$

The force field parameters in all of the above equations are typically determined for an example set of molecules, all of similar type. In order to achieve good results from a molecular mechanics calculation, the molecule of interest should be similar to those used in the parameterization procedure. Some force fields were developed for small organic molecules, while others apply better to proteins, or solid-state oxides, or inorganic molecules.

Applications:

As discussed above the applications of molecular mechanics will depend on the force fields one has available. The North Carolina High School Computational Chemistry Server uses a program called Tinker to do molecular mechanics calculations. This program includes the MM2, MM3, and OPLS-AA force fields. The MM2 and MM3 force fields were designed for use with organic molecules, although some parameters are included for “nonorganic” elements such as Fe, Ni, and Co. The MM3 method was created to deal with some of the problems that became apparent in the MM2 method. Some of these problems include nonbonded H-H repulsions that were too large, inaccurate energy differences in some dihedral angles, and troubles in handling compounds with small (3-, or 4-membered) rings. When developed, the emphasis of both MM2 and MM3 was to model the structures, vibrational frequencies (e.g. infrared spectra), conformational energies and energy barriers, and heats of formation for individual molecules. In a laboratory situation where students are performing calculations on organic molecules, the speed of molecular mechanics combined with the excellent structural parameters obtained through the geometry optimization process make the MM2 and MM3 methods highly attractive for this application. Students could also investigate conformational energy changes of a molecule as single bonds are rotated. The energies reported by the program are not externally referenced - that is, there is no uniform “zero” of energy that all calculated results are calibrated by. Comparisons of energy results between *different* molecules is not likely to work well, although looking at conformational energy differences in the *same* molecule can give useful information.

The OPLS-AA force field was designed to model organic molecules with an emphasis on proteins and condensed phase (liquid or solid) simulations. Unlike the MM2 and MM3 methods, OPLS-AA can also be used to model *intermolecular* (between molecules) as well as *intramolecular* (within the same molecule) interactions. So OPLS-AA is better at condensed phase modeling where intermolecular interactions become more important.

Molecular mechanics methods are widely used to study interactions in biomolecular systems because of the low computational cost. However, before such a task is undertaken it is important to note that the computational time required for these calculations increases as something close to N^2 , where N is the number of atoms in the molecule. The calculation speed for a small organic molecule with a few dozen atoms will be *quite different* than that for a small protein that may have several thousand atoms. Calculations on large biomolecules require multiprocessor machines in order to speed things up. Even with the proper hardware, such calculations can take several days!

A typical application for molecular mechanics is in understanding the interactions between potential drug molecules and the sites they interact with, usually in proteins. Changes can be made in the structure of a molecule to see if a stronger interaction with the target site is produced. This is an essential aspect of drug design, and pharmaceutical companies spend a large amount of time and money on computational modeling of these interactions.

Finally, it is up to the user to decide which method to use for a given application. A comparison of structural results for the same molecule obtained using MM2, MM3, and OPLS-AA would be a worthwhile endeavor, especially if the actual experimental results are available. After some practice using the various methods with different molecules, the choice of which method to use in a given situation will become apparent.

Molecular Mechanics Methods:

Both the MM2 and MM3 parameter sets, developed by the Allinger group at the University of Georgia, are targeted at small organic molecules with a range of functional groups, and have been in wide use for over twenty years. These programs are parameterized to provide accurate ground state geometries. Of the various computational methods, molecular mechanics provides the “best” geometrical data that agrees well with experimentally determined geometries. In fact, molecular mechanics is often used to first calculate the optimized geometry of a given molecule before another type of calculation is performed. This is done so that the molecular geometry that the calculation is performed on will be as close as possible to the experimental geometry. If both the calculation and experimentation are performed on a molecule with the same geometry, the calculated and experimental results should be directly comparable.

The OPLS/AA (Optimized Potential for Liquid Simulations/All Atom) parameter set was developed by the Jorgensen group at Yale University and is optimized to fit experimental properties of liquids, such as heat of vaporization and density.

Molecular Mechanics Software Tools:

The TINKER molecular modeling program available on the North Carolina High School Computational Chemistry Server includes MM2, MM3, and OPLS/AA. TINKER also has the ability to use other common parameter sets such as AMBER, CHARMM, and AMOEBA, all of which are commercially available.

Advantages:

The computational speed of molecular mechanics makes this the only viable method for study of large molecules or solid-state materials with many thousands of atoms. Calculations on large systems are tackled using appropriate hardware, typically a high-end multiprocessor machine. Force fields are available for a variety of molecules of interest.

Disadvantages:

In order to perform a molecular mechanics calculation, we must have the required parameters for the molecule of interest. These parameters consist of the set of the various constants from the equations discussed earlier. To have *all* of the constants required for *any* molecule that we might want to study turns out to be highly unlikely. To understand the parameter problem, let's do a crude calculation and see just how many parameters we might need.

The elements that appear most often in typical molecules are a subset of the Periodic Table that includes everything up through Krypton (atomic number 36). Leaving out the Noble Gases (He, Ne, Ar, and Kr) let's pretend that each of the remaining 32 elements could form a bond with every other element and that each element can also form a bond with another atom of the same type. So, with 32 elements we would have:

$$[32(32+1)]/2 = 528$$

We would need 528 spring constants to handle all of the single bonds between these 32 elements. Of course we may also have multiple bonds between elements. One way to look at this is to consider different atom hybridizations (sp^3 , sp^2 , sp) for single, double, and triple bonds between each of our 32 elements. Now we have 96 different element types, which would lead to:

$$[96(96+1)]/2 = 4656$$

To handle all the bonds would require 4656 different spring constants! We would also need to know the equilibrium bond lengths (l_0) for each of these bonds, giving a total of 9312 parameters. If we include other things we need to know, such as k_θ and θ_0 values for *every possible* bond angle, various dihedral angle force constants (V_n values), A and B values for van der Waals forces, C and D values for hydrogen bonding forces, atomic charge values (q_n) and dielectric constant values (ϵ_{ab}) for electrostatic interactions for every possible bond type, etc., we would need something on the order of 10^7 (10 million) parameters! And recall we left out the other ~70 elements of the Periodic Table in our estimate.

The task of experimentally determining (or using theory to calculate) this many parameters is daunting, to say the least! Various approximations are made so that the problem becomes tractable. A simple approach is to have some distance cut-off for terms involving r . Another way to is to limit the number of elements included in a given force field, as discussed previously. Proteins are often simulated via "bead" models that represent each amino acid using two to four

particles, rather than individual atoms. Even with these approximations, ca. 80% of all known molecules do not have adequate parameters for molecular mechanics calculations.

The other drawback of the method is the inability to model certain things of interest to chemists, such as chemical reactions. The harmonic oscillator approximation allows bonds to stretch and compress, but not break and reform new bonds. Also, because we do not have electrons and orbitals in the model, we also can't use molecular mechanics to predict reactivity.