

Molecular Mechanics

Tutorial

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Introduction

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An accompanying manual with exercises specific to MOE is available at:

<http://www.colby.edu/chemistry/CompChem/MOEtutor.pdf>

Introduction to Molecular Mechanics

Section 1

Summary The goal of molecular mechanics is to predict the detailed structure and physical properties of molecules. Examples of physical properties that can be calculated include enthalpies of formation, entropies, dipole moments, and strain energies. Molecular mechanics calculates the energy of a molecule and then adjusts the energy through changes in bond lengths and angles to obtain the minimum energy structure.

Steric Energy

A molecule can possess different kinds of energy such as bond and thermal energy. Molecular mechanics calculates the steric energy of a molecule--the energy due to the geometry or conformation of a molecule. Energy is minimized in nature, and the conformation of a molecule that is favored is the lowest energy conformation. Knowledge of the conformation of a molecule is important because the structure of a molecule often has a great effect on its reactivity. The effect of structure on reactivity is important for large molecules like proteins. Studies of the conformation of proteins are difficult and therefore interesting, because their size makes many different conformations possible.

Molecular mechanics assumes the steric energy of a molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bonds beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge^{1,2}. The total steric energy of a molecule can be written as a sum of the energies of the interactions:

$$E_{\text{steric energy}} = E_{\text{str}} + E_{\text{bend}} + E_{\text{str-bend}} + E_{\text{oop}} + E_{\text{tor}} + E_{\text{VdW}} + E_{\text{qq}} \quad (1)$$

The bond stretching, bending, stretch-bend, out of plane, and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Van der Waals and electrostatic (qq) interactions are between non-bonded atoms.

Bonded Interactions

E_{str} represents the energy required to stretch or compress a bond between two atoms, Figure 1.

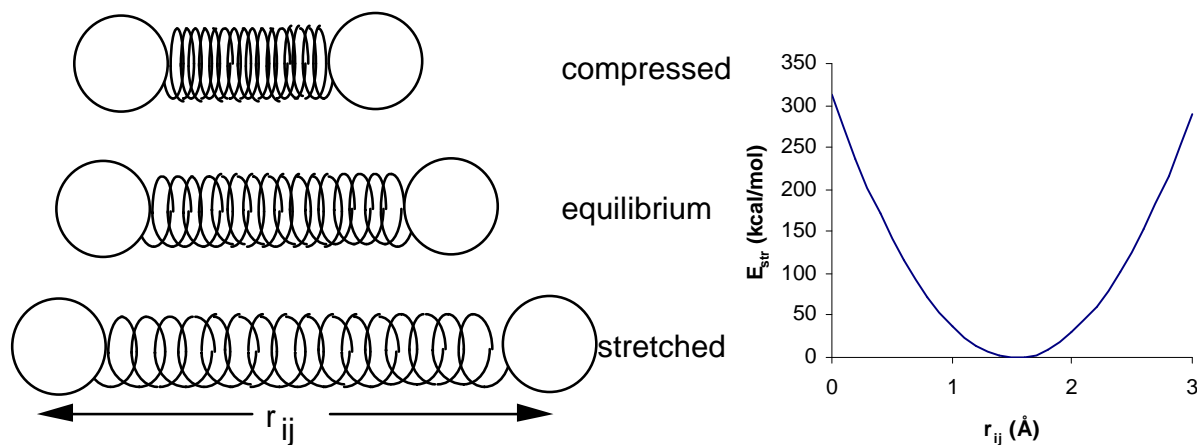


Figure 1. Bond Stretching

A bond can be thought of as a spring having its own equilibrium length, r_o , and the energy required to stretch or compress it can be approximated by the Hookian potential for an ideal spring:

$$E_{str} = 1/2 k_{s,ij} (r_{ij} - r_o)^2 \quad (2)$$

where $k_{s,ij}$ is the stretching force constant for the bond and r_{ij} is the distance between the two atoms, Figure 1.

E_{bend} is the energy required to bend a bond from its equilibrium angle, θ_o . Again this system can be modeled by a spring, and the energy is given by the Hookian potential with respect to angle:

$$E_{bend} = 1/2 k_{b,ijk} (\theta_{ijk} - \theta_o)^2 \quad (3)$$

where $k_{b,ijk}$ is the bending force constant and θ_{ijk} is the instantaneous bond angle (Figure 2).

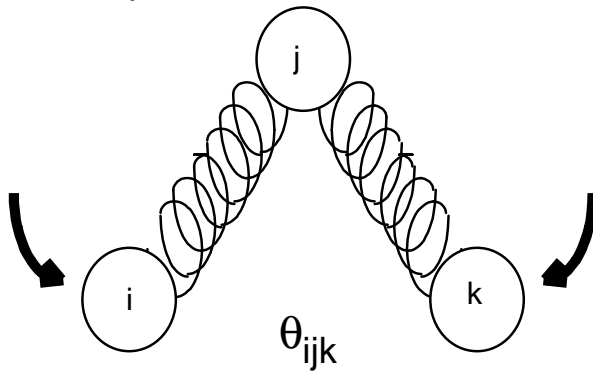


Figure 2. Bond Bending

$E_{str-bend}$ is the stretch-bend interaction energy that takes into account the observation that when a bond is bent, the two associated bond lengths increase (Figure 3). The potential function that can model this interaction is:

$$E_{str-bend} = 1/2 k_{sb,ijk} (r_{ij} - r_o) (\theta_{ijk} - \theta_o) \quad (4)$$

where $k_{sb,ijk}$ is the stretch-bend force constant for the bond between atoms i and j with the bend between atoms i, j, and k.

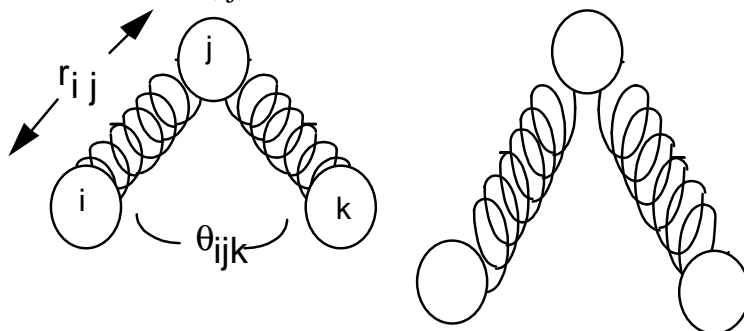


Figure 3. Stretch-Bend Interaction

E_{oop} is the energy required to deform a planar group of atoms from its equilibrium angle, ω_o , usually equal to zero.³ This force field term is useful for sp^2 hybridized atoms such as doubly bonded carbon atoms, and some small ring systems. Again this system can be modeled by a spring, and the energy is given by the Hookian potential with respect to planar angle:

$$E_{\text{oop}} = 1/2 k_{\text{o,ijkl}} (\omega_{\text{ijkl}} - \omega_0)^2 \quad (5)$$

where $k_{\text{o,ijkl}}$ is the bending force constant and ω_{ijkl} is the instantaneous bond angle (Figure 4).

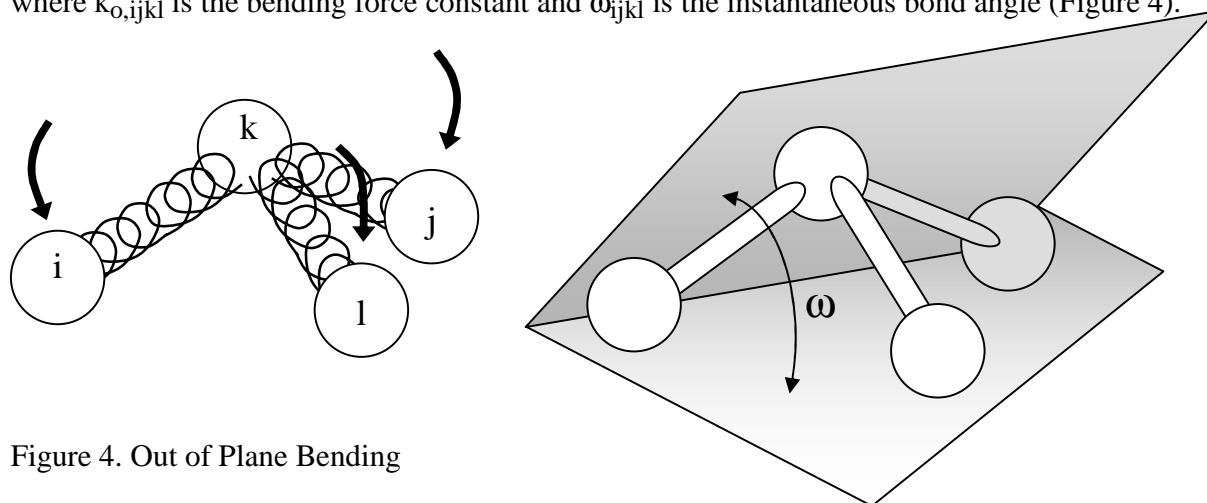


Figure 4. Out of Plane Bending

The out of plane term is also called the improper torsion in some force fields. The oop term is called the improper torsion, because like a dihedral torsion (see below) the term depends on four atoms, but the atoms are numbered in a different order. Force fields differ greatly in their use of oop terms. Most force fields use oop terms for the carbonyl carbon and the amide nitrogen in peptide bonds, which are planar (Figure 5).

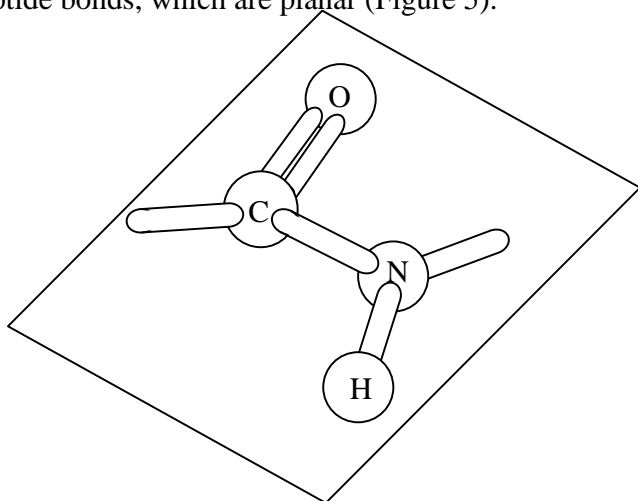


Figure 5. Peptide Bond is Planar.

Torsional Interactions: E_{tor} is the energy of torsion needed to rotate about bonds. Torsional energies are usually important only for single bonds because double and triple bonds are too rigid to permit rotation. Torsional interactions are modeled by the potential:

$$E_{\text{tor}} = 1/2 k_{\text{tor},1} (1 + \cos \phi) + 1/2 k_{\text{tor},2} (1 + \cos 2 \phi) + 1/2 k_{\text{tor},3} (1 + \cos 3 \phi) \quad (6)$$

The angle ϕ is the dihedral angle about the bond. The constants $k_{\text{tor},1}$, $k_{\text{tor},2}$ and $k_{\text{tor},3}$ are the torsional constants for one-fold, two-fold and three-fold rotational barriers, respectively. The

three-fold term, that is the term in 3ϕ , is important for sp^3 hybridized systems (Figure 6a and b). The two-fold term, in 2ϕ , is needed for example in F-C-C-F and sp^2 hybridized systems, such as C-C-C=O and vinyl alcohols¹. The one-fold term in just ϕ is useful for alcohols with the C-C-O-H torsion, carbonyl torsions like C-C-C(carbonyl)-C, and the central bond in molecules such as butane that have C-C-C-C frameworks (Figure 6c).

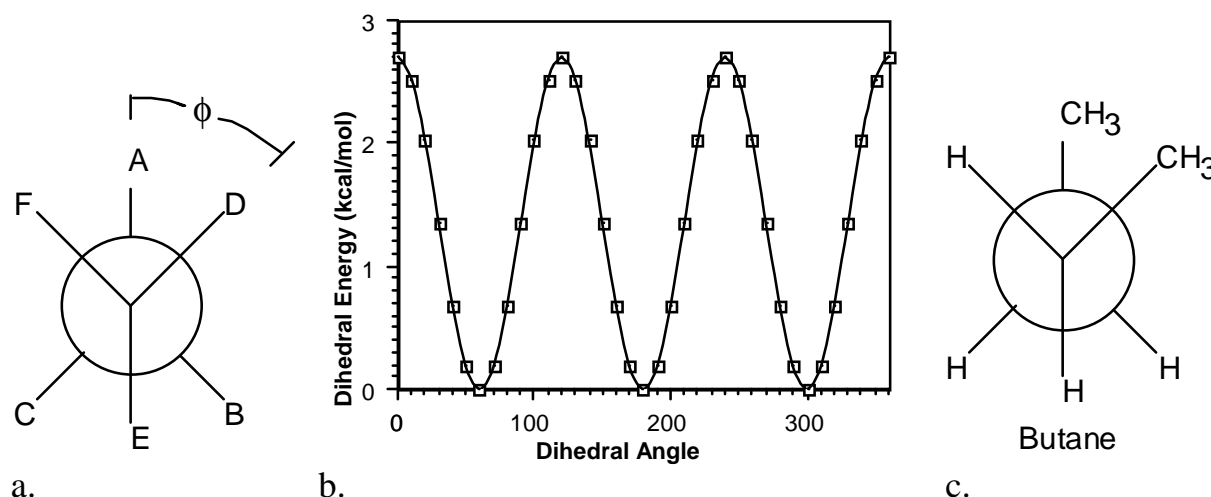


Figure 6. Torsional Interactions, (a) dihedral angle in sp^3 systems. (b) three-fold, 3ϕ , rotational energy barrier in ethane. (c) butane, which also has a contribution of a one fold, ϕ , barrier.

The origin of the torsional interaction is not well understood. Torsion energies are rationalized by some authors as a repulsion between the bonds of groups attached to a central, rotating bond (i.e., C-C-C-C frameworks). Torsion terms were originally used as a fudge factor to correct for the other energy terms when they did not accurately predict steric energies for bond twisting. For example, the interactions of the methyl groups and hydrogens on the "front" and "back" carbons in butane were thought to be Van der Waals in nature (Figure 7). However, the Van der Waals function alone gives an inaccurate value for the steric energy.

Bonded Interactions Summary: Therefore, when intramolecular interactions stretch, compress, or bend a bond from its equilibrium length and angle, the bonds resist these changes with an energy given by the above equations summed over all bonds. When the bonds cannot relax back to their equilibrium positions, this energy raises the steric energy of the entire molecule.

Non-bonded Interactions

Van der Waals interactions, which are responsible for the liquefaction of non-polar gases like O₂ and N₂, also govern the energy of interaction of non-bonded atoms within a molecule. These interactions contribute to the steric interactions in molecules and are often the most important factors in determining the overall molecular conformation (shape). Such interactions are extremely important in determining the three-dimensional structure of many biomolecules, especially proteins.

A plot of the Van der Waals energy as a function of distance between two hydrogen atoms is shown in Figure 7. When two atoms are far apart, an attraction is felt. When two atoms are very close together, a strong repulsion is present. Although both attractive and repulsive forces exist,

the repulsions are often the most important for determining the shapes of molecules. A measure of the size of an atom is its Van der Waals radius. The distance that gives the lowest, most favorable energy of interaction between two atoms is the sum of their Van der Waals radii. The lowest point on the curve in Figure 7 is this point. Interactions of two nuclei separated by more than the minimum energy distance are governed by the attractive forces between the atoms. At distances smaller than the minimum energy distance, repulsions dominate the interaction. The formula for the Van der Waals energy is:

$$E_{\text{VdW},ij} = -\frac{A}{r_{ij}^6} + \frac{B}{r_{ij}^{12}} \quad (7)$$

where A and B are constants dependent upon the identities of the two atoms involved and r_{ij} is the distance, in Angstroms, separating the two nuclei. This equation is also called the Lennard-Jones potential. Since, by definition, lower energy is more favorable, the $-A/r^6$ part is the attractive part and the $+B/r^{12}$ part is the repulsive part of the interaction. For two hydrogen atoms in a molecule:

$$A = 70.38 \text{ kcal } \text{\AA}^6 \quad B = 6286. \text{ kcal } \text{\AA}^{12}$$

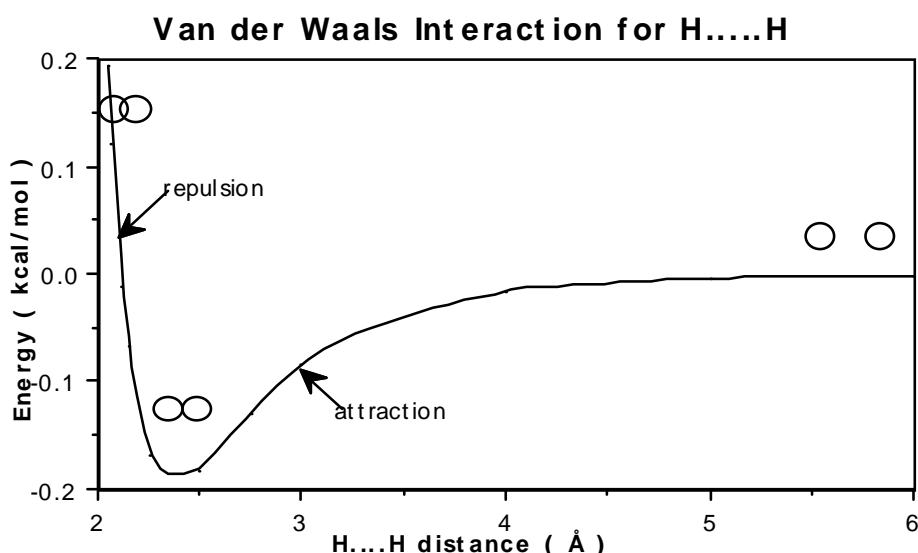


Figure 7: Van der Waals interactions between two hydrogen atoms in a molecule, such as H_2O_2 or $\text{CH}_3\text{-CH}_3$

An equivalent and commonly used form of the Lennard-Jones potential is

$$E_{\text{VdW},ij} = \epsilon \left[-\left(\frac{r_0}{r_{ij}}\right)^6 + \left(\frac{r_0}{r_{ij}}\right)^{12} \right] \quad (8)$$

Where ϵ is the minimum energy and r_0 is the sum of the Van der Waals radii of the two atoms, $r_i + r_j$. Comparing Eq 7 and 8 gives $A = 2 r_0^6 \epsilon$ and $B = r_0^{12} \epsilon$. For two hydrogens, as in Figure 7, $\epsilon = 0.195 \text{ kcal/mol}$ and $r_0 = 2.376 \text{ \AA}$. When looking for close contacts between atoms it is best to use the hard-core Van der Waals radius, σ_{HC} . This distance is the point where the Van der Waals potential is zero. When two atoms are closer than the sum of their σ_{HC} values then strong repulsions are present. For an atom $\sigma_{\text{HC}} = 2^{-1/6} r_i$.

Electrostatic Interactions: If bonds in the molecule are polar, partial electrostatic charges will reside on the atoms. The electrostatic interactions are represented with a Coulombic potential function:

$$E_{qq,ij} = \frac{c Q_i Q_j}{4\pi\epsilon_r r_{ij}} \quad (9)$$

The Q_i and Q_j are the partial atomic charges for atoms i and j separated by a distance r_{ij} . ϵ_r is the relative dielectric constant. For gas phase calculations ϵ is normally set to 1. Larger values of ϵ_r are used to approximate the dielectric effect of intervening solute or solvent atoms in solution. c is a units conversion constant; for kcal/mol, $c = 4172.8 \text{ kcal mol}^{-1} \text{ \AA}$. Like charges raise the steric energy, while opposite charges lower the energy. The Del Re method is often used for estimating partial charges. The Coulomb potential for a unit positive and negative charge is shown in Figure 8a and the Coulomb potential for the hydrogens in H_2O_2 is shown in Figure 8b.

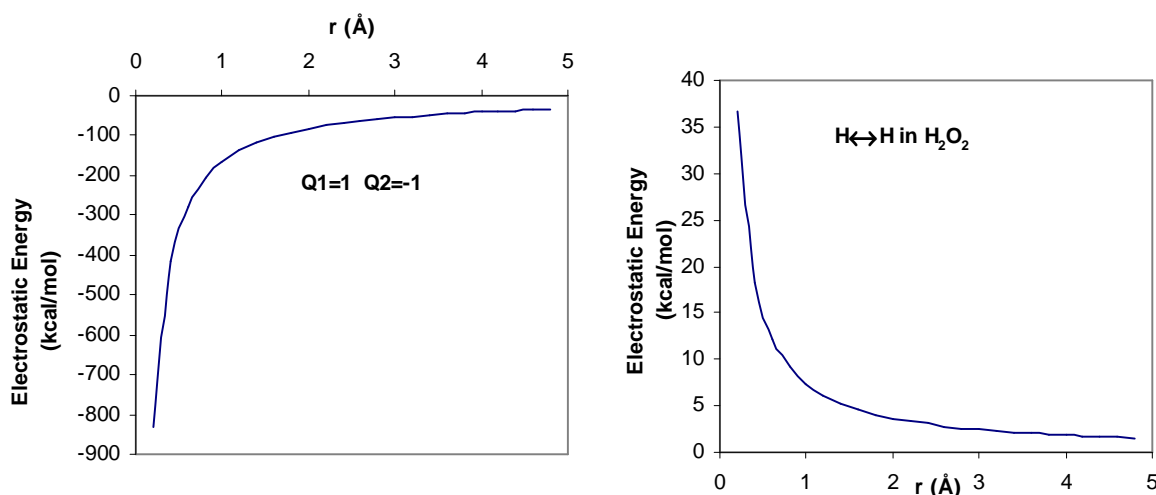


Figure 8. (a) Coulomb attraction of a positive and a negative charge. (b) Coulomb repulsion of the two hydrogens in H_2O_2 , with the charge on each hydrogen as $Q_1 = Q_2 = 0.210$.

Nonbonded Summary: The Van der Waals and electrostatic potential functions represent the various non-bonded interactions that can occur between two atoms i and j . A full force field determines the steric energy by summing these potentials over all pairs of atoms in the molecule.

The bond stretching, bond bending, stretch-bend, out-of-plane, torsion, Van der Waals, and electrostatic interactions are said to make up a force field. Each interaction causes a steric force that the molecule must adjust to in finding its lowest energy conformation.

Empirical Force Fields

All the potential functions above involve some force constant or interaction constant. Theoretically, these constants should be available from quantum mechanical calculations. In practice, however, it is necessary to derive them empirically. That is, the constants are adjusted so that the detailed geometry is properly predicted for a number of well known compounds. These constants are then used to calculate the structures of new compounds. The accuracy of these constants is critical to molecular mechanics calculations. Unfortunately, no single best set of force constants is available because of the diversity of types of compounds. For example, the MM2 force field works best on hydrocarbons because most of the known compounds used in deriving the force field were hydrocarbons¹. MM2 is less accurate for oxygen-containing

compounds and even less reliable for nitrogen and sulfur species. This is because there aren't as many hetero-atom containing compounds in the learning set for MM2 and hydrocarbons are a more homogeneous class of compounds than substances with hetero-atoms. However, the MM2 force field is one of the best available and the most widely accepted force field for use with organic compounds. MM2 was specifically parameterized to reproduce experimental enthalpies of formation.¹

It is important to realize that the force field is not absolute, in that not all the interactions listed in Equation 1 may be necessary to accurately predict the steric energy of a molecule. On the other hand, many force fields use additional terms. For example, MM2 adds terms to the bonded interactions to better approximate the real potential function of a chemical bond. These additional terms take into account anharmonicity, which is a result of the fact that given enough vibrational energy, bonds will break. Purely quadratic potentials have steep "walls" that prevent bond dissociation (Figure 9a). Cubic terms are added to Equation 2 to adjust for this:

$$E_{\text{str}} = 1/2 k_{s,ij} (r_{ij} - r_0)^2 - 1/2 k_{s,ij} C_s (r_{ij} - r_0)^3 \quad (10)$$

where C_s is the cubic stretch constant. For example, for a $C(\text{sp}^3)\text{-}C(\text{sp}^3)$ bond the cubic stretch constant is 2.00 \AA^{-1} , see Figure 9b:

$$E_{\text{str}} = 317 \text{ kcal/mol/\AA}^2 (r - 1.532 \text{ \AA})^2 - 317 \text{ kcal/mol/\AA}^2 [2.00 \text{ \AA}^{-1}] (r - 1.532 \text{ \AA})^3 \quad (11)$$

The addition of the cubic term makes the small r portion steeper or more repulsive. This is realistic for real bonds. At larger r the curve is less steep, as desired. For r very large ($r > 3\text{ \AA}$) the energy decreases, which is unphysical; the curve should approach a constant value. Even though the large r behavior is incorrect, the bond length in compounds remains less than this value, so this region is unimportant under normal conditions. Some force fields add a quartic term, $(r_{ij} - r_0)^4$, to help improve the large r behavior.

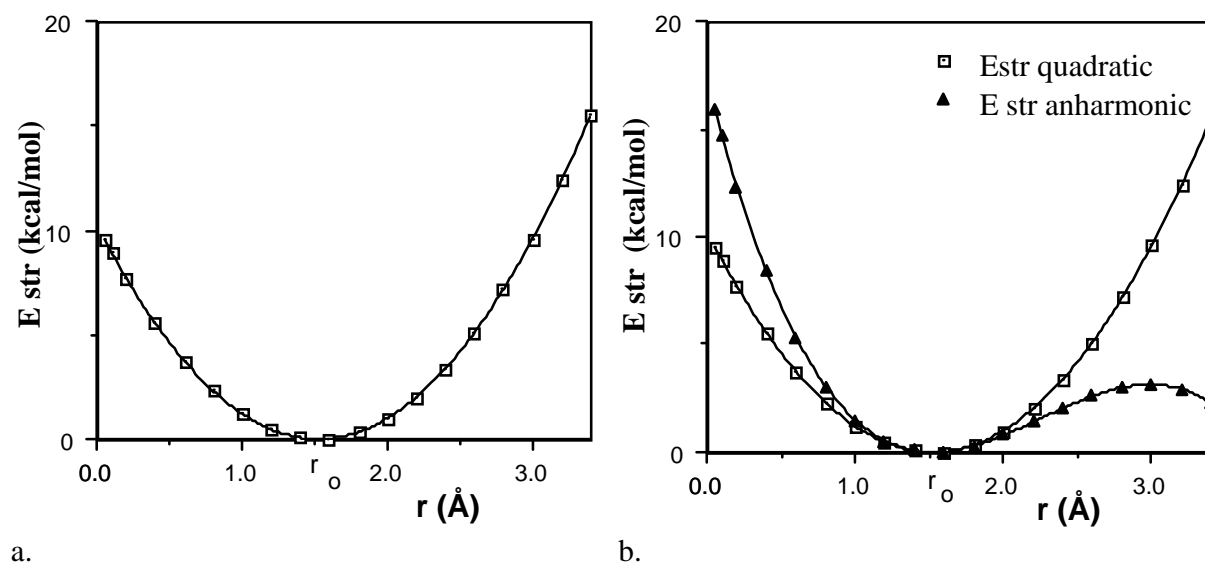


Figure 9. (a). Energy for the stretching of a C-C bond with only the $(r-r_0)^2$ harmonic term., Eq. 2 (b), Comparison of the harmonic term with Eq. 8, which includes the $(r-r_0)^3$ term for anharmonicity.

Force Field Atom Types and Parameters

MM2 is a good example of a molecular mechanics force field. The force constants will give a good idea of what typical force constants are like. The first step in starting a calculation is to identify the different atom types in the molecule. In some programs this must be done manually by the user. In many programs a routine does this step automatically. However, automatic atom type assignments can be incorrect, and the user should check to make sure the atom types are assigned properly. A list of some MM2 atom types is given in Table 1.

Table 1. MM2 Atom types. The typical atom symbol is listed and the radius used in the Van der Waals force field term and approximate Van der Waals radii for judging close contacts.

Atom Type	atom	Description	Type	R (Å)	σ_{HC} (Å)
1	C	C(sp ³)	C	1.969	1.75
2	C	C(sp ²) alkene	Csp2	2.097	1.87
3	C	C(sp ²) carbonyl	C=	1.992	1.77
4	C	C(sp) alkyne; C=C=O	Csp	2.077	1.85
5	H	Attached to C and Si	HC	1.485	1.32
6	O	C-O-H, C-O-C	O	1.779	1.58
7	O	=O carbonyl	O=	1.746	1.56
8	N	N(sp ³)	N	2.014	1.79
9	N	N(sp ²) amide	NC=O	1.894	1.69
10	N	N(sp)	#N	1.945	1.73
11	F	Fluoride	F	1.496	1.33
12	Cl	Chloride	CL	2.044	1.82
15	S	-S- sulfide	S	2.185	1.95
16	S+	>S+, sulfonium	>S+	2.333	2.08
17	S	>S=O, sulfoxide	>SO	2.128	1.90
18	S	>SO ₂ , sulfone	SO ₂	1.998	1.78
20	LP	Lone pair	LP	1.969	1.75
21	H	-OH alcohol	HO	1.307	1.16
22	C	cyclopropane	CR3R	1.992	1.77
23	H	NH amine	HN	1.307	1.16
24	H	COOH carboxyl	HOCO	1.307	1.16
28	H	H on N(sp ²); amide	HN2	1.307	1.16
36	H	ammonium	HN+	1.497	1.33
37	N	-N=; pyridine	NPYD	1.820	1.62
39	N	N+(sp ³); ammonium	N+	2.250	2.00
40	N	N(sp ²); pyrrole	NPYL	1.900	1.69
46	N	NO ₂ ; nitro, nitrate	NO3	1.740	1.55
47	O	carboxylate	OM	2.052	1.83

MM2 types up to type 28 are similar to MMFF types, however imines are type 9, amides are type 10, terminal S in S=C type 16, and C(sp³) in four membered rings are type 20 in MMFF. For MM2 types: http://europa.chem.uga.edu/allinger/mm2mm3/mm2_type.html

MM2 uses the Buckingham equation instead of the Lennard-Jones equation for the Van der Waals interaction. The general form of the Buckingham equation for the Van der Waals potential energy is:

$$E_{\text{VdW},ij} = \varepsilon \left\{ \frac{6}{\alpha-6} e^{-\alpha(r_{ij}-r_0)/r_0} - \frac{\alpha}{\alpha-6} \left(\frac{r_0}{r_{ij}} \right)^6 \right\} \quad (12)$$

This potential uses the r^6 attractive part of the Lennard-Jones functional form, Eq. 7. The exponential part of the Buckingham potential matches the repulsive part of the Lennard-Jones 6-12 potential best with an α of 14-15. However, MM2 uses a “softer” repulsion of $\alpha=12.5$:

$$E_{\text{vdW},ij} = \epsilon \left\{ e^{-12.5 r_{ij}/r_o} - 2.25 \left(\frac{r_o}{r_{ij}} \right)^6 \right\} \quad (13)$$

The MM2 force field shows that equilibrium bond lengths and angles change depending on hybridization and bonding partners. In Table 2 are listed the bond parameters that MM2 uses in its force field for a few bond types. These parameters are the starting point for energy minimizations. Any deviations from these equilibrium distance and angle values will be reflected in increases in steric energy. These parameters are derived by finding the “best fit” to experimental data for a reference set of compounds. This reference set of compounds is often called the learning set. The learning set experimental data is from electron and x-ray diffraction studies. (The k 's are for the quadratic terms, there are also cubic and quartic terms included to account for anharmonicity.) The values in Table 2 are provided to show you typical values for the various force constants.

Table 2. MM2 force field parameters, bond stretch and bend.

Bond	r_o (Å)	k (kcal/Å)	Angle	θ_o	k (kcal/rad ²)
C-C	1.523	317	C-C-C	109.47	32.4
C-O	1.407	386	C-C-O	107.5	50.4
Csp ² *-C	1.497	360	C-Csp ² -C	117.2	32.4
			Csp ² -C-C	109.47	32.4
C(carbonyl)-C	1.509	317	C-C(carbonyl)-C	116.60	28.8
			C(carbonyl)-C-C	107.80	32.4
C=O	1.208	777	C-C=O	122.50	67.5
H-C	1.113	331	H-C-H	109.40	23.0
			H-C-C	109.39	25.9
H-O	0.942	331	H-O-C	106.90	57.1

* sp² hybridized but not conjugated.

A typical stretch-bend interaction constant is the value for C-C-C of 8.6 kcal/Å/radian. A typical oop force constant is the value for >C=C of 2.16 kcal/radian. For torsional force constants, the expansion for the C-C-C-C torsion has one, two, and three fold terms:

$$E_{\text{tor}} = 0.051 (1 + \cos \phi) - 0.341 (1 + \cos 2 \phi) + 0.166 (1 + \cos 3 \phi) \quad (14)$$

When the different units of distance and angle are considered, these values show that typically the force constants have relative sizes of:

$$\text{Stretch} \gg \text{bend} > \text{stretch-bend} \sim \text{out-of-plane} > \text{torsion}$$

In other words, it is difficult to stretch a bond, easier to bend a bond, and very easy to twist a bond if it is singly bonded.

The peptide bond is particularly important, since it is the linkage between amino acids in proteins. Figure 8 shows the peptide bond with the MM2 type force constants for a stretch, bend, and oop bend.

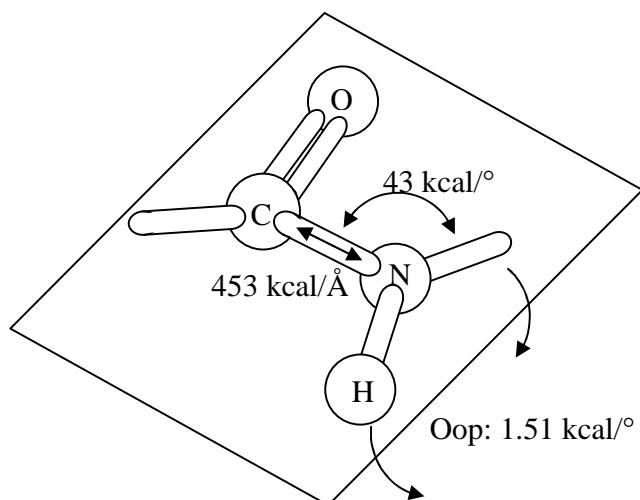


Figure 8. MM2 force field parameters for the amide nitrogen in a peptide bond.

MMFF and MM2 The Merck Molecular Force Field, MMFF, is also a very commonly used force field.⁴⁻⁶ Example parameters for the MMFF force field are given in Tables 3 and 4 so that you can compare the different parameters from one force field to another. MMFF uses a 14-7 Van der Waals term instead of the more common 12-6 Lennard-Jones or Buckingham potential. Overall MMFF has more terms in the force field, including cubic and quartic terms in the bond stretch, and cubic terms in angle bending potential energy. Notice that there are large differences between MM2 and MMFF. The differences show that the specific terms in the force field make a big difference in the overall parameters. These differences also show that parameters are not transferable from one force field to another.

Table 3. Some MMFF Atom types.

Atom Type	atom	Description	Type	R (Å)
1	C	C(sp ³)	C	1.969
2	C	C(sp ²) alkene	Csp2	2.097
3	C	C(sp ²) carbonyl	C=	1.992
4	C	C(sp) alkyne; C=C=O	Csp	2.077
5	H	Attached to C and Si	HC	1.485
6	O	C-O-H, C-O-C	O	1.779
7	O	=O carbonyl	O=	1.746
8	N	N(sp ³)	N	2.014
9	N	N(sp ²) imines	N=C	1.894
10	N	N(sp ²) amides	NC=O	1.945
11	F	Fluoride	F	1.496
12	Cl	Chloride	CL	2.044
15	S	-S- sulfide	S	2.185
16	S	Terminal S=C	S=C	2.333
17	S	>S=O, sulfoxide	>SN	2.128
18	S	>SO ₂ , sulfones and sulfates	SO ₂	1.998
20	C	C(sp ³) in 4-membered ring	CR4R	1.969
21	H	-OH alcohol	HO	1.307
22	C	cyclopropane	CR3R	1.992

Table 4. MMFF94 force field parameters, bond stretch and bend. The MMFF has an additional cubic and quartic term in the bond stretch for which the constants are not shown.

Bond	r_0 (Å)	k (kcal/Å)	Angle	θ_0	k (kcal/rad ²)
C-C-	1.508	306	C-C-C	109.61	61.2
C-O	1.418	363	C-C-O	108.13	71.4
Csp ² *-C	1.482	339	C-Csp ² -C	118.04	54.1
			Csp ² -C-C	109.44	53.0
C(carbonyl)-C	1.492	302	C-C(carbonyl)-C	118.02	82.8
			C(carbonyl)-C-C	107.52	55.9
C=O	1.222	932	C-C=O	124.41	67.5
H-C	1.093	343	H-C-H	108.84	37.1
			H-C-C	110.55	45.8
H-O	0.972	561	H-O-C	106.50	57.1

* sp² hybridized but not conjugated.

Note that even though the MMFF C-C r_0 is listed as 1.508 Å the minimized central C-C bond length in butane is 1.527 Å. This compromise bond length takes into account the cubic and quartic terms in the bond stretch term in conjunction with the Van der Waals repulsions for the attached hydrogens. So even in the case of "unstrained" butane, the central C-C stretch energy is 0.114 kcal/mol and the final bond length is greater than r_0 as set in the force field. The minimized central C-C bond in butane using MM2 is 1.531 Å showing the same effect, but not the same magnitude of increase from the force field r_0 value of 1.523 Å.

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Introduction Section 2 Enthalpy of Formation

The steric energy of a molecule can be used to calculate the enthalpy of formation. First, the steric energy is calculated from Equation 1. Then a bond energy calculation is done using standard tabular values. The bond energy, or enthalpy, is the energy needed to make all the chemical bonds in the molecule starting from the elements in their standard states. It is customary to use bond increments rather than the bond energy calculations that you did in General Chemistry for the bond energy calculation. However, the principle is the same. Thermal energy terms must then be added to account for the energy of translation and rotation of the molecule. The energy of translation (x, y, z motion of the center of mass of the molecule) is $3/2RT$. The rotational energy of a non-linear molecule is also $3/2RT$ ($1/2RT$ for each rotational axis).

The steric energy calculation in molecular mechanics corresponds to an internal energy calculation. Since $\Delta H = \Delta U + \Delta(PV)$, $PV = nRT$ for an ideal gas, and we want the molar enthalpy of formation with $n=1$, we must also add RT to convert from internal energy to enthalpy.

We have not yet considered molecular vibrations, especially internal rotations. In principle, every vibration, including internal rotations, contributes to the enthalpy. However, the contribution of vibrations is difficult to calculate. In practice the contributions are often small so they can be ignored. However, the internal rotation of the methyl group is always included; in fact the effect is automatically included in the bond increment calculation. For careful work extra terms must also be added for non-methyl free internal rotations. This contribution, which is called the torsional increment, is estimated as 0.36 kcal/mol or 1.51 kJ mol⁻¹ for each internal rotation¹. For example, butane, CH₃-CH₂-CH₂-CH₃, has one additional internal rotation, other than the methyl group rotations; so the torsional increment for butane would be 0.36 kcal/mol. In summary the enthalpy of formation for non-linear molecules is then,

$$\Delta_f H^\circ = 3/2RT + 3/2RT + RT + \text{bond energy} + \text{steric energy} + \text{torsional increments} \quad (1)$$

This formula also assumes that there is only one low energy conformation of the molecule. If there are several low energy conformations, each must be accounted for in Equation 1.

Bond Energy

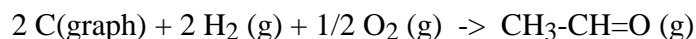
You are familiar with bond energy calculations from General Chemistry. The energy of a molecule is assumed to be an additive function of the energy of individual bonds (Table I). The $\Delta_r H$ for a reaction is given from $\Delta H^\circ(\text{bonds broken}) - \Delta H^\circ(\text{bonds formed})$.

Table I. Bond Enthalpies, $\Delta H^\circ(\text{A-B})$ (kJ/mol)

	H	C	O
H	436		
C	412	348 – 612 =	
O	463	360 – 743 =	146 – 497 =

C (graph) → C (g) $\Delta H^\circ = 716.7$ kJ/mol

For example, the enthalpy of formation of acetaldehyde is calculated as:



#	Bonds Broken	-	#	Bonds Formed	
2	C (graph)	2 (716.7 kJ/mol)	1	C=O	743 kJ/mol
2	H-H	2 (436 kJ/mol)	4	C-H4	(412 kJ/mol)
1/2	O=O	1/2 (497 kJ/mol)	1	C-C	348 kJ/mol
total		2553.9 kJ/mol	-	total	2739 kJ/mol = -185.1 kJ

The experimental value is -166.19 kJ, so the value derived from Table I is not very accurate.

The bond energy calculations in molecular mechanics are done slightly differently, using bond increments. Again the bond energies are assumed to be additive. The contributions are taken not only from each bond, but increments are added for certain structures, such as tertiary carbon linkages. The bond energy calculation for acetaldehyde from the MM2 program is given below, with energies in kcal. MM2 also calculates entropies, which are also listed for your interest.

#	Bond or Structure	Each	Total	Tot S contrib.
3	C-H ALIPHATIC	-3.205	-9.615	38.700
1	C=O	-25.00	-25.00	-2.300
1	C-H ALDEHYDE	-2.500	-2.500	26.800
1	C-C SP3-SP2 C=O	-3.000	-3.000	-0.600
1	ME-CARBONYL	<u>-2.000</u>	<u>-2.000</u>	
		bond energy = -42.115 kcal	S° = 62.600 cal/K	

The bond energy is -42.115 kcal or -176.2 kJ. However, caution should be used since these calculations are designed to be used in conjunction with steric energies in a molecular mechanics calculation and not as general bond energy values. Using Equation 1, with the steric energy calculated by molecular mechanics gives the final $\Delta_f H^\circ = -169.33$ kJ/mol, which is a significant improvement over the bond energy calculation from Table I of -185.1 kJ.

References:

1. Pitzer, Kenneth S., Quantum Chemistry, Prentice-Hall, New York, NY, 1953, pp 239-243, Appendix 18, pp 492-500.

Introduction Section 3 Comparing Steric Energies

You must be careful when comparing steric energies from molecular mechanics calculations. Strictly speaking you can only compare steric energies directly for conformational isomers or geometric isomers that have the same number and types of bonds. Some examples using MM2 will make this important point clearer.

Example 1: Different number of atoms:

Table 1 gives the MM2 results for pentane, hexane, and heptane. First note that each of the individual force field terms and the total steric energy increase on going from pentane to hexane to heptane. It would be tempting to conclude that the larger molecules have “more steric hindrance” from these numbers, but this would be incorrect. Rather, the changes are caused by the fact that you are simply adding more atoms so the number of terms in the force field are increasing causing the molecule’s totals to increase. This conclusion is reinforced by the MM2 sigma strain energy results that show each molecule to have no strain energy. This example shows that you can’t directly compare steric energies for molecules with different numbers of atoms.

MM2, MMX, and MM3, however, take the molecular mechanics calculation one step further. The use of bond enthalpy calculations to calculate the enthalpy of formation for the molecule adjusts for the new bonds that are formed as the molecular size increases. Enthalpies of formation can be compared directly. For example, the bond enthalpy and enthalpy of formation from MM2 are also shown in Table 1. These results show correctly that the enthalpy of formation of these molecules decreases with size, even though the total steric energy is increasing. The enthalpies of formation can, of course, be used to calculate the enthalpies for any reactions using pentane, hexane, and heptane.

Table 1. MM2 results for linear C5, C6, and C7 hydrocarbons and branched C5 hydrocarbons.

kcal/mol	Pentane	Hexane	Heptane	2-Methylbutane	2,2-Dimethylpropane
Bond Stretch	0.2267	0.2968	0.3664	0.3180	0.4038
Bending	0.3797	0.4689	0.5553	0.6512	0.3308
Stretch-bend	0.0731	0.0938	0.1142	0.0969	0.0641
Lennard-Jones	2.1316	2.5911	3.0512	2.0967	1.4712
Dihedral	0.0116	0.0161	0.0212	0.4649	0
Total Steric	2.8226	3.4667	4.1084	3.6279	2.2699
Bond Enthalpy	-41.50	-47.91	-54.32	-42.93	-45.22
Sigma Strain	0	0	0	1.03	0
Enthalpy of Formation	-36.27	-42.04	-47.82	-36.90	-40.55

The bond enthalpy calculations in MM2 are done using tabulated values for bond increments for each specific bond and chemical environment. See the enthalpy of formation discussion earlier in this manual for more information. The sigma strain energy calculations in MM2 are done using similarly tabulated increments for each specific bond and chemical environment, but in a hypothetical “strainless environment.” Differences in total enthalpy of the values based on the actual and the strainless bond enthalpies give the sigma strain energy.

Example 2: Same formula different types of bonds:

Table 1 also has the MM2 results for the branched pentanes, 2-methylbutane and 2,2-dimethylpropane, to compare with linear pentane. The corresponding structures are shown in Figure 1. Each isomer has the same number of atoms and the same number of C-H and C-C bonds. Here again, however, comparing steric energies directly is dangerous. The higher steric energy of pentane compared to 2,2-dimethylpropane does not indicate that linear pentane has “more steric hindrance.” Rather, both linear pentane and 2,2-dimethylpropane show no sigma strain. Likewise, both branched pentanes have lower enthalpies of formation than the linear isomer. Even though all three isomers have the same number of C-H and C-C bonds, the C-C bond energy increases with increased branching. That is, a tertiary C-C bond is more stable than a secondary, which is more stable than a primary.

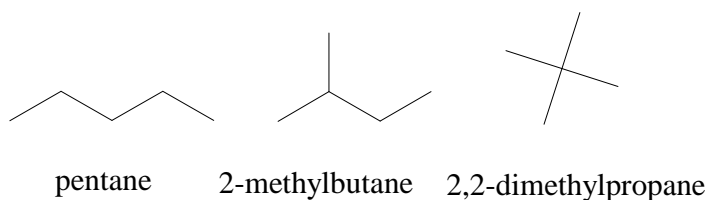


Figure 1. Pentane geometric isomers

Once again, the final enthalpy of formation calculations adjust for these bond strength differences and are then directly comparable. Does this mean that the steric energies by themselves are useless? No, you just need to be careful when doing comparisons.

For example, why does 2-methylbutane have a higher steric energy than linear pentane? The Lennard-Jones term is actually lower in energy for the branched isomer, because of favorable, attractive Van der Waals interactions. Looking at the other force field terms, we see that the dihedral terms increase the most. The increase in the branched isomer results from a gauche interaction. Draw a Newman projection to show that this is so. This example shows that comparing steric energies, and in particular, comparing the different force field terms can be very helpful in understanding the energetics of the molecule, especially for geometric isomers. Remember that, however, it is the enthalpy of formation of the molecule that determines its reactivity and the enthalpy of formation may or may not follow the same trends as you compare one geometric isomer to another.

An analogy might help. One person may be taller than another, but the taller person may not be the better basketball player. It is fair to compare the height of two individuals, but basketball ability depends on many more things than height alone.

Example 3: Making fair comparisons:

Most biostructure molecular mechanics programs don't use MM2 or MM3, so that the sigma strain energy and the enthalpy of formation are not calculated. In addition, MM2 and MM3 have limited parameter sets, so your compound of interest may not run with MM2 and MM3, and you must use a different force field. How can you make fair comparisons if you can't get the enthalpy of formation? Often, it is possible to build a reference structure and then look at differences with the reference structure as a fair comparison. To illustrate this point we will look at the strain energy of five, six and seven membered rings, Table 2. We will use MM2 results to check our comparisons, to make sure our reference structures provide a fair comparison. But the utility of building reference structures is really most useful when MM2 isn't available.

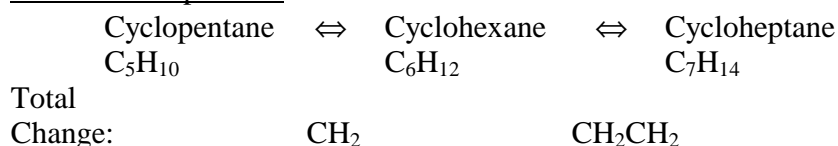
Table 2. MM2 Results for five, six and seven membered hydrocarbon rings.

kcal/mol	Cyclopentane	Cyclohexane	Cycloheptane
Bond Stretch	0.3264	0.3374	0.4116
Bending	2.1899	0.3652	2.8389
Stretch-bend	-0.0976	0.0826	0.2399
Lennard-Jones	2.6501	3.6100	5.3694
Dihedral	6.3279	2.1556	5.4476
Total Steric	11.4049	6.5510	14.3075
Bond Enthalpy	-32.07	-38.48	-44.90
Sigma Strain	8.12	2.61	9.71
Enthalpy of Formation	-18.27	-29.53	-28.19
(Cyclic-Linear) Steric Energy	8.58	3.08	10.20

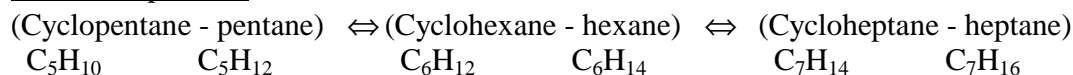
First note that the total steric energy and the enthalpy of formation follow completely different trends. Therefore, the steric energy is a poor predictor of chemical reactivity. This example is similar to Example 1, above, in that the molecules we wish to compare have increasing numbers of atoms. However, the strain energy of rings is an important concept and has helped to guide organic chemist's intuition about chemical reactivity for over a century. Of course, MM2 calculates the strain energy, and we get the expected order cyclohexane < cyclopentane < cycloheptane. Students are often surprised at this order, thinking that the cyclopentane ring is unusually strained, but this is not so in comparison with cycloheptane.

We can make a fair comparison of the ring strain energies of these molecules by comparing each cyclic structure with a linear reference structure. The reference structure is just the cyclic molecule "opened up." We then compare this difference in energy for the cyclopentane, cyclohexane, and cycloheptane rings. In Table 2 is listed the difference in steric energy between the cyclic structure and the linear structure. These differences mirror the MM2 strain energies nicely. The difference with the linear reference structure is successful in finding the strain energy because the difference between the cyclic and linear form is the breaking of two C-H bonds and the formation of a new C-C bond for each of our cyclic molecules. Using the differences in energy then makes the comparison fair because we are adjusting for the fact that the rings have an increasing number of atoms. The following chart may be helpful in seeing why this difference procedure works:

Incorrect comparison:



Better comparison:



Using differences with reference structures helps to cancel out the effects of having different numbers of atoms and bonds. In fact, the differences with the references (last row of Table 2) are each 0.47 kcal/mol larger than the corresponding MM2 sigma strain energy. So the trend in strain energy is exactly reproduced. The 0.47 kcal/mol results from the way in which MM2 tabulates the expected values of bond energy for “strainless structures.”

In summary, comparisons of steric energies can be made using differences with reference structures. The reference structures should be built so that the energy term of interest is highlighted. In this example, the reference was constructed from the linear form of the cyclic molecule to highlight the strain energy. The reference structures should be as similar as possible in every other way to the compound under study.

Example 4: Different number of atoms, but ask a different question:

Steric energies, as we have seen, usually can't be compared directly when trying to predict chemical reactivity. We need enthalpies of formation for reactivity comparisons. However, we can ask a different question, for which steric energies are useful for comparisons. We can ask which terms in the force field have a big influence on the steric energy of the molecule and how that influence changes from molecule to molecule. In other words, by comparing relative contributions, we can trace through the important differences among our molecules. The relative contributions of the different force field terms to the steric energy, based on Table 2, are given in Table 3.

Table 3. Relative contributions to the total steric energy of cyclic hydrocarbons.

%	Cyclopentane	Cyclohexane	Cycloheptane
Bond Stretch	2.9	5.2	2.9
Bending	19.2	5.6	19.8
Stretch-bend	0.9	1.3	1.7
Lennard-Jones	23.2	55.1	37.5
Dihedral	55.5	32.9	38.1

The primary contributor to the steric energy for cyclopentane is the dihedral (torsional) interaction. But for cycloheptane the steric energy results more from a combination of dihedral and unfavorable Lennard-Jones (Van der Waals) contacts. For cyclohexane, angle bending is relatively unimportant, compared to the other ring systems. Comparisons such as these are invaluable for building your intuition about the energy components of molecules. These comparisons are fair because the contributions are all relative to the steric energy of the same molecule. That is, the percentages are calculated from the energies of one molecule.

However, it is important to remember what such relative contributions don't tell you. The results in Table 3, by themselves don't tell you which molecule has the highest strain, nor even the highest steric energy. These relative contributions also don't tell you which molecule has the highest enthalpy of formation. So you can't predict which molecule will be the most reactive.

Another analogy may be helpful. Jane gets a higher percentage of her points from foul shots than Susan. This statistic, however, doesn't tell you who gets more points per game. On the other hand, the statistic suggests that Susan should work on her foul shots, which is helpful information.

Comparing relative contributions is most useful when the various force field terms have comparable reference energies. For example, the various terms in Table 2 from MM2 are all very

small for linear hydrocarbons where the strain energies are quite small. However, some implementations of force fields shift the energy zero for the torsional interaction so that even for linear hydrocarbons the torsional terms are quite large. This does not mean that linear hydrocarbons are torsionally strained! So when getting used to a new program and new force field start by minimizing trans-butane and looking at the size of the different force field terms. If the force field terms are all small for butane then comparisons of the type in this example will be easy to interpret. If one or more terms for butane are much larger than the others you will need to remember that the relative size of that interaction in your molecule will be over-emphasized when looking at relative contributions. Making comparisons in the changes in relative contributions from one molecule to another will still be useful, however.

Conclusion

The discussions in the examples above are summarized in Table 4. Comparing steric energies directly gives the most information, but you can only compare steric energies directly if the molecules have the same formula and the same number and types of bonds. We even need to consider that not all C-C single bonds are equal, when we compare steric energies. In other words the chemical environments of all the bonds must be equivalent. You can always compare enthalpies of formation.

Table 4. Molecular mechanics steric energy comparisons between molecules.

Comparison	Steric Energy Directly	Difference with Reference	Relative contributions
Conformational Isomers	yes	yes	yes
Geometric Isomers	if same environments	yes	yes
Different Formulas	never	yes	yes

Introduction Section 4 Energy Minimization

The steric energy of a molecule is the sum of the bonded and nonbonded terms (Van der Waals energy, and the electrostatic energy). The lowest energy conformation is the set of bond lengths and angles that gives the smallest steric energy. In other words, bonds find a compromise among competing forces to determine the lowest energy conformation. The goal of molecular mechanics is to determine the lowest energy conformation of a molecule. The process is called energy minimization. The computer makes small changes in the position of every atom and calculates the energy after every move. The move is kept if the energy is lowered, otherwise the atom is returned to its original position. This process is repeated many times until an overall energy minimum is reached. One full cycle, where each atom is moved once, is called a minimization step or iteration. Hundreds of steps may be necessary to find a reasonable structure for the molecule.

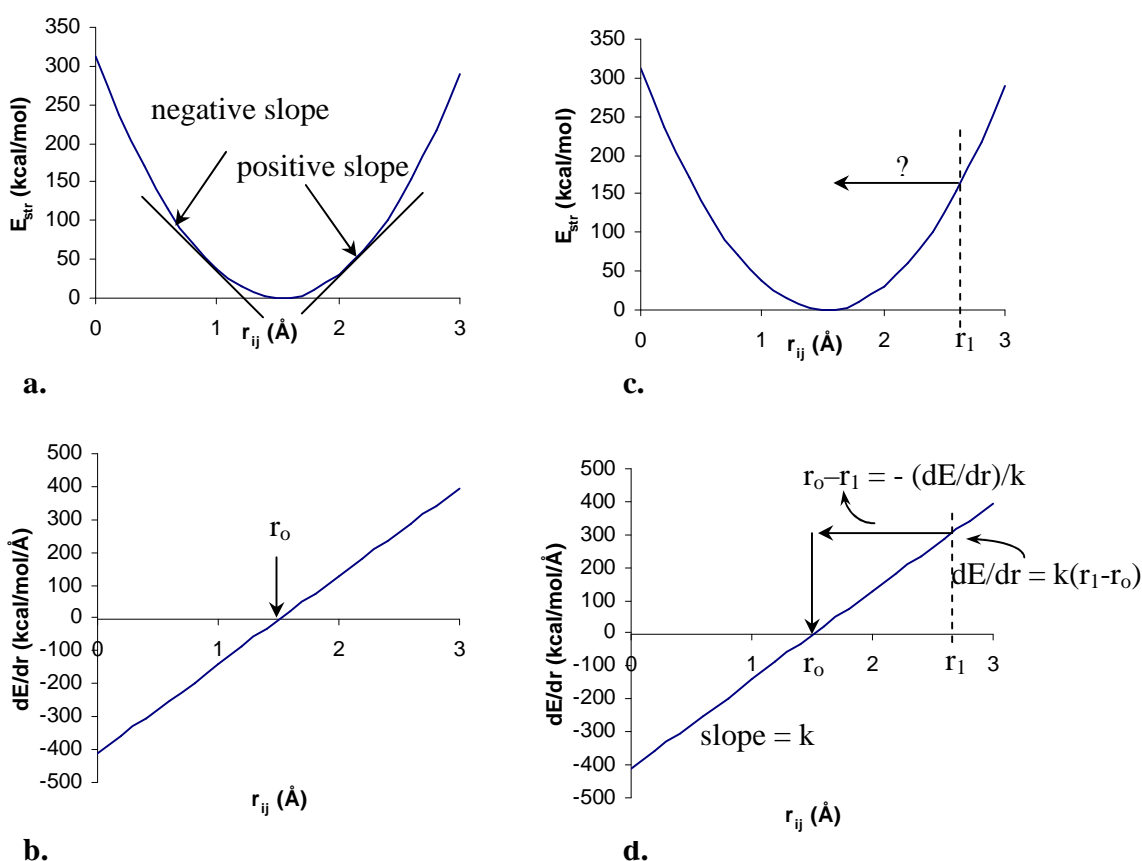


Figure 1. Finding the change in bond length to minimize the potential energy. (a.) The potential energy curve for a stretching bond. (b.) The slope of the potential energy is linear and changes sign as the molecule passes through the equilibrium bond length. (c.) The starting geometry is with bond length r_1 . Now calculate the change in bond length that minimizes the potential energy. (d.) The slope of the potential energy at r_1 is $k(r_1 - r_0)$, and the slope of the line in the dE/dr graph is k . To calculate the change in bond length to find the minimum potential, extrapolate down the line to the zero point.

Many methods have been developed to accelerate the minimization process. These methods use information from the derivatives of the potential energy function to calculate the change in the coordinates for each step¹. The Newton-Raphson method is the most basic of these techniques, and we discuss this method first using a simple example. We start with a diatomic molecule. The only coordinate to minimize is the bond length, r . The potential energy function is just the bond stretching term, Figure 1a:

$$E_{\text{str}} = \frac{1}{2} k (r - r_0)^2 \quad (1)$$

where k is the force constant for the bond and r_0 is the equilibrium bond length. The derivative of E_{str} is the slope of the curve in Figure 1a:

$$\frac{dE_{\text{str}}}{dr} = k (r - r_0) \quad (2)$$

The derivative is plotted in Figure 1b. Equation 2 shows that the slope of the potential energy is linear and changes sign as the molecule passes through the equilibrium bond length. For example, in Figure 1a, when $r > r_0$ the slope is positive, when $r < r_0$ the slope is negative, and the slope is zero at r_0 . The slope of the line in Figure 1b is the second derivative of the potential energy:

$$\frac{d^2E_{\text{str}}}{dr^2} = k \quad (3)$$

Lets say that the starting guess for the bond length before minimization is r_1 , Figure 1c. Now we wish to calculate the change in bond length that minimizes the potential energy. In other words, we wish to calculate the distance we need to move to find r_0 , or $r_0 - r_1$. The change in bond length is easiest to calculate using the derivative of the potential, Figure 1d, because the derivative is a linear function. All we need do is extrapolate down the line to the zero point. In reference to Figure 1d, the derivative of the potential at r_1 is:

$$\frac{dE_{\text{str}}}{dr} = k (r_1 - r_0) \quad \text{at } r_1 \quad (4)$$

Solving this linear equation for the change in bond length just requires dividing by $-k$:

$$(r_0 - r_1) = -\frac{1}{k} \frac{dE_{\text{str}}}{dr} \quad (5)$$

This change in bond length is also shown in Figure 1d. For harmonic potentials, like Equation 1, the calculated change is exact, so only one iteration step is needed. When there are many force field terms or non-harmonic potentials (eg. torsions, Van der Waals, Coulomb) the derivative of the potential is not linear, and equation 5 is just an approximation. Therefore, in the general case many steps are necessary to find the minimum, but the derivative of the potential still gives a good guess.

Newton-Raphson: Equation 5 is specific to a harmonic potential. We can obtain a more general solution by substituting for k using Equation 3:

$$(r_0 - r_1) = -\frac{1}{\frac{d^2E_{\text{str}}}{dr^2}} \frac{dE_{\text{str}}}{dr} \quad (6)$$

Equation 6 is the basis of the Newton-Raphson method¹. The first derivative of the potential is called the gradient. The second derivative is called the Hessian, especially when more than one dimension is involved. The Newton-Raphson method is also used for molecular orbital calculations. You will see the Hessian mentioned in Spartan and other molecular orbital software packages. When many atoms are present, the Hessian can be time consuming to calculate and to invert. The many different methods for minimization differ in the way they approximate the Hessian. The Newton-Raphson method requires the fewest steps, but each step is time

consuming. The number of steps required to minimize strychnine, Figure 2, for several methods is given in Table 1. The Newton-Raphson method was almost the fastest in this case because strychnine is a very small molecule, for larger molecules Newton-Raphson is very slow.

Table 1. Iterations necessary to minimize strychnine from a crude starting geometry.

Method	Seconds	Steps
Steepest Descents	32.4	3042
Conjugate Gradient	14.1	237
Newton-Raphson	13.0	15
Adopted Basis Newton-Raphson	3.7	279

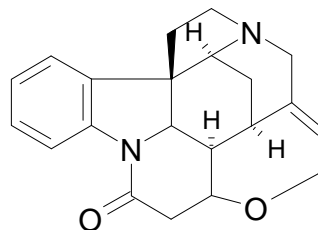


Figure 2. Strychnine

Steepest Descents: In the steepest descents method, the Hessian is just approximated as a constant, γ :

$$(r_0 - r_1) = -\frac{1}{\gamma} \frac{dE_{\text{str}}}{dr} \quad (7)$$

You can think of γ as an effective force constant as in Equation 5. γ is calculated at the beginning of the first step to give a specified step size. The dialog for the minimization parameters for CHARMM and MOE are shown in Figure 3. The Initial Step Size entry is used to fix γ .

<u>CHARMM</u>		<u>MOE</u>		
Number of Minimization Steps	50	Iteration Limit	RMS Gradient	
Coordinate Update Frequency	5		Test	
Energy Gradient Tolerance	0.0001	Steepest Descents	100	1000
Energy Value Tolerance	0	Conjugate Gradient	100	100
Initial Step Size	0.02	Truncated Newton	200	0.001
Step Value Tolerance	0			

Figure 3. CHARMM and MOE parameters for energy minimization.

Too small a step size can slow the minimization process. Too large a step size can prevent convergence. Table 2 lists the effect of the step size on the number of steps to give a minimized structure. After the first steepest descents stage, the next steepest descents stage is taken in a direction perpendicular to the previous direction. This change in direction is efficient in optimizing all the variables for the minimization.

Table 2. Steps necessary to minimize strychnine for different step sizes.

Method	Step Size		
	0.01	0.02	0.04
Steepest Descents	3998	3042	no converge
Conjugate Gradient	237	237	237
Newton-Raphson	15	15	15
Adopted Basis Newton-Raphson, ABNR	311	279	331

The conjugate gradient and Newton-Raphson methods only use the step size in determining the initial gradient, so they are not strongly effected by the choice of the step size.

Table 1 shows that steepest descents has very poor convergence properties. So why is steepest descents used at all? Conjugate gradients can often fail with a poor initial structure, such as a Protein Database file for a protein. Steepest descents is less sensitive to the starting conditions. Therefore, a few steps of steepest descents is usually used to refine a poor starting structure before switching to a better method, such as conjugate gradient.

Conjugate Gradient: Conjugate gradient is a variation of the steepest descents method. The calculation of the gradient is improved by using information from previous steps. After the first steepest descents initial stage, a second steepest descents stage is taken in a direction that is predicted to be optimal for minimizing the remaining variables. This direction is called the conjugate direction. Pure steepest descents algorithms always take 90° turns after each stage, which may move the first minimization stage away from the optimal value. The conjugate direction leaves the previous minimization at the optimum value while finding an efficient direction to optimize the remaining variables. For example, for the minimization of the structure of water the OH bond length and bond angle must be adjusted to minimize the energy. A schematic representation of the potential energy surface for the two variables is shown in Figure 4. Lets say that the initial steepest descents finds the minimum along the initial direction. The next best direction to look for the overall minimum is not necessarily perpendicular to the initial path, Figure 4.

Table 1 shows that the conjugate gradients method is vastly better than steepest descents while remaining nearly as fast per step. Conjugate gradients is a good general purpose technique.

Adopted Basis Newton-Raphson, ABNR: For very large systems like proteins and nucleic acids, energy minimization can require hours. The search for very efficient minimization methods for such large biological macromolecules has led to a modified version of the Newton-Raphson method that maintains excellent convergence properties but in a much shorter time. Each step of the ABNR method begins with a steepest descents stage. Then the bond lengths and angles that change the most are noted, and only these coordinates are used in a second stage of Newton-Raphson minimization. For strychnine, Table 1, and for biological macromolecules in general, ABNR is clearly the best method.

Truncated Newton-Raphson: The use of second derivatives in Newton-Raphson minimization is responsible for the excellent convergence properties. However, the inversion of the Hessian is time consuming. An approach has been developed that uses conjugate gradients to determine the directions for the minimization and then the Hessian to determine the minimum in that direction². The “direction” of the minimization determines the particular bond lengths and angles that will be changed. The minimum in that “direction” determines how much to change those bond lengths and angles. Truncated Newton-Raphson has similar and often better convergence characteristics to ABNR without a significant difference in time. The Hessian is calculated

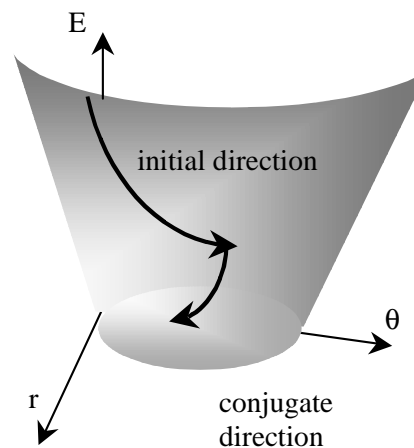


Figure 4. One iteration of conjugate gradients minimization.

directly from the second derivatives, which are evaluated numerically, but some small second derivatives between distant atoms are neglected (or truncated)³.

The general approach to energy minimization is to use a “cascade” of techniques. First 50-200 steps of steepest descents is used to remove close contacts (atoms closer than the sum of their Van der Waals radii). Then 50-200 steps of conjugate gradients is applied, followed by final minimization using ABNR or truncated Newton-Raphson. For small molecules only 10-20 initial steepest descent steps are needed, and the intermediate conjugate gradient steps can be skipped.

Minimization Criteria: How do you determine when the molecule is minimized? Molecular modeling programs provide a number of alternate methods for deciding when to stop, Figure 3. The Number of Minimization Steps (Iteration Limit) can be used to stop the calculation. This option is dangerous; you need to realize that if the minimization stops for this reason that the molecule is not minimized and you need to continue to submit the molecule for minimization until the energy no longer changes on successive steps. A better option is to set the number of minimizations steps to a very large number and then use an energy based criterion, like the energy gradient tolerance (test).

Remember that the gradient is the derivative of the energy. The energy gradient approaches zero at the energy minimum. The criterion then is to stop if the gradient is less than a selected value. This method is illustrated in Figure 5. In program listings you will often see the term rms gradient. Rms stands for root mean squared. For some coordinates (e.g. a bond stretch) the gradient might be positive, while for other coordinates (e.g. an angle) the gradient might be negative. So that the positive and negative gradients don't cancel out, the gradients are squared to give positive numbers before adding them together to make the comparison. (The standard deviation is likewise an rms statistic).

An alternate method to stop the minimization is to compare the change in energy between the current step and the previous step, ΔE in Figure 6. If the change in energy is below the set tolerance, then the minimization is halted.

Finally, the last available criterion is the step size. The size of the change in the coordinates is monitored and when this change is smaller than the set tolerance, the minimization is halted. This criterion, where Δr is the step size, is also illustrated in Figure 6. The step size criterion is useful for shallow potentials, where the energy doesn't change much for large changes in conformation or distances between molecules. For example for complexes, the energy gradient can be small and still give large changes in the distance between the two molecules. In some programs, the step size is called the rms displacement.

When several criteria are specified, the first criterion to be met stops the minimization. For example, as mentioned above if you set the number of minimization steps to a small number, the calculation

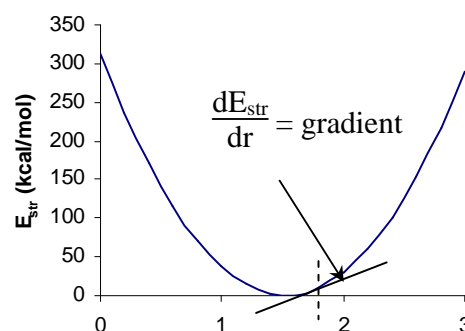


Figure 5. Stop if the energy gradient is below the tolerance.

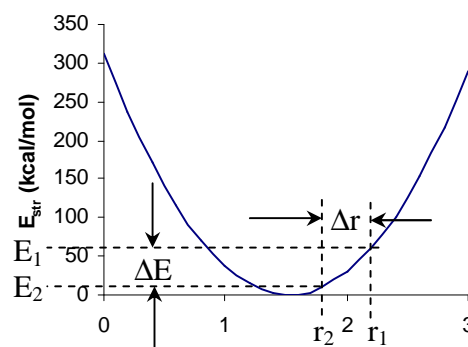


Figure 6. Stop if the energy change or step size is below the tolerance.

will probably stop before a minimum is achieved. To determine if the step count has stopped the calculation, look at the output and determine if the last minimization step is the same as the number of minimization steps that you specified as a control parameter (i.e. Figure 3). To avoid this problem, set the number of minimization steps to a large number. On the other hand, if you have a large molecule, there is a danger in specifying too large a number of minimization steps. The calculation may take too long to run and then the computer is tied up so that you can't do other things. Or, you may have made a mistake, and a long minimization keeps you from quickly making changes.

In CHARMM, as a default, we normally choose 500 steps for small molecules and 50 steps for large molecules. Then we make sure to resubmit the minimization if the last step matches the 500 or 50 that we set. Other than minimization steps, the criterion that you use is a matter of your choice. The very best approach is to enter a value for each and see which is satisfied first. Entering all this data is tedious, so as a default we usually use just the energy gradient tolerance. A value of 0.0001 is useful for very small molecules, however, you will find it necessary to use 0.001 or 0.01 for biological macromolecules or for solvated systems to save time. The units are in kcal/mol/Å in most programs.

References:

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2. "Forcefield-Based Simulations," Accelrys, Corp, San Diego, CA. Chapter 4 Minimization.
3. Jensen, Frank, *Introduction to Computational Chemistry*, John Wiley, Chichester England, 1999, p322.

Introduction Section 5 Molecular Dynamics

Introduction

One of the most important developments in macromolecular chemistry is molecular dynamics. Molecular dynamics is the study of the motions of molecules. The time dependence of the motion of a molecule is called its trajectory. The trajectory is determined by integrating Newton's equations of motion for the bond stretching, angle bending, and dihedral torsions of the molecule. Molecules are always in motion. The motion of molecules is important in essentially all chemical interactions and are of particular interest in biochemistry. For example, the binding of substrates to enzymes, the binding of antigens to antibodies, the binding of regulatory proteins to DNA, and the mechanisms of enzyme catalysis are enhanced and sometimes completely determined by the conformational flexibility of the molecules. Different domains of an enzyme can have very different motional freedom. The problem of protein folding is the determination of the trajectory of the macromolecule as it assumes its active conformation after or during protein synthesis.

Most chemistry is done in solution. Molecular dynamics has proved to be an invaluable tool in studies of solvation energetics. Solute-solvent interactions are governed by the relative motions of the solute and solvent molecules and the motional-response of the solute to the presence of the solvent. Some of the earliest dynamics studies were to determine solvation Gibbs Free energies. In biochemistry, solute-solvent interactions play a particularly important role in determining the secondary and tertiary structure of biomolecules.

Another important use of dynamics is in the search for the global energy minimum in conformationally flexible molecules. Molecular mechanics find the energy minimum that is closest to the starting conformation of the molecule. This "local" energy minimum is rarely the lowest energy, or "global", minimum for the molecule. Finding the "global" minimum can be a very difficult task. In molecular mechanics a common procedure is to start with many different initial conformations and minimize them all looking for the lowest energy result. This kind of search can be very time consuming. Molecular dynamics, on the other hand, can help a molecule "explore" its conformation space more efficiently. The trajectory of the molecule is run at a high temperature, so that the atoms will move very far from their equilibrium positions. Such high temperature trajectories can overcome energy barriers that lead to more stable conformations. The trajectory often starts in one conformation and then ends up in another more stable conformation.

Molecular dynamics is an active area of research in biochemistry, molecular biology, and polymer chemistry. Current work is directed towards making molecular dynamics a reliable tool for the estimation of Gibbs free energies of solvation, conformational equilibria, and equilibrium constants for binding interactions. These thermodynamic parameters are determined by doing free energy perturbation studies using molecular dynamics trajectories; see Section 7 for more on free energy perturbation.

The difference between molecular mechanics and dynamics can be illustrated with a simple example. Let's direct our attention to a single bond in a molecule, a C-H bond for example. Assume that we start with the bond length too large, say 2 Å. If we were to run molecular mechanics, the bond length would decrease until the minimum in the potential energy was reached, Figure 10.1a. Further minimization would not change the bond length. If we were to run molecular dynamics on our stretched bond, the trajectory would decrease the bond length, but the bond length would continue decreasing past the equilibrium length until it was too short. Being too short, the bond length would then begin to increase. Over time the bond length will oscillate

about its equilibrium value, never coming to rest, Figure 10.1b. In other words, in mechanics the potential energy is minimized, while the kinetic energy of the molecule is ignored. In a dynamics trajectory, both potential and kinetic energy are studied and the total energy is conserved by the motion.

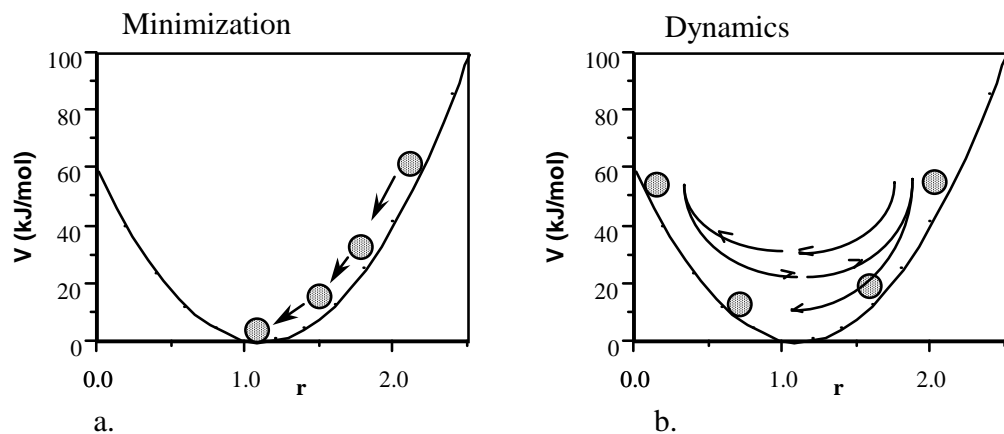


Figure 10.1. The potential energy function for a bond. The initial bond length at 2 angstroms is too long. (a) Molecular mechanics finds the lowest energy state of the molecule. b. Molecular dynamics find the time dependent motion of the molecule. The vibration continues forever.

As chemists we often have too static a picture of molecules. Our mental images of molecular structure are derived from the printed page. Rather, molecules are always in motion. The results of molecular dynamics are very instructive, because dynamics trajectories show us how important motion is in chemical interactions. We should remember that chemical reactions, by their very nature, involve the motion of atoms as bonds are broken and made.

Dynamics Trajectories: Integrating Newton's Laws

Integrating Newton's Laws of motion is actually very straightforward. First, we use the molecular mechanics force field as the potential energy for our molecule. Therefore, the potential energy of our molecule involves bond stretching, angle bending, dihedral torsions, Van der Waals interactions, and electrostatic interactions. We then solve for the motion of each atom in the molecule as a function of time using this potential energy. However, as we begin to learn about dynamics, let's simplify our system to make things less complicated. Let's start with a diatomic molecule. The results of our work on a diatomic molecule will involve everything we need to know about more complicated systems. The molecular mechanics potential energy of a diatomic system has only one term, the potential energy for bond stretching:

$$V = \frac{1}{2} k (r - r_0)^2 \quad 1$$

where r is the current bond length, r_0 is the equilibrium bond length, and k is the force constant for the bond. We can simplify Eq. 1 even further if we let $x = r - r_0$, then

$$V = \frac{1}{2} k x^2 \quad 2$$

The force that acts on the system is the derivative of the potential:

$$F = - \frac{dV}{dx} \quad 3$$

Taking the derivative of Eq. 2 gives:

$$F = - k x \quad 4$$

which is just the familiar Hooke's Law for a mass on a spring. Here the bond is the spring. Newton's Law tells us that $F = m a$, where a is the acceleration. The acceleration is the rate of change of the velocity:

$$F = - k x = m \frac{dv}{dt} \quad 5$$

The position of the system, x , is determined by integrating the equation:

$$\frac{dx}{dt} = v \quad 6$$

Integrating Eq. 5 gives the velocity as a function of time, starting from an initial velocity of v_1 :

$$\int_{v_1}^{v_2} dv = \int_{t_1}^{t_2} \frac{F}{m} dt \quad 7$$

giving
$$v_2 = v_1 + \frac{F}{m} (t_2 - t_1) \quad 8$$

assuming a constant force over the time interval and where m is the reduced mass for the vibrating bond. Integrating Eq. 6 gives the position as a function of time, starting from an initial position of x_1 :

$$\int_{x_1}^{x_2} dx = \int_{t_1}^{t_2} v_2 dt \quad 9$$

giving
$$x_2 = x_1 + v_2 (t_2 - t_1) \quad 10$$

assuming a constant velocity over the time interval. Since the force, velocity, and position are all changing with time, Eqs 8 and 10 are solved repeatedly over short time steps, first updating the velocity and then updating the position. The value of x for each of these successive time intervals is then the trajectory of the system. In dynamics simulations the time step is very short, usually $dt = t_2 - t_1 = 1 \times 10^{-15}$ sec or 1 femtosec.

All that remains is to determine the initial conditions. A common choice for the position is to choose $x_1 = 0$ at $t_1 = 0$. But what about the velocity? The average velocity of a system is related to the temperature; the higher the temperature the larger amplitude the motions. At $x = 0$ all of the energy of an oscillating molecule is in kinetic energy. The kinetic energy is given as

$$KE = \frac{1}{2} m v^2 \quad 11$$

The Equipartition Principle of thermodynamics gives an estimate of the kinetic energy in a bond vibration as $1/2 RT$, where R is the gas constant; $R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$. Setting $KE = 1/2 RT$ and solving for the velocity gives:

$$v = \sqrt{RT / m} \quad 12$$

We therefore set $v_1 = \sqrt{RT / m}$ at $t_1 = 0$.

Eqs 8 and 10 are all that is meant by "integrating" Newton's Laws of motion. However, our example is a "one dimensional" system: there is only one motional variable. In more complicated molecules, equations 8 and 10 would be solved for the x , y , and z motion of each atom. However, no new theory is needed; the problem just becomes more tedious. Computers are very good at solving simple, repetitive problems. In fact the advancement of molecular dynamics is very closely tied to the advancement of computer technology. The availability of fast computers means that molecular dynamics can now become one of the standard tools in computational chemistry.

Periodic Boundary Conditions

Molecular dynamics is commonly used to calculate properties in solution. The molecule to be studied is surrounded by solvent molecules, Figure 10.2.

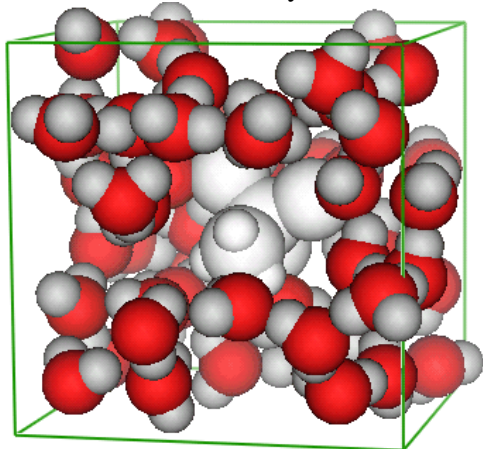


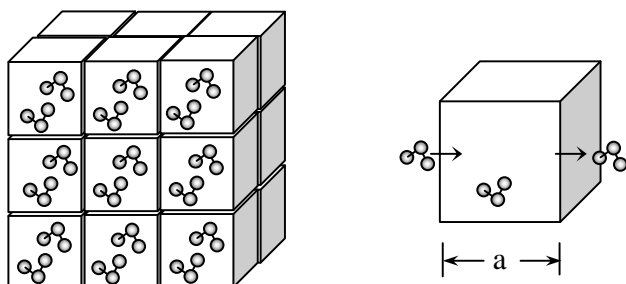
Figure 10.2 Molecular dynamics using explicit water molecules. 1,1,1-trichloroethane is shown in the light shading.

Such explicit solvation treatments are especially useful when hydrogen bonding between the solute and the solvent is expected to play an important role. All the extra solvent atoms, however, greatly increase the time to do the molecular dynamics run. There is a real tradeoff between accuracy and computation time. As a consequence, the number of added water molecules is kept to a practical minimum, usually in the hundreds for small molecule simulations.

With small numbers of solvent molecules, the surface to volume ratio of the system is large, so that surface effects dominate. Surface effects include the imbalance of forces between the bulk of the solvent and the vacuum surrounding the solution droplet. This imbalance produces surface tension. The surface tension is great if you are studying aerosols, however we usually are trying to model homogeneous solutions where surface tension plays no role. Another surface effect is

evaporation. Just like real solutions, water molecules can escape into the surrounding vacuum and in essence evaporate. The best way to avoid surface effects is to use periodic boundary conditions.

Using periodic boundary conditions, we don't have to worry about what happens at the sides of the box of waters. Exact images of the box are stacked next to each other in all directions so that there are no surfaces to the solution, Figure 10.3. Periodic boundary conditions eliminate any surface tension effects.



(a)

(b)

Figure 10.3 (a) Periodic boundary conditions effectively create copies of the system in all directions to avoid surface effects. (b) If a molecule leaves the box the net effect is that a copy of the same molecule enters the box from the opposite side. In this way the molecule never really can leave the box, i.e. evaporate.

The way boundary conditions are done in the computer algorithm is to first check if the coordinates of a molecule lie inside the box. If not, the molecule is translated so that it enters the opposite side of the box. For example for a cubic box with side length a , if the x coordinate of a molecule is found to be outside of the box, $x > a$, then the coordinate is replaced by $x = x - a$.

SHAKE, Rattle and Roll

One of the main difficulties in molecular dynamics calculations is accurately modeling systems that have motions on very different times scales. To accurately model high frequency vibrations like C-H stretches, very short times intervals on the femtosecond time scale are necessary. Therefore, setting $dt = 1 \times 10^{-15}$ s in Eqs. 8 and 10 is required. However, the interesting motions in proteins, such as hinge motions of the backbone, take place on the microsecond time scale. To model a one microsecond motion with the time interval for the dynamics trajectory set at one femtosecond requires $1 \times 10^{-6} / 1 \times 10^{-15} = 1 \times 10^9$ or one billion time steps. Computer are getting faster, but run times of months still would be required for large proteins with large numbers of explicit waters of solvation. To get around this problem, it is possible to ignore the very fast vibrations, such as C-H stretches, by applying constraints to these bonds. In so doing, the time interval for the dynamics can be lengthened several fold. This approach is called the SHAKE method in CHARMM. For example, in a methyl group the C-H bonds can no longer stretch (SHAKE) but the C-H bond angles can still bend (rattle), and the torsion angles can still change (roll).

Applying constraints to high frequency vibrations has been found to be very effective in conformational studies. However, free energy perturbation studies have determined that the SHAKE method does not work when accurate thermodynamic values are required (see Section 7 for more on free energy perturbation studies). Because of this problem, biochemists are some of the most voracious users of supercomputer time. Another approach to solvation called continuum solvation electrostatics is a more approximate but much faster method (see Section 8).

Problem 5.1: Dynamics trajectories

Write a short EXCEL spreadsheet or BASIC program to determine the trajectory for a diatomic molecule. To make the problem more realistic, assume the bond is anharmonic, with potential energy function:

$$V = \frac{1}{2} k x^2 - \frac{1}{2} k \chi x^3 \quad 13$$

Please see the Section 1 for more information on anharmonic potentials for bond stretching. With your dynamics trajectory you will be able to see the time dependence of the vibration. You will also be able to determine the conditions for breaking a bond. For example, you can increase the anharmonicity to determine how anharmonic the bond must be to be broken at room temperature. Conversely, you can keep the anharmonicity constant and increase the temperature until the bond breaks, which is just what synthetic chemists do when they heat a reaction mixture. Differentiation of Eq. 13 gives:

$$F = -k x + \frac{3}{2} k \chi x^2 \quad 14$$

Display the results graphically as two asterisks separated by the distance x. To make the graphics a little easier, you can use the program fragments below. Start with:

```
R=8.314
T=298.2
k=200
m=10
χ=0.05
dt=0.1
x=0
```

With these constants, increasing χ to 0.1075 will cause the molecule to dissociate at 298.2K. Solve Eq. 12 for the initial velocity, v. Because of the way that computer languages handle the "=" sign, you can drop the subscripts on v and x, for example write:

$$v = v + F/m \text{ dt} \quad 15$$

and $x = x + v \text{ dt}. \quad 16$

After you get your spreadsheet or program to work, change the force constant k, the anharmonicity, and the temperature to note the effect.

The Spreadsheet Version: Set up columns using the integrated Newton's equations 15 and 16 to calculate x. Then to do the graphics, set up a column with values = x+10. The 10 is an arbitrary offset to make the graphics look good. In the next column, put in statements similar to

```
=REPT(" ",15-D17/2)&"*"&REPT(" ",D17)&"*"
```

but, instead of "D17" use the cell address of the adjacent column with the x+10 values. The result should look something like:

v	x	F	x+10	plot	
15.74559		0	0	10	* *
12.96835	1.574559	-277.72	11.5746		* *
8.462302	2.871394	-450.61	12.8714		* *
3.100163	3.717624	-536.21	13.7176		* *
-2.52184	4.02764	-562.2	14.0276		* *
-7.93464	3.775457	-541.28	13.7755		* *
-12.5648	2.981993	-463.01	12.982		* *
-15.5692	1.725515	-300.44	11.7255		* *
-15.9021	0.168595	-33.293	10.1686		* *
-12.7557	-1.42162	314.639	8.57838		* *
-6.27013	-2.69719	648.561	7.30281		* *
2.03583	-3.32421	830.596	6.67579		* *
9.737817	-3.12062	770.199	6.87938		* *
14.72284	-2.14684	498.502	7.85316		* *
16.1402	-0.67456	141.737	9.32544		* *

The BASIC program : The program listed below will then take care of the plotting. Just slip in your constants and initial conditions before the loop. Then put the integrated Newton's equations 15 and 16 inside the loop. The IF statement is put in to signal the dissociation of the bond. When the molecule dissociates the program will print out "rrrip." With these constants, increasing χ to 0.1075 will cause the molecule to dissociate at 298.2K.

REM program to solve Hooke's Law dynamics

```

.
.
put constants and initial conditions in here
.
.
FOR i=1 TO 100
.
.
put Eq. 14, 15, and 16 in here
.
.
p=x+6
IF p>50 THEN LOCATE 1,1:PRINT"<<rrrip>>":GOTO qt
LOCATE 1,1
PRINT SPC(15-p);"*";SPC(INT(p+.5)+p);"*"
LOCATE 1,1
PRINT SPC(15-p);" ";SPC(INT(p+.5)+p);" ";
NEXT i
:
qt:
LOCATE 2,1
INPUT"type return to finish";a$

```

Introduction Section 6

Distance Geometry and 2D to 3D Model Conversion

Distance geometry is a general technique for generating 3D-models for chemical substances. Distance geometry is used in consort with energy minimization techniques to find low energy conformations for small molecules and large biomolecules.

Biomolecules: It is very difficult to find the global energy minimum for complex molecules. Proteins, for example, have many tens of thousands of local minima. Determining the lowest of the local minima can be a daunting task. Consider for example the ϕ and ψ angles along the protein backbone. For both angles there are roughly three low energy conformations, two gauche and one trans. Therefore each amino acid has roughly $3 \times 3 = 9$ possible conformations. If a protein has 20 amino acids the total possible backbone conformations is $9^{20} = 1.2 \times 10^{19}$ conformations. However, 20 amino acids is a very small protein. The addition of side chain torsion angles greatly compounds the calculations. This problem is summarized by stating that proteins and nucleic acids have a very rough energy landscape. The valleys are the local minima and we need to visit each valley to find the lowest energy structure. We need help. Experimental information must be used to simplify the search for the tertiary structure of proteins and nucleic acids. Distance geometry is the mathematical technique that allows the construction of three-dimensional structures subject to the constraints provided by experimental information.¹⁻³ NMR is a particularly rich source of experimental constraints. The Protein Data Bank, PDB, has 22,000 protein structures, 15% of which were determined by NMR.^{4,5}

The NMR solution structure for a model of the nicotinic acetylcholine receptor complexed with a potent natural antagonist is shown in Figure 1a. The larger structure is the antagonist, α -bungarotoxin, and the smaller is a portion of the antagonist binding site of the α -subunit of the nicotinic receptor showing amino acids 185 – 190. The distance geometry calculation used 325 distance constraints and 64 dihedral angle constraints.⁶ Even so, the conformation of the peptides is still not completely specified. As a result, distance geometry was repeated producing a set of possible structures, Figure 1b. The NMR based structures in the Protein Data Bank are routinely sets of closely related structures that all satisfy the available experimental constraints. The ability of distance geometry to generate multiple structures is an important advantage for conformational searches in large and small molecules.

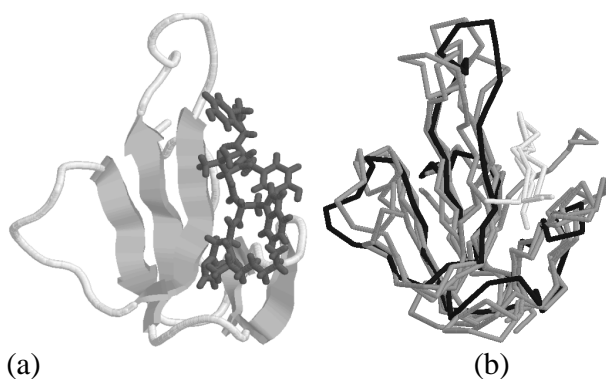


Figure 1. (a). α -bungarotoxin (ribbon), and the antagonist binding site model of the α -subunit of the nicotinic acetylcholine receptor (stick); PDB entry 1ABT. (b) Four alternate structures for the complex derived by distance geometry, superimposed (backbone traces, with alternate solutions for bungarotoxin in different shades of gray and black and the protein receptor models in white).

2D to 3D Model conversion: Another closely related problem is the construction of the initial coordinates for molecular mechanics or molecular orbital calculations. The input for such

programs typically starts with the output of 2D “sketchers” or just connection tables. Molecular mechanics is a wonderful technique for predicting accurate 3D structures, however molecular mechanics programs routinely fail if the input structure is grossly distorted. Therefore, to get an accurate molecular mechanics calculation, you need to start with a structure that is not too far from a reasonable conformation. Molecular orbital programs also require that the input have a structure that is somewhat close to the geometry that you are seeking. Otherwise, the wrong atoms may end up being bonded to each other in the final structure. Therefore, it is very common to use molecular mechanics to produce the input file for molecular orbital calculations. When you use Spartan, the default is to build the input structure using the Merck Molecular Force Field when you minimize the structure in the Builder.⁷ Most molecular orbital programs also use molecular mechanics to produce an initial guess for the Hessian. So even for molecular orbital calculations we have the same problem; we need a reasonable input structure even if the user isn’t very adept at drawing the desired molecule on the screen.

The list of atom connections for a molecule is called the connection table. All molecular mechanics programs require a connection table for the input for each molecule, in addition to approximate atom positions. 2D-sketchers in their simplest form produce the connection table and 2D coordinates as drawn by the user. The third, z dimension needs to be added before a molecular mechanics calculation can proceed. The two common ways of building the approximate 3D-structure are functional group templates and distance geometry.

Functional group templates are simply the bond distances and angles specific to a given functional group taken from standard tables. For example, the bond angles around sp^2 hybridized carbons in alkenes and ketones are about 120° . The typical C=O bond length is 1.22Å. In other words, the ideal bond lengths and angles from standard force fields are used to guess the 3D-structure. The torsion angles present a problem since several torsion angles are possible, e.g. two gauche and trans angles for sp^3 systems. Most builders start with all trans structures unless the trans structure produces a close contact, at which point the gauche conformations are used. From the user’s perspective there are two types of sketchers. The sketchers or builders in Spartan and MOE, for example, require the use of pre-built fragments to assemble the molecule.⁸ These pre-built fragments already have the appropriate bond lengths and angles for the chosen functional group. As the molecule is built, the result is automatically constructed in 3D. The second approach for sketchers is to draw the molecule free-hand in 2D. Sketchers in chemical drawing programs and the Java Molecular Editor (JME)⁹ are examples of this style. Free-hand sketchers present a real challenge since users can input structures that are wildly distorted. The coordinates presented by the user must be carefully adjusted to approximate real molecules. Rings systems present a particular problem with free-hand sketchers and require somewhat complex algorithms to set up using the template approach. Some sketchers maintain a database of the torsion angles for a wide variety of ring systems. Other sketchers use very approximate force fields and simplified minimization algorithms to guess the torsion angles around rings. Distance geometry is often an easier approach for ring systems. The Concord¹⁰ and Corina programs are template based builders and provide amazingly accurate structures, even when compared to X-ray crystal structures.¹¹⁻¹³

2D-sketchers work well for hands-on operation. However, completely automated procedures are also necessary. The rapid acceleration of the drug discovery process through combinatorial chemistry and high throughput screening has added an additional dimension to the 2D-3D conversion problem. Drug companies currently maintain storerooms filled with hundreds of thousands of compounds and develop combinatorial libraries (groups of compounds) of hundreds of thousands more. It is often necessary to store and retrieve information on all these compounds from exceedingly large computer databases. The efficient computer generation of 3D-models for

all these compounds is a daunting task. Often the structural information for these compounds is stored only as a connection table, so even 2D-information is not available. The connection table just specifies which atom is connected to which and the corresponding bond order. For example the connection table for ethylene, $\text{H}_2\text{C}=\text{CH}_2$, in the common format used by “.mol” files is given in Figure 2.

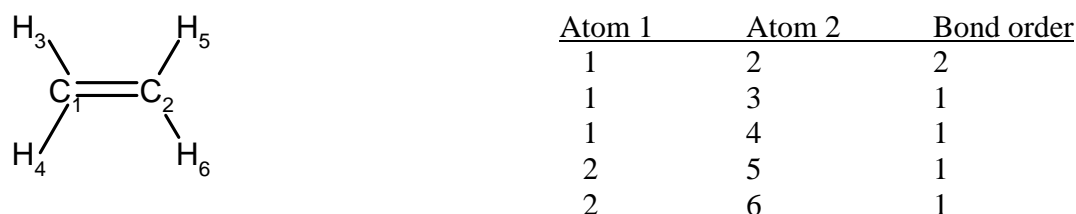


Figure 2. Connection Table for Ethylene. The atom numbering is arbitrary.

The lack of any coordinates makes conversion of connection tables to molecular mechanics input files even harder. Corina, Concord, and distance geometry are designed to work from connection tables. One popular form of connection table is the “Smiles” string. Smiles strings are very efficient for storing large amounts of structural information.^{14,15} The Smiles string for ethylene is just C=C. Some example Smiles strings are given in table I. Single bonds are assumed unless otherwise indicated. Hydrogens are omitted. Branching is shown by parentheses, i.e. *tert*-butanol is CC(C)(C)O. Ring closing connections are shown with numbers. Aromatic atoms are given in lower case. JME, drawing programs, and MOE can all be used to generate Smiles strings from sketches, so you don’t really need to know the rules for generating Smiles.

Table I. Smiles strings for some molecules.

Butane	<chem>CCCC</chem>	Ethanol	<chem>CCO</chem>	Acetaldehyde	<chem>CC=O</chem>
2-methylpropane	<chem>CC(C)C</chem>	Acetone	<chem>C(=O)C</chem>	Acetic acid	<chem>CC(=O)O</chem>
Cyclohexane	<chem>C1CCCCC1</chem>	benzene	<chem>c1ccccc1</chem>	Toluene	<chem>c1ccccc1C</chem>
Nitrobenzene	<chem>c1ccccc1[N+](=O)[O-]</chem>	Phenylalanine	<chem>NC(C(O)=O)Cc1ccccc1</chem>		

In summary, efficient calculation methods are needed for the construction of the 3D-coordinates of complicated molecules. Template based methods are very useful especially for small molecules. In many cases, however, some experimental information is known for a few distances or dihedral angles and the final structure must be built to include these structural parameters. Distance geometry can be applied to small and very large molecules and can easily incorporate experimental structural information in the form of distance constraints.

Distance Constraints

Distance constraints are ranges of allowable distances between pairs of atoms. An example is that you can specify that two atoms are to be within a normal hydrogen bond distance of each other, 1.8-2.1 Å. NMR spectra are very useful for experimentally determining distance constraints using nuclear Overhauser effects, nOe’s. nOe based two-dimensional NMR spectra are called NOESY

spectra. Distance constraints from NOESY are particularly useful for studies of the tertiary structure of proteins. The combination of NOESY, distance geometry, and X-ray diffraction has spawned a new field in the molecular life sciences called Structural Biology. Using NOESY spectra it is possible to determine that pairs of atoms are within the range of about 3-4 Å of each other.³ Just a few nOe based distance constraints can greatly simplify the search for the low energy structures of biomolecules.

Distance constraints and distance geometry can also be very useful for small molecule work. Hydrogen bond constraints and through-space nOe distances can be also useful for determining the conformation of small molecules as well as proteins. Distance constraints can also be values that you make up to help guide the conformation of the final molecule. For example, you may want a conformation that puts two parts of a long molecule close to each other rather than the default all-trans structures that most 2D-3D conversion programs generate.

Metric Matrix Distance Geometry

The input data for distance geometry are the distances between all the atoms in the molecule. The goal of distance geometry is to find the atom positions, x_i, y_i, z_i for each atom i . The metric matrix is used to calculate 3D atom coordinates using a process called embedding.¹⁻³ A triatomic molecule, Figure 3, will be used as an example as we discuss the steps in embedding. The atom coordinates are

For atom 1: x_1, y_1, z_1 For atom 2: x_2, y_2, z_2 For atom 3: x_3, y_3, z_3 (1)

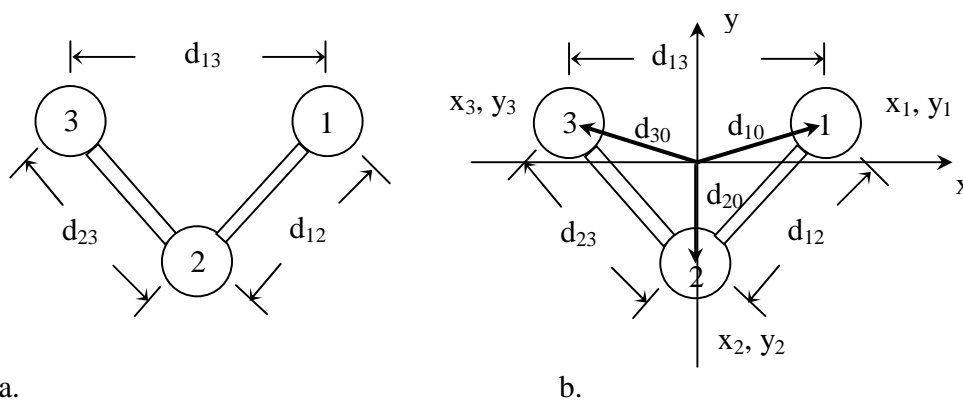


Figure 3. A triatomic molecule with (a) the input atom-atom distances and (b) the coordinate system for building the metric matrix from distances. The molecule is in the x-y plane, so $z = 0$ for all atoms.

The metric matrix is constructed from the dot products of the coordinate vectors. For example the dot product for atoms 1 and 2 is $(x_1x_2+y_1y_2+z_1z_2)$. The elements of metric matrix for atom pair i,j is then in general given by:

$$g_{ij} = x_i x_j + y_i y_j + z_i z_j \quad (2)$$

However, we don't know the atom coordinates at the beginning of the calculation; these coordinates are the final goal. Surprisingly, the metric matrix can also be constructed from atom

distances. The coordinate system for the important distances is shown in Figure 3b. The origin is the geometric center or centroid of the molecule. The centroid is constructed so that

$$\sum x_i = 0 \quad \sum y_i = 0 \quad \sum z_i = 0. \quad (3)$$

The elements of the metric matrix can then be calculated from (see appendix A).

$$g_{ij} = \frac{1}{2} (d_{i0}^2 + d_{j0}^2 - d_{ij}^2) \quad (4)$$

However, we still have a problem. The distances to the origin, d_{i0} and d_{j0} , can't be calculated until we know the atom coordinates. However, a little bit of geometric reasoning allows the calculation of these distances (see appendix B). For N atoms:

$$d_{i0}^2 = \frac{1}{N} \sum_{j \neq i}^N d_{ij}^2 - \frac{1}{N^2} \sum_{j=1}^N \sum_{k>j}^N d_{jk}^2 \quad (5)$$

For our triatomic example:

$$d_{10}^2 = \frac{1}{3} (d_{12}^2 + d_{13}^2) - \frac{1}{3^2} (d_{12}^2 + d_{13}^2 + d_{23}^2) \quad (6)$$

A simple numerical example may help at this point. Let the bond distances, d_{12} and d_{23} , be 5 and the non-bonded distance, d_{13} , be 6. Then

$$d_{10}^2 = \frac{1}{3} (5^2 + 6^2) - \frac{1}{3^2} (5^2 + 6^2 + 5^2) = 10.777 \quad \text{or} \quad d_{10} = 3.283 \quad (7)$$

$$d_{20}^2 = \frac{1}{3} (5^2 + 5^2) - \frac{1}{3^2} (5^2 + 6^2 + 5^2) = 7.111 \quad \text{or} \quad d_{20} = 2.667 \quad (8)$$

Now the metric matrix entries can be calculated. For example g_{11} is easy since d_{11} in the second term of Eq 4 is 0. Substituting Eq 7 and 8 into Eq 4 gives:

$$g_{11} = \frac{1}{2} (d_{10}^2 + d_{10}^2) = 10.778 \quad g_{12} = \frac{1}{2} (d_{10}^2 + d_{20}^2 - d_{12}^2) = -3.556 \quad (9)$$

Similar calculations give the final metric matrix:

$$G = \begin{pmatrix} 10.778 & -3.556 & -7.222 \\ -3.556 & 7.111 & -3.556 \\ -7.222 & -3.556 & 10.778 \end{pmatrix} \quad (10)$$

Given the metric matrix, as calculated from the atom-atom distances, we now need a way to work back to the original coordinates. The atom coordinates can be calculated from the eigenvalues and eigenvectors of the metric matrix. We find the eigenvalues λ_q , and the eigenvectors w_q by solving the equation:

$$G w_q = \lambda_q w_q \quad (11)$$

Where q corresponds to the x, y, or z axes. Eigen means "the same" in German, and Eq 11 shows that starting with w_q on the left gives back w_q on the right, multiplied by a constant, λ_q . In other

words, the same thing, w_i , appears on both sides of the equation. The eigenvalues are a measure of the size of the molecule in the x, y, and z directions (principle moments of inertia, but with unit mass for each atom). The atomic coordinates can then be calculated for each atom i:

$$x_i = \lambda_1^{1/2} w_{i1} \quad y_i = \lambda_2^{1/2} w_{i2} \quad z_i = \lambda_3^{1/2} w_{i3} \quad (12)$$

You can calculate the eigenvalues and eigenvectors using an on-line Web applet.¹⁶ For our triatomic example, the eigenvalues and eigenvectors for the x and y directions are:

$$\lambda_1 = 18 \quad w_1 = \begin{pmatrix} 0.707 \\ 0 \\ -0.707 \end{pmatrix} \quad \lambda_2 = 10.67 \quad w_2 = \begin{pmatrix} 0.408 \\ -0.816 \\ 0.408 \end{pmatrix} \quad (13)$$

Giving the final coordinates:

$$\begin{aligned} x_1 &= 18^{1/2} \cdot 0.707 = 3 & y_1 &= 10.67^{1/2} \cdot 0.408 = 1.333 \\ x_2 &= 18^{1/2} \cdot 0 = 0 & y_2 &= 10.67^{1/2} \cdot -0.816 = -2.667 \\ x_3 &= 18^{1/2} \cdot -0.707 = -3 & y_3 &= 10.67^{1/2} \cdot 0.408 = 1.333 \end{aligned} \quad (14)$$

These final coordinates are shown in Figure 4. Notice also that as Eq 3 requires, the sum of the x coordinates is zero and the sum of the y coordinates is also zero.

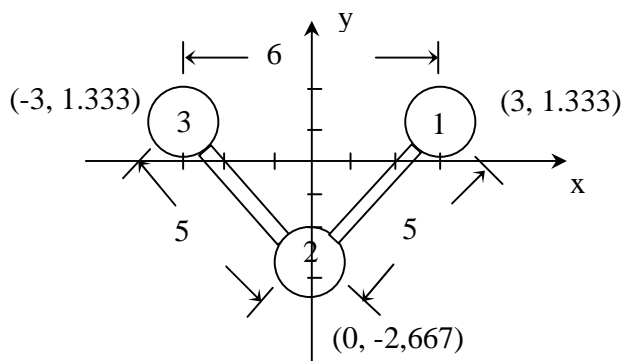


Figure 4. Final coordinates after embedding.

The remarkable thing about distance geometry is that it works just as well for thousands of atoms as it does for triatomic molecules. However, the calculation of the eigenvalues and vectors for large systems like proteins requires considerable computer time.

General Procedure¹⁻³

The input for distance geometry programs is just the connection table. The complete embedding process requires four steps.

Step 1: The first step is to specify the distance range between every 1-2, 1-3, and 1-4 atom pair using standard bond lengths and angles from a table. For 1-4 distances the minimum distance is set for a 1-2-3-4 dihedral angle of 0° and the maximum distance for 180° . For non-bonded atoms the minimum is set to the sum of the Van der Waals radii. Any distance constraints that you input are also included in the list of distances. All the distance ranges are then checked for consistency using the triangle inequality, Figure 5. For example, the maximum distance between a 1-3 atom pair is the sum of the 1-2 and 2-3 bond distances, $d_{13} \leq d_{12} + d_{23}$:

If the atoms are C-C-C, the standard bond length is 1.53Å giving a maximum 1-3 distance of $2 \times 1.53\text{Å}$.

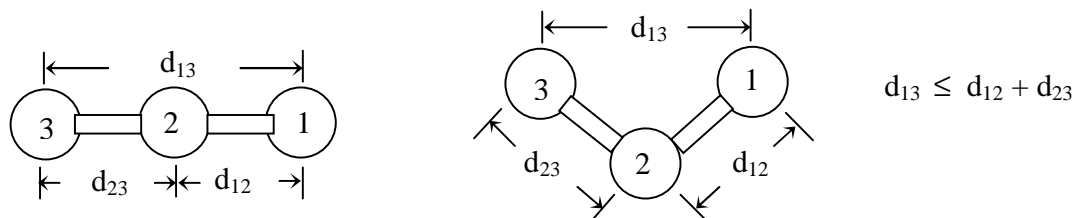


Figure 5. Checking distance maximums for consistency.

If an initially chosen maximum distance is larger than allowed by the triangle inequality, the value is lowered. This “smoothing” process helps to tighten the distance constraints. The minimum distances are also smoothed in the same way. The result is a set of consistent upper and lower bounds for all the pair-wise distances between the atoms.

Step 2: Next a distance between each atom pair is chosen at random between the upper and lower bounds set in step 1. This step is an important feature of distance geometry. The assignment of a random distance means that you will obtain a different result each time you run the algorithm. This element of randomness is one of the advantages (and disadvantages) of the distance geometry approach that can be exploited for conformational searches.

Step 3: The metric matrix is calculated from the chosen random distances. The eigenvalues and vectors are then calculated and used to find the final coordinates using Eq 12.

Step 4: The coordinates generated by distance geometry are very rough. The atom positions must be optimized using molecular mechanics with a simplified force field. This adjustment process is done in two steps. First any chiral constraints are enforced. Working with chiral constraints first is necessary because molecular mechanics minimization can switch chirality inadvertently, and also enforcing chirality first makes subsequent minimization faster. After chiral constraints are satisfied, the coordinates are adjusted with a force field that greatly penalizes atom positions that violate the distance bounds that were established in Step 1.

The force field first checks to see if the distance between atom i and atom j , d_{ij} , is outside of the distance bounds; if outside an error term is calculated:

$$e = \frac{(d_{ij}^2 - B_{ij}^2)^2}{B_{ij}^2} \quad (15)$$

where B_{ij} is the violated upper or lower bound. This error term is summed over all atom pairs that violate the distance bounds. Violations of the chiral constraints are also added to the distance errors to complete the force field. This force field is minimized using standard conjugate gradient techniques. The force field does not include bond stretch, angle bending, out-of-plane, and torsional constraints directly. Therefore, the optimized structure is only as good as the original distance bounds. In other words, the final structure is still quite crude and must be further minimized using a traditional force field or molecular orbital calculations.

For example, Figure 6a shows the results for toluene. The ring atoms are not flat as expected for sp^2 hybridized atoms. The conformation around sp^2 atoms can be improved by specifying the atoms as chiral atoms, even though they are not, alternating (+) and (-) around the ring. The distance geometry program will enforce a flat geometry, Figure 6b.

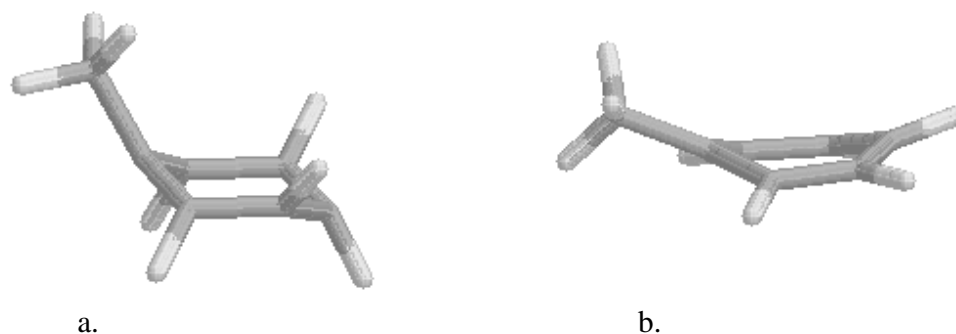


Figure 6. (a) Distance geometry results for toluene. (b) Distance geometry with sp^2 C atoms specified as chiral.

Even so, the results are still quite distorted from the expected planar geometry. Submitting the distance geometry results to a conventional molecular mechanics or molecular orbital calculation quickly clears up any remaining problems. The distance geometry results for complicated ring systems can often be quite good, however.

Extensions to Distance Geometry

Many extensions of the basic distance geometry procedure have been implemented that provide final structures with less strain.^{17,18} Distance geometry is also used in conjunction with molecular dynamics for energy minimization.^{19,20} The technique is often used for conformation searches,^{2,19,20} in aspects of drug discovery,^{21,23} and protein folding studies.^{24,25}

Appendix A:

Given atom 1 with coordinates x_1, y_1, z_1 and atom 2 with coordinates x_2, y_2, z_2 the distance between the two atoms is:

$$d_{12}^2 = (x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2 = x_1^2 + 2x_1x_2 + x_2^2 + y_1^2 + 2y_1y_2 + y_2^2 + z_1^2 + 2z_1z_2 + z_2^2 \quad (17)$$

The dot product between the two atoms coordinates is $x_1x_2 + y_1y_2 + z_1z_2$. Rearranging Eq 17 to isolate the dot product gives:

$$d_{12}^2 = (x_1^2 + y_1^2 + z_1^2) + (x_2^2 + y_2^2 + z_2^2) + 2(x_1x_2 + y_1y_2 + z_1z_2) \quad (18)$$

The first term in parenthesis is the squared distance of atom 1 from the origin, d_{10}^2 . The second term is the distance of atom 2 from the origin, d_{20}^2 . Rearranging Eq 18 gives:

$$(x_1x_2 + y_1y_2 + z_1z_2) = \frac{1}{2} (d_{10}^2 + d_{20}^2 - d_{12}^2) \quad (19)$$

(Many authors on distance geometry describe Eq 19 as the Law of Cosines, which is a standard geometrical construction. Given two vectors \vec{v} and \vec{w} , the dot product is:

$$\vec{v} \cdot \vec{w} = |\vec{v}| |\vec{w}| \cos \theta = d_{10} d_{20} \cos \theta$$

which explains the connection with the cosine of the angle and the name “Law of Cosines.”)

Appendix B:

The fact that the distance of an atom from the origin can be calculated completely from the atom-atom distances using Eq 5 is surprising. A derivation for three atoms, Eq. 6, is given in this appendix. A more general derivation is given by Havel, et. al.²⁶ However, the general formula is easily obtained from the three atom result. The distance of atom 1 from the origin is

$$d_{10}^2 = x_1^2 + y_1^2 + z_1^2 \quad (20)$$

The origin is the centroid of the atoms, Eq. 3:

$$x_1 + x_2 + x_3 = 0 \quad y_1 + y_2 + y_3 = 0 \quad z_1 + z_2 + z_3 = 0 \quad (21)$$

Solving for the coordinates of atom 1 gives:

$$x_1 = -x_2 - x_3 \quad y_1 = -y_2 - y_3 \quad z_1 = -z_2 - z_3 \quad (22)$$

Substituting Eq 22 into Eq 20 for one factor of x_1 , y_1 , and z_1 gives:

$$d_{10}^2 = -x_1x_2 - x_1x_3 - y_1y_2 - y_1y_3 - z_1z_2 - z_1z_3 \quad (23)$$

Rearranging gives two dot products:

$$d_{10}^2 = - (x_1x_2 + y_1y_2 + z_1z_2) - (x_1x_3 + y_1y_3 + z_1z_3) \quad (24)$$

Using Eq 19 for the dot products gives:

$$d_{10}^2 = -\frac{1}{2} [(d_{10}^2 + d_{20}^2 - d_{12}^2) + (d_{10}^2 + d_{30}^2 - d_{13}^2)] \quad (25)$$

Rearranging gives:

$$4 d_{10}^2 = (d_{12}^2 - d_{20}^2) + (d_{13}^2 - d_{30}^2) \quad (26)$$

Subtracting a term in d_{10}^2 from both sides gives:

$$3 d_{10}^2 = d_{12}^2 + d_{13}^2 - (d_{10}^2 + d_{20}^2 + d_{30}^2) \quad (27)$$

The corresponding results for the other two atoms are

$$3 d_{20}^2 = d_{12}^2 + d_{23}^2 - (d_{10}^2 + d_{20}^2 + d_{30}^2) \quad (28)$$

$$3 d_{30}^2 = d_{13}^2 + d_{23}^2 - (d_{10}^2 + d_{20}^2 + d_{30}^2) \quad (29)$$

Adding Eqs 27-29 gives:

$$3(d_{10}^2 + d_{20}^2 + d_{30}^2) = 2(d_{12}^2 + d_{13}^2 + d_{23}^2) - 3(d_{10}^2 + d_{20}^2 + d_{30}^2) \quad (30)$$

Solving for the sum squared distances to the origin gives a result entirely in terms of atom-atom distances:

$$(d_{10}^2 + d_{20}^2 + d_{30}^2) = \frac{1}{3} (d_{12}^2 + d_{13}^2 + d_{23}^2) \quad (31)$$

Finally substituting Eq 31 for the last term in Eq 27 gives:

$$3 d_{10}^2 = d_{12}^2 + d_{13}^2 - \frac{1}{3} (d_{12}^2 + d_{13}^2 + d_{23}^2) \quad (32)$$

Finally division by 3 gives Eq. 6.

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Introduction Section 7 Free Energy Perturbation Theory, FEP

The greatest value in molecular dynamics is the ability to model the internal motions of a molecule. Internal energy, enthalpy, entropy, and Gibbs Free Energy all include contributions from the motion of a molecule. Therefore, molecular dynamics provides a way to estimate these important thermodynamic parameters. The current best method for practical calculations of Gibbs Free Energies is free energy perturbation theory, based on molecular dynamics. Free energy perturbation (FEP) theory is now in use in calculating ΔG for a wide variety of processes. For example, the Gibbs Free Energy of solution of hydrophobic molecules¹, of binding of crown ethers to polar organics², and the binding of NADP and NADPH to dihydrofolate reductase³ have been studied. In fact, the combined insights of x-ray crystal structure determination, NMR solution structure determination, and FEP studies have led to the consensus that the motions of proteins and nucleic acids play a major role in binding interactions. W. L. Jorgensen, in his article "Rusting of the Lock and Key Model for Protein-Ligand Binding," states simply that:

*"These examples confirm the reasonable expectation that flexible molecules distort to form optimal interactions with binding partners."*⁴

A dynamic view of binding interactions is necessary to understand biochemical phenomena.

Molecular mechanics calculates the steric energy of a molecule at absolute zero in temperature. What is the connection of the molecular mechanics steric energy to the thermodynamic internal energy and Gibbs Free energy of a substance? The hypothesis that makes the most sense is that the internal energy, ΔU , is the time average of the total energy of the molecule. The total energy of the molecule is the kinetic plus potential energy:

$$E = \text{kinetic energy} + \text{potential energy} \quad 1$$

The potential energy is just the molecular mechanics steric energy. Molecular dynamics provides us with the time dependent energy of the molecule; all we need do to get ΔU is average the total energy during the trajectory calculation.

Now we turn to the relationship of the steric energy to the Gibbs Free Energy. In statistical mechanics, we find that the probability of a given state of a system occurring is proportional to the Boltzmann weighting factor:

$$\text{probability of occurrence} \propto e^{-E/RT} \quad 2$$

where E is the total energy of the system, Eq. 1. In other words, states with low total energy are more likely to occur than states with high energy. A state of the system is determined by the conformation and motion of the molecule. The conformation determines the steric energy and the motions determine the kinetic energy.

In perturbation theory, we look at the effect of a small change in the structure of a molecule on its energy. To do the perturbation, the total energy is divided into two parts

$$E = E_0 + E_1 \quad 3$$

where E_0 is a reference structure and E_1 is a small perturbation from the reference structure. The perturbation is a small change that we place upon the system, say a small change in bond angle or a small change in the charge on an atom. The corresponding change in free energy of the system caused by the perturbation is given as^{5,6}

$$G - G_0 = -RT \ln \langle e^{-E_1/RT} \rangle_0 \quad 4$$

where $\langle \rangle_0$ denotes the time average over the motion of the reference structure from a molecular dynamics run. The $e^{-E_1/RT}$ term is the probability of occurrence for the small change in energy caused by the perturbation, from Eq. 2. The free energy then depends on the time average of the probability of occurrence of the perturbed structure. In other words, if the perturbation produces a small change in energy, that change will contribute to the Gibbs Free energy.

In our case however, we wish to find the change in free energy for large changes in a molecule. These changes, or mutations, include changing the conformations of bonds, or attaching a hydrogen ion, or changing a hydrogen to a methyl group or even a phenyl group. For example, we might like to mutate glycine into alanine⁷ for a study of site-specific mutagenesis of an enzyme. How do we apply Eq. 4 to such large changes? Assume that we wish to mutate molecule B into a different molecule A. First we define a total energy for mutating molecule B to A as

$$E_\lambda = \lambda E_A + (1 - \lambda) E_B \quad 5$$

where E_A is the total energy for A and E_B is that for B, and λ is the coupling parameter. When $\lambda = 1$ the energy corresponds to molecule A, and when $\lambda = 0$ the energy corresponds to molecule B. When λ is at intermediate values, the system is a hypothetical superposition of A and B. It might seem quite strange to have such a combination of two molecules, in fact it is very unphysical; however, the theory is well-behaved and very useful none-the-less.

For the complete mutation to take place we vary λ from 0 to 1 over the course of the dynamics run. We divide this full range into short time slices, which are short enough that we can treat the change in each time slice as a perturbation. Then we apply Eq. 4 to each time slice and then add up the result for all the time slices. Let the λ value at each time slice be numbered $\lambda_1, \lambda_2, \lambda_3$, etc. Then the difference in Eq. 4 is $\Delta G(\lambda_i)$ for each time slice, $i=1, 2, 3, \dots, n$, for n total time slices. Then the total change in ΔG for the perturbation is

$$\Delta G_{B \rightarrow A} = \sum_{i=1}^n \Delta G(\lambda_i) \quad 6$$

Since each time slice in the mutation is a small change, we can simplify Eqs. 4 and 6. We do the mutation in small steps; therefore $E_1 \ll RT$ for each time slice in the perturbation. Remembering that $e^{-x} \approx 1 - x$, we can expand the exponential in the Boltzmann distribution:

$$e^{-E_1/RT} \approx 1 - E_1/RT \quad 7$$

Then Eq. 4 simplifies to:

$$G - G_0 = -RT \ln \langle 1 - E_1/RT \rangle_0 = -RT \ln (1 - \langle E_1 \rangle_0 / RT) \quad 8$$

Next remember that $\ln(1-x) \approx -x$, when x is small. This approximation on Eq. 8 gives:

$$G - G_0 = -RT (- \langle E_1 \rangle_0 / RT) = \langle E_1 \rangle_0 \quad 9$$

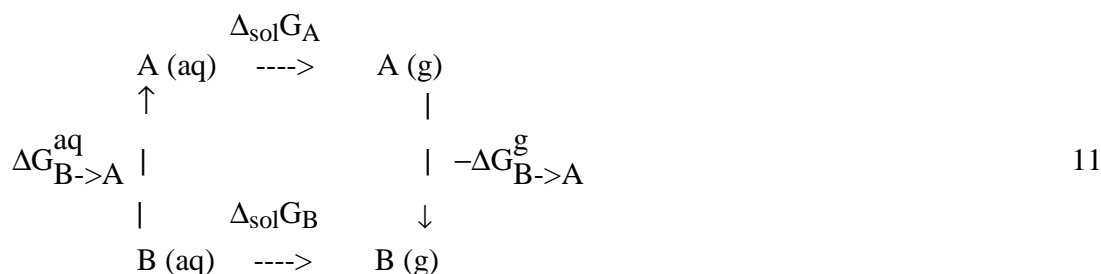
In words, this simple result means that the change in Gibbs Free Energy for a perturbation is just the time average of the total perturbation energy. Now applying Eq. 9 to each time slice in the total mutations simplifies Eq. 6 to:

$$\Delta G_{B \rightarrow A} = \sum_{i=1}^n \langle E(\lambda_i) \rangle_0 \quad 10$$

where $E(\lambda_i)$ is the total energy for the time slice in the mutation from Eq. 5. This very simple result makes FEP studies easy to do. The time average in Eq. 9 is automatically calculated during trajectory calculations. All we need do is to change λ in small steps during the trajectory. This approach to FEP simulations is called the slow-growth method.

Our initial efforts to use molecular dynamics are frustrated, however, because molecular dynamics is a classical theory, which gives too high a weight to high frequency vibrations. We must be careful to account for the difference between classical theories and the true distribution of vibrational energies in molecules. We can do this by always calculating the difference between our system and a reference system. In calculating differences, errors tend to cancel, and in so doing, classical molecular dynamics is a surprisingly useful tool for understanding complex systems. The success of classical dynamics is due in part to the observation that the major contributions to ΔG for solvation and binding interactions are low frequency vibrations, especially torsions, which are handled adequately by classical theory. In addition, these low frequency vibrations tend to change the most in systems of interest; high frequency vibrations change little, therefore the high frequency vibrations cancel out in comparisons.

For example, to study the Gibbs Free Energy of solvation of molecule B, $\Delta_{\text{sol}}G_B$, we will choose molecule A as the reference structure. The mutation will then be from B to A. To determine the difference in Free Energy of solvation between B and A, we will construct the following thermodynamic cycle:



where $\Delta G_{B \rightarrow A}^{\text{aq}}$ is the Free Energy of perturbation of B to A in the solution phase, and $\Delta G_{B \rightarrow A}^{\text{g}}$ is the Free Energy of perturbation in the gas phase. Adding contributions around the cycle gives:

$$\Delta_{\text{sol}}G_B = \Delta G_{B \rightarrow A}^{\text{aq}} + \Delta_{\text{sol}}G_A - \Delta G_{B \rightarrow A}^{\text{g}} \quad 12$$

We then determine the difference

$$\Delta_{\text{sol}}G_B - \Delta_{\text{sol}}G_A = \Delta G_{B \rightarrow A}^{\text{aq}} - \Delta G_{B \rightarrow A}^{\text{g}} \quad 13$$

These kinds of differences are often called $\Delta\Delta G$ values:

$$\Delta\Delta G = \Delta_{\text{sol}}G_B - \Delta_{\text{sol}}G_A = \Delta G_{B \rightarrow A}^{\text{aq}} - \Delta G_{B \rightarrow A}^{\text{g}} \quad 14$$

We choose a reference system, A, where $\Delta_{\text{sol}}G_{\text{A}}$ is known from experiment. We can then predict our final result:

$$\Delta_{\text{sol}}G_{\text{B}} = \Delta_{\text{sol}}G_{\text{A}(\text{experimental})} + \Delta\Delta G \quad 15$$

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Section 8: Continuum Solvation Electrostatics

Molecular binding events control most of the processes in living cells. Binding interactions include enzyme substrate binding, allosteric control of enzyme activity, protein nucleic acid binding, and protein-protein binding. Protein-protein binding is important because most of the enzymes in the cell function as a part of a protein complex and are not active as individual molecules. Molecular binding is very specific. Biomolecules have evolved over time to interact only with specific substrates or other biomolecules. This specificity is achieved through careful control of molecular recognition. Molecular recognition is the result of specific intermolecular forces. These forces include, in order of strength, hydrogen-bonding, charge-charge interactions (salt bridges), dipole-dipole interactions, π - π interactions, and hydrophobic interactions. The strength of all these forces also depend critically on interactions with the solvent. For example, hydrophobic interactions are completely solvent driven. It is the central role of the solvent that this section will explore.

The effect of solvation on molecular recognition can be striking. For example, the hydrogen bond that forms in proteins, the peptide hydrogen-bond, Figure 1a, is quite strong in the gas phase. The gas phase interaction energy is roughly 20 kJ/mol. However, in aqueous solution the peptide hydrogen-bond strength is much weaker, less than ~ 5 kJ/mol¹.

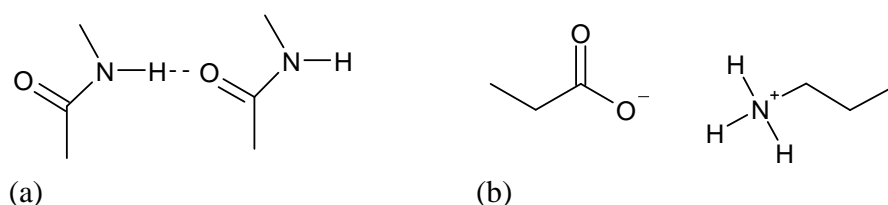


Figure 1. (a) Peptide hydrogen bond, (b) Salt bridge between glutamate and lysine.

Salt bridges in proteins are another example of strong solvation effects. Salt bridges form in proteins from the electrostatic interaction of acidic and basic amino acid side chains. The salt bridge between glutamate and lysine is a common structural element, Figure 1b. Salt bridges in proteins can be either stabilizing or destabilizing depending on the solvation Gibbs Free energy of the ions and the environment of the salt bridge in the folded protein. In short, it is impossible to study molecular recognition without a detailed knowledge of solvation.

It is frustrating that so little is really known about these fundamental forces that are so important in molecular recognition and protein folding. Changing our calculations from the gas phase to the aqueous environment, where the dielectric constant is ~ 80 , should have a large effect on molecular interactions. The difficulty is how to treat the solvent waters. In several exercises in this Tutorial we do molecular dynamics calculations using discrete water molecules. However, these calculations can be very time consuming. Continuum solvation models have been developed by Clark Still's group at Columbia and many others that are designed to improve molecular mechanics calculations in solvent. Many molecular mechanics and molecular orbital programs include continuum solvation calculations.

In continuum solvation models, the solvent is modeled as a continuous, uniform environment with a relative dielectric constant, ϵ_r . Since there are no discrete water molecules, very specific interactions such as extensive hydrogen bonding to the primary solvation sphere or very directional dipole-dipole interactions cannot be studied. However, the continuous solvent model does allow the study of the stabilization and destabilization of polar species in a polar solvent

environment. Continuum solvation treatments are also very popular with organic chemists for studies of solution conformations of molecules and the stabilization of polar transition states.

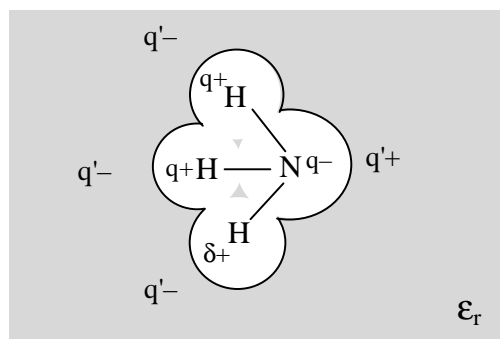


Figure 1: Continuum solvation model

Continuum solvation energetics are roughly based on the following model. The electrostatic distribution in the molecule is modeled by point charges that are placed at each nucleus. The molecule is then placed in a cavity in the uniform solvent. The size of the cavity is determined roughly by the Van der Waals surface of the molecule. The dielectric constant inside this cavity is taken to be that of a vacuum. The solvent is assumed to have a uniform constant relative dielectric constant of ϵ_r , which for water is 78.54. The presence of charges in the molecule polarizes the solvent, Figure 1. These induced charges, or image charges, effectively “mirror” the charges on the molecule. Remember that the electrostatic energy of two charges, q_i and q_j , separated by a distance r in a medium with constant relative dielectric constant ϵ_r is given by the Coulomb energy, Figure 1:

$$\epsilon_{\text{Coulomb}} = \frac{q_i q_j}{4\pi\epsilon_r \epsilon_0 r} \quad (1)$$

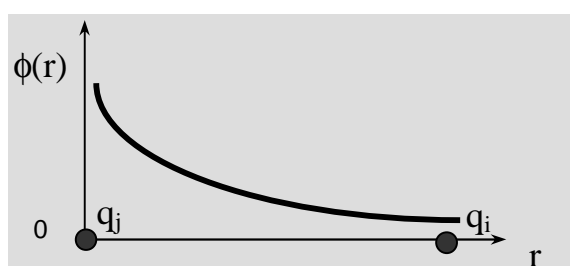


Figure 1. The Coulomb potential for two charges, q_i and q_j , of the same sign in a uniform dielectric. The relative dielectric constant of the solvent screens, that is attenuates, the interaction. The screening is symbolized by the gray background.

The effect of the polar environment of the solvent can then be roughly described as being calculated from the electrostatic energy of interaction of the induced image charges in the solvent with the point partial charges on the atoms in the molecule.

Gibbs Free Energy of Solvation

The Gibbs Free Energy of solvation is approximated as

$$\Delta_{\text{sol}}G = \Delta_{\text{sol}}G_{\text{vdW}} + \Delta_{\text{sol}}G_{\text{cav}} + \Delta_{\text{sol}}G_{\text{elec}}$$

where $\Delta_{\text{sol}}G_{\text{VdW}}$ is the solute-solvent Van der Waals interaction, and $\Delta_{\text{sol}}G_{\text{cav}}$ is the work necessary to create the cavity in solvent. $\Delta_{\text{sol}}G_{\text{cav}}$ is calculated by

$$\Delta_{\text{sol}}G_{\text{cav}} = (\text{surface tension})(\text{surface area}) = \gamma \sigma$$

This term arises from the entropy penalty for rearrangement of water molecules and is unfavorable. The $\Delta_{\text{sol}}G_{\text{VdW}}$ and $\Delta_{\text{sol}}G_{\text{cav}}$ terms are often combined since both are approximately proportional to the solvent accessible surface area. The combined Van der Waals and cavity surface tension, γ , is approximately in the range $7\text{-}10 \text{ J}/\text{\AA}^2$. Different authors and programs use different values; we will use $\Delta_{\text{sol}}G_{\text{VdW}} + \Delta_{\text{sol}}G_{\text{cav}} = 7 \text{ J}/\text{\AA}^2 \text{ ASA}$. $\Delta_{\text{sol}}G_{\text{elec}}$ is the work necessary to transfer ion from vacuum to solution with the calculated electrostatic potential.

Now consider a small spherical ion in solution. In electrolyte solutions $\Delta_{\text{sol}}G_{\text{elec}}$ also includes the potential of the ionic atmosphere of neighbor ions j . The neighborhood of an ion is predominately comprised of the counter ions of opposite charge. For example for a positive ion, q_i , the counter ions of charge q_j form a negatively charged halo around the positive ion. The Coulomb interaction of the ion with this halo is then stabilizing, that is negative in energy, Figure 2.

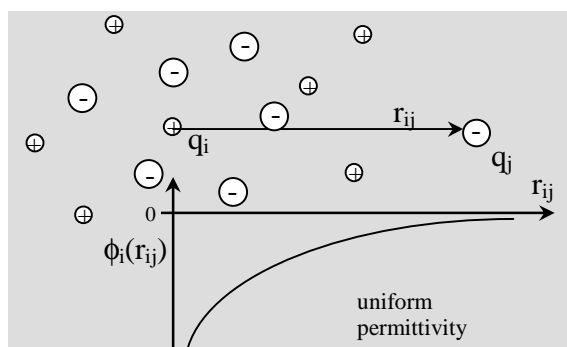


Figure 2. For electrolyte solutions a positive ion is surrounded by a halo of negative ions. The Coulomb interaction is negative for these interactions.

The Coulomb potential energy can be broken into the product of the electric potential multiplied by the charge on the ion of interest. We will call the ion of interest the central ion, i .

$$V(r) = \phi_i q_j$$

Comparison with Eq. 1 shows that the electric potential at ion i due to the presence of ion j is

$$\phi_i = \frac{q_j}{4\pi\epsilon_r\epsilon_0 r_{ij}}$$

The effect of the dielectric constant of the solvent, ϵ_r , is to attenuate the charge-charge interaction. However, the presence of counter ions also screen the interaction of two charges.

The screening caused by the ionic atmosphere is determined by the distribution of counter ions near the solute ion, $p(r) dr$, which is the probability of finding a counter ion at a distance r to $r+dr$. This distribution is given by the Boltzmann distribution using the energy of the interaction of the solute ion, i , with a counterion, j , given by $\phi_i(r)q_j$. The number of counterions that will be found at a given point a distance r from the solute ion is

$$N_j = N_{oj} e^{\frac{-\phi_i(r)q_j}{kT}}$$

where N_{oj} is the number of ions j in solution. The Boltzmann constant k is the gas constant per molecule, R/N_A . The probability of finding an ion j at any angle at a radius of r from the central ion is:

$$p_j(r) dr = 4\pi r^2 N_{oj} e^{\frac{-\phi_i(r)q_j}{kT}} dr$$

Here the $4\pi r^2 dr$ is the annular volume at all angles between the radius of r and $r+dr$. This probability distribution of the counter ion halo is shown in Figure 3.

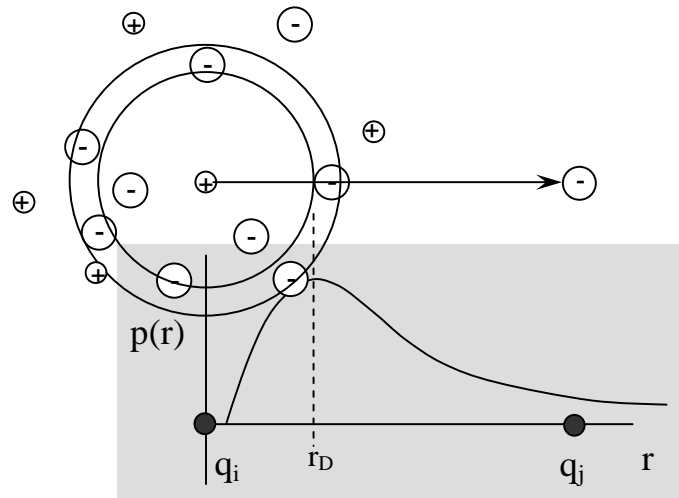


Figure 3. The distribution of counter ions around a solute ion. This oppositely charged halo has a probability maximum at the Debye length, r_D .

The Boltzmann distribution takes into account the thermal jostling of molecular collisions within the solvent that disrupt the ionic halo. The exponential decrease of the Boltzmann distribution at a point and the r^2 increase of the volume at r to $r+dr$ multiply to give a distribution that has a maximum. This distance is called the Debye length, r_D . The Debye length is a measure of the thickness of the ionic atmosphere. Finding the maximum in the probability distribution gives, for very dilute solutions with uniform solvent dielectric and unipositive and uninegative ions (e.g. NaCl)

$$r_D = \frac{305 \text{ pm}}{(m/m^\circ)^{1/2}} = \frac{1}{\kappa}$$

Where the term in the denominator is just the square root of the ionic strength. The Debye length is often specified by the reciprocal parameter κ . The polarization of the solvent and the ionic halo determine the electric potential at each point in the solution. Once the electric potential is known the probability distribution of the ions can be calculated. Unfortunately, these calculations depend on each other. A common approach is to first make a rough guess of the potential and then to solve for the counterion distribution. This distribution is then used to calculate a better guess for the electric potential. This process of successive approximations is continued until the electric potential no longer changes.

The electric potential is then used to calculate $\Delta_{\text{sol}}G_{\text{elec}}$. First the work necessary to charge the solute ion within the solution is calculated:

$$w_{\text{el}} = \int_0^{Z_i e} \phi_i dq$$

The electrostatic contribution to the Gibbs Free Energy of solvation can then be calculated by finding the difference between the electrical work necessary to charge the ion in the solvent and the work to charge the ion in vacuum:

$$\Delta_{\text{sol}}G_{\text{elec}} = N_A w_{\text{elec}}(\text{real}) - N_A w_{\text{elec}}(\text{ideal}) = N_A w_{\text{solution}} - N_A w_{\text{vacuum}}$$

Poisson Equation¹

The electric potential is calculated from the Poisson equation, for non-electrolyte solutions or the dilute solution limit for electrolyte solutions. The Poisson equation depends on the charge density within the solution. For ion type i with the charge on the ion q_i the charge density is:

$$\rho_i(r) = q_i p_i(r)$$

The charge density is the charge per unit volume, which depends on the polarization of the solvent and the distribution of ions in the halo around the solute. The Poisson equation also depends on the spatial variation of the dielectric constant, $\epsilon(r) = \epsilon_0 \epsilon_r(r)$. The Poisson equation is

$$\nabla^2 \phi_i(r) = -\frac{\rho_i(r)}{\epsilon(r)}$$

where

$$\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$$

is the curvature or wiggleness of the electric potential. The Poisson equation shows that the higher the charge density the faster the potential drops, Figure 4.

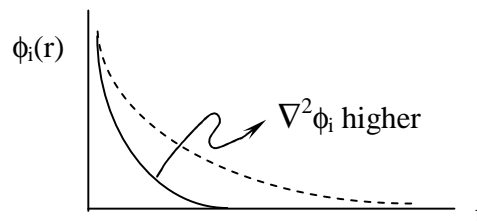


Figure 4: The higher the charge density, the higher the curvature of the electric potential. The higher the curvature, the faster the electric potential decreases with distance away from the solute. The charge density screens the electrostatic interactions.

For a spherical potential the curvature simplifies to¹:

$$\frac{1}{r} \frac{\partial^2 (r \phi_i(r))}{\partial r^2} = -\frac{\rho_i(r)}{\epsilon(r)}$$

To get a feeling for the Poisson equation we start with a very simple model. This model is for electrolyte solutions of small ions. The result is the Debye-Hückel model, when applied to very dilute solutions. The ions are modeled as point charges embedded in a uniform solvent. Ions in

this model do not have a "size." For a uniform solvent dielectric, $\epsilon_r(r) = \epsilon_r$. The charge density is the sum of the charge density for the positive and negative ions in solution:

$$\rho_+ = q_+ \frac{N_+}{V} e^{-\frac{\phi_i(r)q_+}{kT}} \quad \rho_- = q_- \frac{N_-}{V} e^{\frac{\phi_i(r)q_-}{kT}}$$

$$\rho_{\text{ions}} = \rho_+ + \rho_- = q_+ \frac{N_+}{V} e^{-\frac{\phi_i(r)q_+}{kT}} + q_- \frac{N_-}{V} e^{\frac{\phi_i(r)q_-}{kT}}$$

The concentration of ions is also assumed to be very small so that $\phi_i(r) \ll kT$ and the exponential term in the Boltzmann distribution simplifies to:

$$e^{-\frac{\phi_i(r)q_i}{kT}} \approx 1 - \frac{\phi_i(r)q_i}{kT}$$

Then the charge density of the ions simplifies to

$$\rho_{\text{ions}} = \rho_+ + \rho_- = q_+ \frac{N_+}{V} \left(1 - \frac{\phi_i(r)q_+}{kT}\right) + q_- \frac{N_-}{V} \left(1 - \frac{\phi_i(r)q_-}{kT}\right)$$

$$\rho_{\text{ions}} = \left(q_+ \frac{N_+}{V} + q_- \frac{N_-}{V}\right) - \left(q_+ N_+ \frac{\phi_i(r)q_+}{kT} + q_- \frac{N_-}{V} \frac{\phi_i(r)q_-}{kT}\right)$$

The first term cancels because of charge neutrality; the numbers of positive and negative charges are equal, which gives:

$$\rho_{\text{ions}} = -\frac{\phi_i(r)}{kT} \left(q_+^2 \frac{N_+}{V} + q_-^2 \frac{N_-}{V}\right)$$

The term in parentheses is the ionic strength. If there are several sources of ions, this sum must include all the ions in solution. With $q_j = z_j e$ and z_j the charge number on ion j :

$$\rho_{\text{ions}} = -\frac{\phi_i(r)}{kT} \sum_{j=1}^s q_j^2 \frac{N_j}{V} = \frac{\phi_i(r)e^2}{kT} \sum_{j=1}^s z_j^2 \frac{N_j}{V}$$

Then κ , the inverse Debye length, is defined as:

$$\kappa^2 = \frac{e^2}{\epsilon_r \epsilon_0 kT} \sum_{j=1}^s z_j^2 \left(\frac{N_j}{V}\right)$$

The N_j/V term is the number concentration with N_j equal to the number of ions of type j in solution, and V the volume of the solution in m^3 . Substitution into the Poisson equation gives the much simpler result:

$$\frac{\partial^2(r\phi_i(r))}{\partial r^2} = \kappa^2 (r\phi_i(r))$$

The solution to this equation is in the form:

$$\phi_i(r) = \frac{A}{r} e^{-\kappa r}$$

The A constant can be evaluated using the appropriate boundary conditions giving

$$\phi_i(r) = \frac{q_i}{4\pi\epsilon_0\epsilon_r r} e^{-\kappa r}$$

This result is called the shielded Coulomb potential, which takes into account the dielectric and the interaction of the solute ion with its oppositely charged ionic atmosphere. The concentrations can be converted into molality using:

$$m_j = \frac{N_j/N_A}{V (1000 \text{ L m}^{-3}) d_o}$$

where d_o is the density of the solution in kg L^{-1} , which is equivalent to g mL^{-1} . The substitution gives:

$$\kappa^2 = \frac{e^2 (1000 \text{ L m}^{-3}) d_o N_A m_o}{\epsilon_r \epsilon_0 kT} \sum_{j=1}^s z_j^2 m_j/m^\circ$$

and the summation is just the ionic strength

$$I = \frac{1}{2} \sum_{j=1}^s z_j^2 m_j/m^\circ$$

This model gives the Debye-Hückel result for the activity coefficient of the ion in solution when the electrical work is calculated (see below for a similar example). The Debye-Hückel approach assumes that $RT \ln \gamma_{\pm} = w_{el} N_A$.

The shielded Coulomb potential reduces to Coulomb's Law for very dilute solutions, because the exponential term in the shielded Coulomb potential approaches 1:

$$I \rightarrow 0, \quad \kappa \rightarrow 0, \quad r_D \rightarrow \infty, \quad e^{-\kappa r} \approx 1 - \kappa r \rightarrow 1, \quad \phi_i(r) \rightarrow \text{Coulomb's Law}$$

Born Approximation

Modeling ions as point charges with no radius is very approximate. A model that takes into account the size of the ion has been developed, which is called the Born approximation. The ion is modeled as a point charge in spherical cavity of radius r_i . The relative dielectric constant inside the sphere is that of a vacuum, $\epsilon_r = 1$, and the solvent outside of the ion radius is assumed to be uniform with dielectric constant ϵ_r , Figure 5. The model applies to very dilute electrolytes or non-electrolyte solutions. In other words there are no counter ions as in the example above. The solution to the Poisson equation is now more involved because the dielectric constant changes with position as well as the charge density. We simply present the results here. The electric potential at the center of a spherical ion of radius r_i in the Born approximation is:

$$\phi_i(0) = \frac{q_i}{4\pi\epsilon_0\epsilon_r r_i}$$

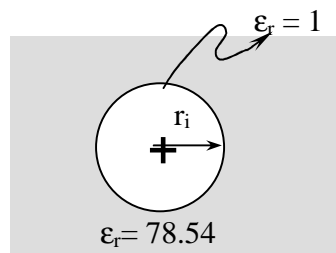


Figure 5: The Born Approximation assumes a charge in a spherical cavity of radius r_i with $\epsilon_r = 1$ inside the cavity and ϵ_r constant for the uniform solvent for $r > r_i$.

The presence of the ion polarizes the dielectric in the bulk solvent. The actual charge density in the bulk of the solvent remains small, because the polarization dipoles in each water molecule cancel each other, except at the boundaries.⁵ However, a surface charge is induced at the cavity surface, which is oppositely charged from the ion, Figure 6. This surface charge creates an electric potential at the center of the sphere. The spatial variation of the electric potential creates an electric field at the center of the ion, which is called the reaction field.⁵ The surface charge can be shown to behave like a "image" charge that is in the bulk of the solvent opposite the point charge on the ion, Figure 1.⁵ These image charges are discussed in the introduction to this section.

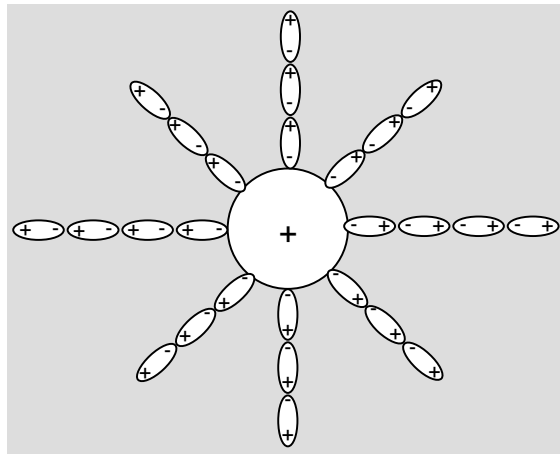


Figure 6: The ion polarizes the solvent. The solvent dipoles don't cancel at the surface of the cavity, giving a surface charge. The surface charge generates a potential at the point charge representing the ion. The field from the induced surface charge is called the reaction field.

The electric work in charging the ion can now be calculated¹:

$$dw_{el} = \phi_i dq$$

$$w_{el} = \int_0^{Z_i e} \phi_i dq = \frac{1}{4\pi\epsilon_0\epsilon_r r_i} \int_0^{Z_i e} q_i dq_i$$

You might wonder why the work is not simply just $\phi_i q_i$, since an ion has an integral charge, $+1e$, $+2e$, $-1e$, etc. The integral takes into account the "self-interaction." That is the charge is visualized as being added in small increments. Each new increment interacts with the charges that have built up from previous increments, Figure 7, and the integral is:

$$\int q_i dq_i = \frac{q_i^2}{2}$$

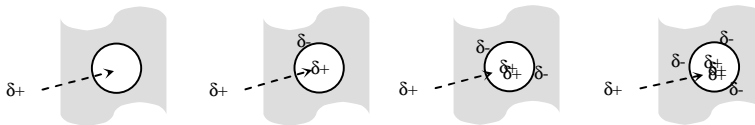


Figure 7: The electrical work integral is done in small steps.

The electrical work is then:

$$w_{el} = \frac{z_i^2 e^2}{8\pi\epsilon_0\epsilon_r r_i}$$

The electrostatic contribution to the Gibbs Free Energy of solvation is then the difference:

$$\Delta_{sol}G_{elec} = N_A w_{solution} - N_A w_{vacuum}$$

which is:

$$\Delta_{sol}G_{elec} = \frac{z_i^2 e^2 N_A}{8\pi r_i} \left(\frac{1}{\epsilon_r \epsilon_0} - \frac{1}{\epsilon_0} \right) = -\frac{z_i^2 e^2 N_A}{8\pi\epsilon_0 r_i} \left(1 - \frac{1}{\epsilon_r} \right)$$

Generalized Born Approximation

The result above is for a simple spherical ion. In the Generalized Born approximation, the electrostatic energy is a sum of this form over all the atoms in a solute molecule¹. For molecules the partial charges that are placed at the nucleus of each atom replace the charge on the ions given above. To complete the calculation of the solvation Gibbs Free Energy, the cavity and Van der Waals terms must be added in. Because these terms depend on the solvent accessible surface area of the solute, the general formulation of the Born approximation for molecules and non-spherical ions is called the Generalized Born/Solvent accessible Surface Area approach, or GB/SA for short.

The GB/SA method is very rapid and does a reasonable job of modeling non-specific solvation effects. These effects are mainly the screening effect of the dielectric constant of the solvent and the ionic halo. The approach also accounts for the stabilization of polar solutes that results from solvent polarization. These electrostatic terms primarily affect the enthalpy of solvation. The entropy changes are accounted for in the cavity term.

The GB/SA approach can be used for any solvent, and not just water. The dielectric constant of the solvent is required. In addition, the average solvent molecule radius is necessary to calculate the solvent accessible surface area. In other words, larger solvents can't approach the solute as closely and the corresponding solvent accessible surface area is larger. The surface tension is also needed for the chosen solvent. These calculations are very useful for organic mechanisms.

The Generalized Born approximation and more advanced electrostatic treatments are also becoming extremely important in modeling the surfaces of proteins and nucleic acids.^{3,4} The combination of the partial charges on the amino acids in a protein and the polarization of the solvent can create strong electric fields near the surface of proteins that may help guide substrates into the active sites of enzymes and may help orient proteins for efficient protein-protein binding. In other words, solvation effects have an important influence on molecular recognition.

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Section 9

Classical Normal Mode Analysis: Harmonic Approximation

The vibrations of a molecule are given by its normal modes. Each absorption in a vibrational spectrum corresponds to a normal mode. The four normal modes of carbon dioxide, Figure 1, are the symmetric stretch, the asymmetric stretch and two bending modes. The two bending modes have the same energy and differ only in the direction of the bending motion. Modes that have the same energy are called degenerate. In the classical treatment of molecular vibrations, each normal mode is treated as a simple harmonic oscillator.

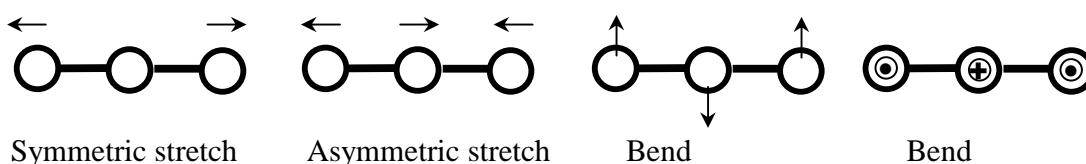


Figure 1. Normal Modes for a linear triatomic molecule. In the last bending vibration the motion of the atoms is in-and-out of the plane of the paper.

In general linear molecules have $3N-5$ normal modes, where N is the number of atoms. The five remaining degrees of freedom for a linear molecule are three coordinates for the motion of the center of mass (x, y, z) and two rotational angles. Non-linear molecules have three rotational angles, hence $3N-6$ normal modes.

The characteristics of normal modes are summarized below.

Characteristics of Normal Modes

1. Each normal mode acts like a simple harmonic oscillator.
2. A normal mode is a concerted motion of many atoms.
3. The center of mass doesn't move.
4. All atoms pass through their equilibrium positions at the same time.
5. Normal modes are independent; they don't interact.

In the asymmetric stretch and the two bending vibrations for CO_2 , all the atoms move. The concerted motion of many of the atoms is a common characteristic of normal modes. However, in the symmetric stretch, to keep the center of mass constant, the center atom is stationary. In small molecules all or most all of the atoms move in a given normal mode; however, symmetry may require that a few atoms remain stationary for some normal modes. The last characteristic, that normal modes are independent, means that normal modes don't exchange energy. For example, if the symmetric stretch is excited, the energy stays in the symmetric stretch.

The background spectrum of air, Figure 2, shows the asymmetric and symmetric stretches and the bending vibration for water, and the asymmetric stretch and bending vibrations for CO_2 . The symmetric stretch for CO_2 doesn't appear in the Infrared; a Raman spectrum is needed to measure the frequency of the symmetric stretch. These absorptions are responsible for the vast majority of the greenhouse effect. We will also use CO_2 as an example, below.

The normal modes are calculated using Newton's equations of motion.¹⁻⁴ Molecular mechanics and molecular orbital programs use the same methods. Normal mode calculations are available on-line.⁵

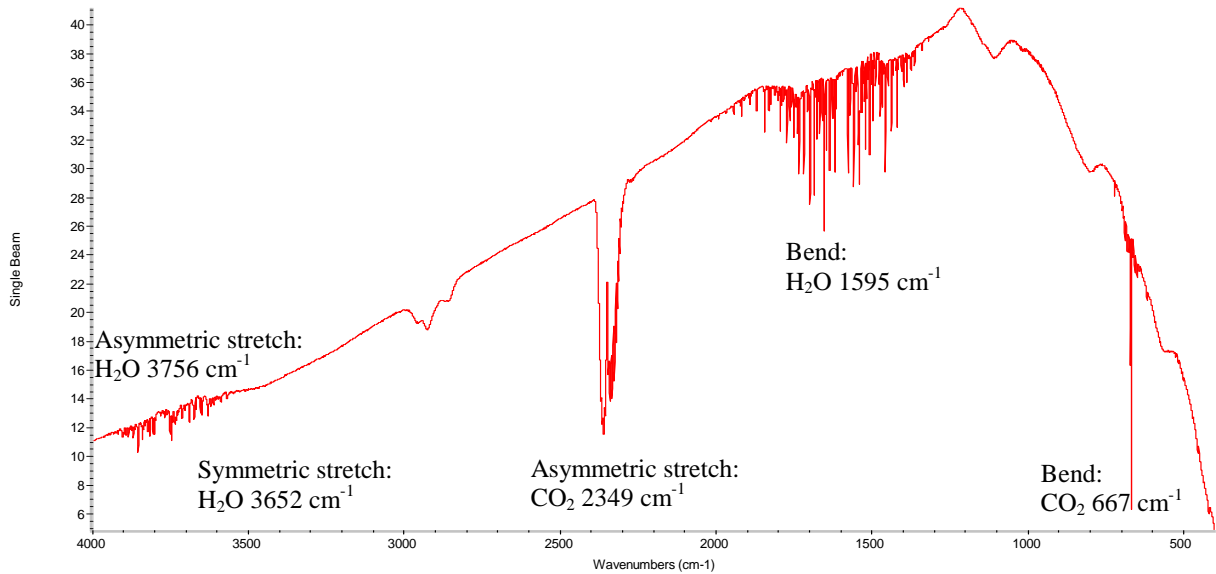


Figure 2. The Infrared spectrum of air. This spectrum is the background scan from an FT-IR spectrometer.

Harmonic Oscillator Review

Lets first review the simple harmonic oscillator. Consider a mass m , supported on a spring with force constant k . Hooke's Law for the restoring force for an extension, x , is $F = -kx$. In other words, if the spring is stretched a distance $x > 0$, the restoring force will be negative, which will act to pull the mass back to its equilibrium position. The potential energy for Hooke's Law is obtained by integrating

$$F = -\frac{dV}{dx} = -kx \quad (1)$$

$$\text{to give } V = \frac{1}{2} k x^2 \quad (2)$$

In molecular mechanics and molecular orbital calculations, the force constant is not known. However, the force constant can be calculated from the second derivative of the potential energy.

$$k = \frac{d^2 V}{dx^2} \quad (3)$$

The Hooke's Law force is substituted into Newton' Law:

$$F = ma \quad \text{or} \quad m \frac{d^2 x}{dt^2} = -kx \quad (4)$$

and solved to obtain the extension as a function of time:

$$x(t) = A \sin(2\pi\nu t) \quad (5)$$

where ν is the fundamental vibration frequency and A is the amplitude of the vibration. Taking the second derivative of the extension gives

$$\frac{d^2 x}{dt^2} = -4\pi^2 \nu^2 x \quad (6)$$

Substituting Eq 6 back into Eq 4 gives:

$$-4\pi^2 \nu^2 m x = -kx \quad (7)$$

which is the basis for the classical calculation of the normal modes of a molecule.

Normal Mode Analysis

For molecules the x, y, z coordinates of each atom must be specified. The coordinates are:

Atom 1: $X_1, Y_1, Z_1,$ Atom 2: $X_2, Y_2, Z_2,$ etc.

The extensions are the differences in the positions and the equilibrium positions for that atom:

$$\begin{array}{lll} \text{Atom 1: } x_1 = X_1 - X_{1,\text{eq}} & y_1 = Y_1 - Y_{1,\text{eq}} & z_1 = Z_1 - Z_{1,\text{eq}} \\ \text{Atom 2: } x_2 = X_2 - X_{2,\text{eq}} & y_2 = Y_2 - Y_{2,\text{eq}} & z_2 = Z_2 - Z_{2,\text{eq}} \\ \text{Atom i: } x_i = X_i - X_{i,\text{eq}} & y_i = Y_i - Y_{i,\text{eq}} & z_i = Z_i - Z_{i,\text{eq}} \end{array} \quad (8)$$

Where $X_{i,\text{eq}}, Y_{i,\text{eq}},$ and $Z_{i,\text{eq}}$ are the equilibrium (energy minimized) positions for atom i. For example, if $x_1, y_1,$ and z_1 are all zero, then atom 1 is at its equilibrium position. Molecular mechanics or molecular orbital calculations are used to find the potential energy of the molecule as a function of the position of each atom, $V(x_1, y_1, z_1, x_2, y_2, z_2, x_3, y_3, z_3, \dots, x_N, y_N, z_N)$.

The second derivative of the potential energy can then be used to calculate the force constants, Eq 3. However, there are now $3N \times 3N$ possible second derivatives and their corresponding force constants. For example,

$$\frac{\partial^2 V}{\partial x_1^2} = k_{xx}^{11} \quad (9)$$

is the change of the force on atom 1 in the x-direction when you move atom 1 in the x-direction.

Similarly,

$$\frac{\partial^2 V}{\partial x_1 \partial y_2} = k_{xy}^{12} \quad (10)$$

is the change of the force on atom 1 in the x-direction when you move atom 2 in the y-direction. The various types of force constants are shown in Figure 3.

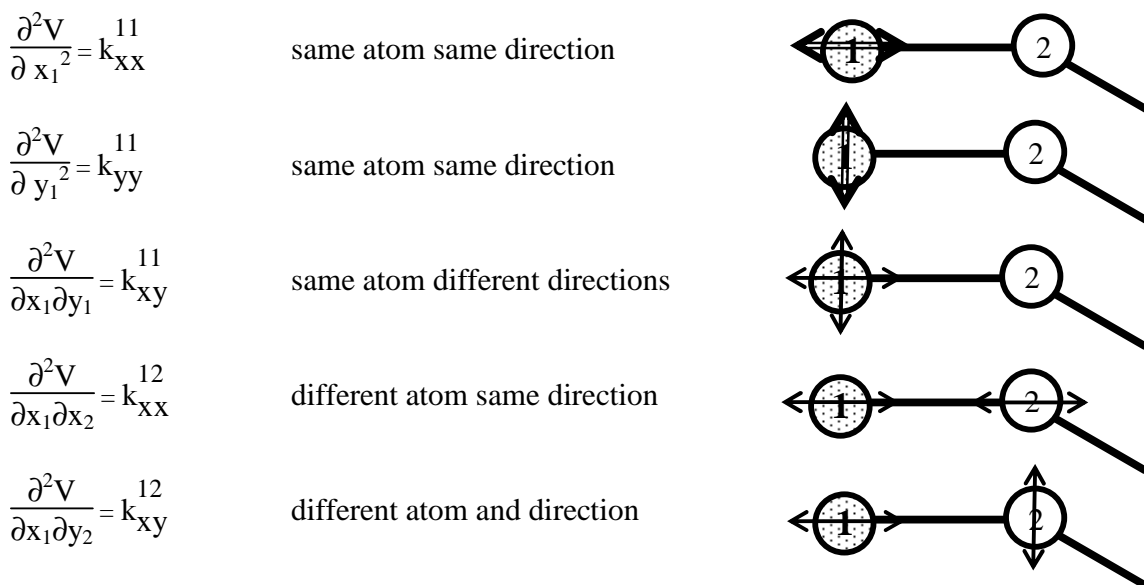


Figure 3. Types of second derivatives and force constants

These force constants are not the force constants for individual bonds, they are force constants for the motion of a single atom subject to all its neighbors, whether directly bonded or not. The

complete list of these force constants is called the Hessian, which is a $3N \times 3N$ matrix. Eq 7 is then applied for each force constant.^{1,2}

$$\begin{aligned}
 -4\pi^2\nu^2 m_1x_1 &= -k_{XX}^{11}x_1 - k_{XY}^{11}y_1 - k_{XZ}^{11}z_1 - k_{XX}^{12}x_2 - k_{XY}^{12}y_2 - \dots - k_{XZ}^{1N}z_N \\
 -4\pi^2\nu^2 m_1y_1 &= -k_{YX}^{11}x_1 - k_{YY}^{11}y_1 - k_{YZ}^{11}z_1 - k_{YX}^{12}x_2 - k_{YY}^{12}y_2 - \dots - k_{YZ}^{1N}z_N \\
 &\vdots \\
 -4\pi^2\nu^2 m_2x_2 &= -k_{XX}^{21}x_1 - k_{XY}^{21}y_1 - k_{XZ}^{21}z_1 - k_{XX}^{22}x_2 - k_{XY}^{22}y_2 - \dots - k_{XZ}^{2N}z_N \\
 &\vdots \\
 -4\pi^2\nu^2 m_Nz_N &= -k_{ZX}^{N1}x_1 - k_{ZY}^{N1}y_1 - k_{ZZ}^{N1}z_1 - k_{ZX}^{N2}x_2 - k_{ZY}^{N2}y_2 - \dots - k_{ZZ}^{NN}z_N
 \end{aligned} \tag{11}$$

In words, the right-hand sides of the above equations simply state that the total force on atom i is the sum of the forces of all the atoms on atom i . In addition, we need to keep track of the x , y , and z directions for each atom. There are a total of $3N \times 3N$ terms on the right. All these terms are confusing. A simple example will help at this point.

For our example consider a symmetrical linear triatomic molecule that can only vibrate along the x -axis, Figure 4. CO_2 is a good example of a symmetrical linear triatomic.

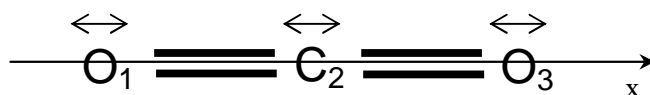


Figure 4. A symmetrical triatomic molecule with vibrations limited along the internuclear axis.

Because we have limited the vibrations to the x -axis, which is the internuclear axis, this model will provide the symmetric and asymmetric stretching modes, only. Eqs 11 then reduce to

$$-4\pi^2\nu^2 m_1x_1 = -k_{XX}^{11}x_1 - k_{XX}^{12}x_2 - k_{XX}^{13}x_3 \tag{12}$$

$$-4\pi^2\nu^2 m_2x_2 = -k_{XX}^{21}x_1 - k_{XX}^{22}x_2 - k_{XX}^{23}x_3 \tag{13}$$

$$-4\pi^2\nu^2 m_3x_3 = -k_{XX}^{31}x_1 - k_{XX}^{32}x_2 - k_{XX}^{33}x_3 \tag{14}$$

since we only need to keep the x -terms. Several numerical techniques are available to solve linear sets of simultaneous equations such as this. Conventionally, however, the problem is simplified by converting to mass weighted coordinates, for example:

$$\tilde{x}_1 = \sqrt{m_1} x_1 \quad \tilde{x}_2 = \sqrt{m_2} x_2 \quad , \text{ etc.} \tag{15}$$

and mass weighted force constants:

$$\tilde{k}_{XX}^{12} = \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} \tag{16}$$

In the new mass weighted coordinates, Eqs 12-14 become:

$$-4\pi^2\nu^2 \tilde{x}_1 = -\tilde{k}_{XX}^{11} \tilde{x}_1 - \tilde{k}_{XX}^{12} \tilde{x}_2 - \tilde{k}_{XX}^{13} \tilde{x}_3 \quad (17)$$

$$-4\pi^2\nu^2 \tilde{x}_2 = -\tilde{k}_{XX}^{21} \tilde{x}_1 - \tilde{k}_{XX}^{22} \tilde{x}_2 - \tilde{k}_{XX}^{23} \tilde{x}_3 \quad (18)$$

$$-4\pi^2\nu^2 \tilde{x}_3 = -\tilde{k}_{XX}^{31} \tilde{x}_1 - \tilde{k}_{XX}^{32} \tilde{x}_2 - \tilde{k}_{XX}^{33} \tilde{x}_3 \quad (19)$$

For example, we can show that Eq 17 is equivalent to Eq 11, by substituting Eqs 15 and 16 into Eq 17.

$$-4\pi^2\nu^2 \sqrt{m_1} x_1 = -\frac{k_{XX}^{11}}{\sqrt{m_1}\sqrt{m_1}} \sqrt{m_1} x_1 - \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} \sqrt{m_2} x_2 - \frac{k_{XX}^{13}}{\sqrt{m_1}\sqrt{m_3}} \sqrt{m_3} x_3 \quad (20)$$

Canceling mass terms and multiplying both sides by $\sqrt{m_1}$ gives Eq 11.

Eq 17-19 are most easily written in the equivalent matrix form:

$$-\begin{pmatrix} \frac{k_{XX}^{11}}{\sqrt{m_1}\sqrt{m_1}} & \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} & \frac{k_{XX}^{13}}{\sqrt{m_1}\sqrt{m_3}} \\ \frac{k_{XX}^{21}}{\sqrt{m_2}\sqrt{m_1}} & \frac{k_{XX}^{22}}{\sqrt{m_2}\sqrt{m_2}} & \frac{k_{XX}^{23}}{\sqrt{m_2}\sqrt{m_3}} \\ \frac{k_{XX}^{31}}{\sqrt{m_3}\sqrt{m_1}} & \frac{k_{XX}^{32}}{\sqrt{m_3}\sqrt{m_2}} & \frac{k_{XX}^{33}}{\sqrt{m_3}\sqrt{m_3}} \end{pmatrix} \begin{pmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \tilde{x}_3 \end{pmatrix} = -4\pi^2\nu^2 \begin{pmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \tilde{x}_3 \end{pmatrix} \quad (21)$$

The mass weighted force constants give a symmetric matrix. In other words, the corresponding off diagonal elements are equal. Eq 21 is an eigenvalue-eigenvector equation. The eigenvalues are the negative of the squared normal mode frequencies. The eigenvectors are the mass weighted normal coordinate displacements (see Appendix). Many efficient algorithms exist for solving eigenvalue equations.⁶

The Hessian and Energy Minimization The matrix of force constants is the matrix of the second derivatives of the potential energy. This matrix is also called the Hessian. The Hessian also plays a central role in energy minimization techniques. The equations in Section 4: “Energy Minimization” apply to one-dimensional systems. For molecules, we must find the x, y, z coordinates of each atom, for a total of 3N coordinates. To minimize the energy for these 3N coordinates, the equations in Section 4 are actually written in terms of the Hessian, instead of a single force constant or the second derivative of the energy for the x-coordinate alone. The use of the Hessian is necessary to minimize the energy of all the atoms in the molecule.

Numerical Example for Carbon Dioxide

The CO₂ example will provide some insight for understanding Eq 21. First, we need to discuss units. The fundamental vibration frequency for a harmonic oscillator is

$$\nu_o = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \quad \text{or} \quad 4\pi^2\nu^2 = \frac{k}{m} \quad (22)$$

with k in N m^{-1} and m in kg molecule^{-1} . Normally, vibrational spectra are plotted versus wavenumber, instead of frequency. To convert to wavenumbers, $\tilde{\nu}$:

$$\tilde{\nu} = \frac{1}{\lambda} \quad \text{or} \quad \nu = \frac{c}{\lambda} = c\tilde{\nu} \quad (23)$$

If $\tilde{\nu}$ is in cm^{-1} , c should be given in cm s^{-1} . Using $\tilde{\nu}$ in cm^{-1} and m in g mol^{-1} , Eq 22 becomes:

$$\frac{4\pi^2 c^2 \tilde{\nu}^2}{1000 \text{ g/kg } N_A} = \frac{k}{m} \quad (24)$$

or solving for the frequency squared in wavenumbers gives a convenient conversion factor

$$\tilde{\nu}^2 = \frac{k/m}{5.8921 \times 10^{-5}} \quad (25)$$

Now for our example. The CO_2 stretches are experimentally measured to be 1340 cm^{-1} for the symmetric stretch and 2349 cm^{-1} for the asymmetric stretch, Fig. 2. Lets roughly see if we can calculate these values through a normal mode analysis using our simplified one-dimensional model. First we will need all the force constants. However, some force constants are related by symmetry, since the left and right hand sides of the molecule are the same.

$$\text{By symmetry:} \quad k_{11}^{11} = k_{33}^{33} \quad k_{12}^{12} = k_{23}^{23} \quad (26)$$

The terms that exchange the atom labels are also equivalent, since atom 1 interacting with atom 2 gives the same result as atom 2 interacting with atom 1. In matrix terms, these corresponding off-diagonal terms are equivalent for a symmetric matrix.

$$\text{Symmetric matrix:} \quad k_{12}^{12} = k_{21}^{21} \quad k_{23}^{23} = k_{32}^{32} \quad (27)$$

These equivalences leave four force constants that we need to guess. First focus on atom 1. By trial an error, a good guess for

$$k_{11}^{11} = 1600 \text{ N m}^{-1} \quad (28)$$

This force constant gives the restoring force as atom 1 is moved. The restoring force, $F = -kx$, will be negative, pulling the atom back to its equilibrium position. Another way to state this is if atom 1 is moved forward to shorten the bond length then atom 1 will try to move back to keep the bond length constant. A reasonable guess for

$$k_{12}^{12} = -k_{21}^{21} \quad (29)$$

Here the 12-force constant is negative, and the restoring force, $F = -kx$, is positive. This positive force results because as you move atom 1's neighbor, atom 1 will try to follow along in the same direction to keep the bond length constant. The absolute value of the two force constants is the same since moving either atom 1 or atom 2 has the same effect on the bond length and, therefore, the force on atom 1. Now focus on atom 2. Lets guess that it is twice as hard to move atom 2 as it is to move atom 1, since moving atom 2 effects two bonds:

$$k_{22}^{22} = 2 k_{11}^{11} = 3200 \text{ N m}^{-1} \quad (30)$$

Finally, we will assume that

$$k_{13}^{13} = 0. \quad (31)$$

We assume that atom 3 doesn't affect atom 1 significantly because the two atoms aren't directly bonded. Substituting Eqs 26-31 into Eq 21 gives the mass weighted force constant matrix. The row and columns correspond to the three different atoms, O₁, C₂, and O₃, respectively.

$$\begin{matrix} & \begin{matrix} \text{O}_1 & \text{C}_2 & \text{O}_3 \end{matrix} \\ \begin{matrix} \text{O}_1 \\ \text{C}_2 \\ \text{O}_3 \end{matrix} & - \begin{pmatrix} \frac{1600}{\sqrt{16}\sqrt{16}} & \frac{1600}{\sqrt{16}\sqrt{12}} & 0 \\ \frac{1600}{\sqrt{12}\sqrt{16}} & \frac{3200}{\sqrt{12}\sqrt{12}} & \frac{1600}{\sqrt{12}\sqrt{16}} \\ 0 & \frac{1600}{\sqrt{16}\sqrt{12}} & \frac{1600}{\sqrt{16}\sqrt{16}} \end{pmatrix} = \begin{pmatrix} -100 & 115.47 & 0 \\ 115.47 & -266.67 & 115.47 \\ 0 & 115.47 & -100 \end{pmatrix} \end{matrix} \quad (30)$$

The "eigen" Web applet is available to solve the eigenvalue problem.⁷ Computer algebra programs like Maple and Mathematica are also handy for solving eigenvalue problems. The output of the "eigen" applet is shown below. The eigenvalues are listed with "E=". The normal mode frequencies are easily calculated using the units conversion factor from Eq 25.

Eigenvector 1: E=-0.000976903 ≈ 0

0.603024

0.522229

0.603024

Eigenvector 2: E=-100

-0.707107

0

0.707107

Eigenvector 3: E=-366.669

-0.369272

0.852805

-0.369272

Symmetric stretch:

$$\tilde{\nu} = \sqrt{\frac{100}{5.892 \times 10^{-5}}} = 1303 \text{ cm}^{-1}$$

Asymmetric stretch:

$$\tilde{\nu} = \sqrt{\frac{366.67}{5.892 \times 10^{-5}}} = 2495 \text{ cm}^{-1}$$

(for about 5% errors)

The three numbers below each eigenvalue are the normal coordinates. For example, the normal coordinates for the second eigenvector show atom 1 (-0.707) moving in the opposite direction as atom 3 (0.707), while atom 2 remains stationary (0). For the CO₂ example we have motion only in the x-direction, so there are only three coordinates listed, one for each atom. In general to display the motion of the atoms during the vibration, the atom coordinates are calculated for atom i as:

$$X_i = X_{i,\text{eq}} + \frac{\tilde{x}_i}{\sqrt{m_i}} q \quad Y_i = Y_{i,\text{eq}} + \frac{\tilde{y}_i}{\sqrt{m_i}} q \quad Z_i = Z_{i,\text{eq}} + \frac{\tilde{z}_i}{\sqrt{m_i}} q \quad (33)$$

where $q = \sin(2\pi\nu t)$. For example, for the asymmetric stretch for CO₂ for the first O atom,

$$X_1 = X_{1,\text{eq}} + \frac{-0.369}{\sqrt{16}} \sin(2\pi\nu t) \quad (34)$$

The first eigenvalue is zero, because it corresponds to the motion of the center of mass of the molecule in the x-direction. You can also tell that the first eigenvector is for the motion of the molecule as a whole because all the normal coordinates have the same sign, that is all the atoms are traveling in the same direction. For fully three-dimensional problems, the first 5 eigenvalues, for linear molecules, or 6 eigenvalues, for nonlinear molecules, will correspond to translation and rotation. (Spartan, however, doesn't show you these first eigenvalues, but other programs do.)

You can tell that eigenvalue 2 is for the symmetric stretch, since the normal coordinates for the oxygen atoms are opposite to each other (i.e -0.707 and 0.707 respectively) and the carbon atom doesn't move. In the asymmetric stretch, eigenvalue 3, the oxygen atoms move backward while the carbon atom moves forward.

How well did our simplified model work? The symmetric stretch is a little low and the asymmetric stretch is a little too high for a combined error of about 5%. It doesn't make sense to try to get the results to agree any better. We have neglected the bending vibration in our treatment, and using a molecular mechanics or molecular orbital program is much more accurate. However, you should try changing the force constant guesses a little to see the effects of each force constant. If you make a change that is not consistent with the force field in a real molecule, then the first eigenvalue will increase. Better sets of guesses give a smaller first eigenvalue.

Normal Mode Analysis and Molecular Mechanics and Molecular Orbital Calculations

Our simple example of CO_2 is not representative of the accuracy available for predicting normal mode frequencies. Molecular mechanics and molecular orbital calculations can quite accurately predict the frequencies for the vibrations of complex molecules. Results for CO_2 are given in Table I. If you haven't gotten to molecular orbital theory yet, suffice it to say that you can calculate normal mode frequencies quite accurately.^{8,9}

Table I. Molecular Mechanics and Molecular Orbital Based Normal Mode Analysis for CO_2 .

Literature	MMFF	AM1	PM3	HF/ 6-31G*	MP2/ 6-311G**	pBP/DN*	BP/DN*	B3LYP/ 6-311G(d)
667	538	526	522	744	656	637	638	666
667	538	526	523	744	656	637	638	666
1340	912	1480	1408	1518	1344	1323	1319	1377
2349	1746	2565	2387	2585	2461	2363	2349	2438
error %	24.1%	15.5%	12.5%	11.6%	2.1%	2.7%	2.5%	1.7%

The MMFF molecular mechanics calculation poorly represents the accuracy for molecular mechanics in general, since the force field parameters aren't optimized for the unusual C=O bonds in CO_2 . Molecular mechanics calculations are common and very useful for large biomolecules. Semi-empirical calculations at the AM1 or PM3 level are more accurate. Hartree-Fock, HF, calculations are even better, especially when MP2 electron-electron correlations are taken into account. Density functional methods like pBP, BP or B3LYP are now the best choice for careful analysis. Molecular orbital calculations are indispensable for helping to assign the vibration bands in Infrared and Raman spectroscopy.

Anharmonicity

The proceeding discussions assume all the vibrations are purely harmonic. Our treatment of molecular mechanics force fields showed that anharmonic corrections are often important for real molecules. What is the effect of anharmonicity on vibrational spectra and normal mode calculations? For weak anharmonicity, vibrational spectra also show overtones and sum and difference bands. Overtones are at integer multiples of the fundamental frequency, $n\tilde{\nu}_A$. Sum and difference bands occur at $\tilde{\nu}_A + \tilde{\nu}_B$, and $\tilde{\nu}_A - \tilde{\nu}_B$, respectively. Frequencies from *ab initio* molecular orbital calculations are normally multiplied by 0.9 to correct for anharmonicity. In Table I, if the HF/6-31G* values are multiplied by 0.9, the average deviation drops to 1%. Frequencies from molecular mechanics are usually too approximate to warrant anharmonicity corrections when comparing with vibrational spectra.

For strong anharmonicity, such as occurs for very loose and floppy vibrations, a more refined treatment is necessary.¹⁰ Such vibrations include bond torsions that have low energy barriers, ring vibrations in large ring systems, and vibrations in hydrogen-bonded systems and molecular complexes. Unfortunately, such vibrations are often the most interesting, especially in studies of proteins and nucleic acids. Treating very flexible, low energy vibrations in biomolecules is an active area of current study.¹¹⁻¹⁵

Vibrations and Thermodynamics

Vibrations increase the Gibbs Free Energy of a substance. Vibrational enthalpy and entropy calculations are very useful in drug discovery for assessing the Gibbs Free Energy of binding.¹⁶ Vibrations also play a central role in protein folding and protein flexibility.¹³⁻¹⁵ The contribution of a vibration to the enthalpy and entropy of a substance is given by¹⁷

$$H_{\text{vib}} = \frac{1}{2} N_A h \nu_0 + \frac{N_A h \nu_0 e^{-h\nu_0/kT}}{1 - e^{-h\nu_0/kT}} \quad (35)$$

$$S_{\text{vib}} = -R \ln(1 - e^{-h\nu_0/kT}) + \frac{N_A h \nu_0 e^{-h\nu_0/kT}}{T (1 - e^{-h\nu_0/kT})} \quad (36)$$

where N_A is Avogadro's number, ν_0 is the frequency of the normal mode, h is Planck's constant, and k is Boltzmann's constant $= R/N_A$. The $\frac{1}{2} N_A h \nu_0$ term in the enthalpy is the zero-point vibrational energy, which is the energy of the vibration at absolute zero temperature, $H_{\text{vib}}(0)$. Eqs 35 and 36 are summed for each normal mode vibration. Following a normal mode analysis, then, it is very easy to calculate the Gibbs Free Energy of a substance.

A specific example will help to clarify the importance of normal mode analysis in thermodynamic considerations. Consider two different conformations of a molecule, A and B:



Examples include the trans and gauche isomers of butane or two conformations of a large protein. For low frequency vibrations Eq 36 simplifies and the entropy difference reduces to¹³

$$\Delta S_{\text{vib,conf}} = R \ln \left(\frac{2\pi\nu_{A1} 2\pi\nu_{A2} 2\pi\nu_{A3} \dots}{2\pi\nu_{B1} 2\pi\nu_{B2} 2\pi\nu_{B3} \dots} \right) \quad (38)$$

This entropy difference is called the configurational entropy difference. The numerator is the product of the low frequency normal modes for A, and the denominator is the product of the low frequency normal modes for B. Therefore, if B has lower frequency modes, the entropy of B will be larger and the entropy difference will favor B. In other words, the lower the mode frequencies, the more the conformation can rattle around, and the more that conformation is favored.

In molecular mechanics the enthalpy of formation of a molecule is given as (see Section 2: "Enthalpy of Formation"):

$$\Delta_f H^\circ = \frac{3}{2} RT + \frac{3}{2} RT + RT + \text{bond energy} + \text{steric energy} + \text{vibrational contributions} \quad (41)$$

Normal mode analysis gives us the tools to calculate the vibrational contributions directly using Eq 35. However, as mentioned in Section 2, for MM2 calculations a series of approximations are made for Eq 41. The zero point energy is often neglected in classical simulations, leaving the temperature dependent contribution from the second term of the vibrational enthalpy, Eq 35. This contribution to the enthalpy is plotted as a function of vibrational frequency in Figure 5.

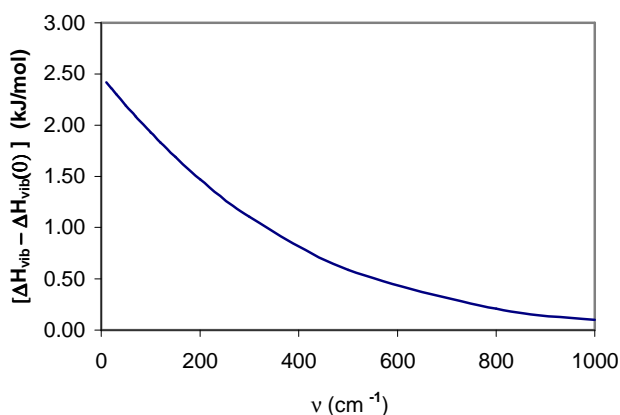


Figure 5. Contribution of a vibration to the Enthalpy of formation of a molecule, above the zero point energy, at 298K.

The contribution of vibrations becomes negligible for frequencies greater than about 500 cm^{-1} . Therefore, only low frequency vibrations contribute strongly. Torsional motions around freely rotating bonds are often the lowest frequency normal modes in molecules. Other low frequency vibrations are often ignored. The vibrational contributions can then be approximated by torsional increments for each freely rotating bond, giving the result presented in Section 2:

$$\Delta_f H^\circ = \frac{3}{2}RT + \frac{3}{2}RT + RT + \text{bond energy} + \text{steric energy} + \text{torsional increments} \quad (42)$$

Our treatment of normal modes now will allow us to discuss these approximations in detail. Examples of low frequency vibrations are bending vibrations and ring vibrations as well as freely rotating bond torsions. Clearly for careful calculations more contributions than just the torsional increments for freely rotating bonds are necessary. In addition, Eq 42 completely neglects the zero point energies. Molecular orbital and molecular mechanics programs readily provide these thermodynamic contributions when normal mode analyses are done, so we don't need to make the extreme approximations inherent in Eq 42.

Molecular Dynamics and Normal Mode Analysis

Molecular dynamics and normal mode analysis are really quite similar. Both include the kinetic and potential energy for the molecule. The force field is the same. They both calculate the Hessian and then integrate Newton's Laws of motion. The motions that you see in molecular dynamics simulations are in fact the normal modes of the molecule. The fluctuations of the atom positions in a molecular dynamics run can be used to extract the normal mode frequencies.^{14,18}

The difference between molecular dynamics and normal mode analysis is that the equations of motion are integrated numerically in dynamics simulations, but sinusoidal solutions are assumed for normal mode analysis. In addition, in molecular dynamics the motions of all the normal modes are studied simultaneously, while in normal mode analysis one mode is studied at a time. The techniques have their strengths and weaknesses. Eqns 35 and 36 show that the link between normal mode analysis and thermodynamics is direct and straightforward. Thermodynamic properties can be calculated from dynamics runs, but particular care must be taken to ensure adequate statistical sampling (i.e. using long time simulations). On the other hand, molecular dynamics more easily handles anharmonicity and explicit solvation.

Valence Force Field Solutions

Normal mode analysis is particularly important in molecular spectroscopy. As a consequence, valence force field solutions have been worked out for many small molecule geometries. These solutions take a different approach to the problem. The force constants that are used are the force constants for individual bonds, rather than the force constants for moving atoms, e.g. Eq 9. Focussing on the bond force constants more closely corresponds to our “chemical intuition.” Another advantage of valence force field calculations is that algebraic solutions can be written. For example, for a symmetric triatomic molecule, where $m_1 = m_3$, the internal coordinates are defined as

$$\begin{aligned} q_1 &= r_{12} - r_o \\ q_2 &= r_{23} - r_o \\ \delta &= \theta - \theta_o \end{aligned} \quad (43)$$

The q 's are bond stretching terms and δ is the bond bending term; r_{12} is the distance between atoms 1 and 2, r_o is the equilibrium bond length, θ is the bond angle, and θ_o is the equilibrium bond angle. The potential energy is chosen as:

$$V = \frac{1}{2} k_1 q_1^2 + \frac{1}{2} k_1 q_2^2 + k_\delta \delta^2 \quad (44)$$

The k_1 force constant is for stretching the 1-2 or 2-3 bond. For CO_2 this is the C=O stretch. The force constant for bond bending is k_δ . The Hessian second derivatives can be obtained by taking explicit derivatives of Eq 44. For this potential energy form the normal mode frequencies are given by^{3,4}

$$4\pi^2 v_{\text{asym}}^2 = \left(1 + \frac{2m_1}{m_2} \sin^2 \frac{\theta_o}{2} \right) \frac{k_1}{m_1} \quad (45)$$

$$4\pi^2 (v_{\text{sym}}^2 + v_{\text{bnd}}^2) = \left(1 + \frac{2m_1}{m_2} \cos^2 \frac{\theta_o}{2} \right) \frac{k_1}{m_1} + \frac{2}{m_1} \left(1 + \frac{2m_1}{m_2} \sin^2 \frac{\theta_o}{2} \right) \frac{k_\delta}{r_o^2} \quad (46)$$

$$16\pi^4 (v_{\text{sym}}^2 v_{\text{bnd}}^2) = 2 \left(1 + \frac{2m_1}{m_2} \right) \frac{k_1}{m_1^2} \frac{k_\delta}{r_o^2} \quad (47)$$

Eqs 46 and 47 show that the frequency of the symmetric stretch depends on the bending force constant. As mentioned above, our example for one-dimensional CO_2 didn't include this effect.

The disadvantage of algebraic solutions is that they depend critically on the details of the potential energy function, e.g. Eq 44. If a stretch-bend interaction or Van der Waals terms are included, as in many molecular mechanics force fields, then Eqs 45-47 are no longer valid. In the early decades of vibrational spectroscopy, it was hoped that solutions to the normal mode problem could be used to determine the force constants for individual bonds, as in Eq 44. However, the dependence of the force constants on such over-simplified potential energy functions causes large errors. The attempt to determine bond force constants directly from spectra has therefore been abandoned. Equations such as 45-47 can still be useful in building our intuition about bond strengths, however the derived force constants must be treated as very approximate and can sometimes be misleading.

Appendix

We wish to show more clearly the relationship between Eqs 17-19 and the normal coordinates, for the curious. First note that substituting Eq 5 into Eq 7 gives:

$$-4\pi^2 v^2 m A \sin(2\pi vt) = -k A \sin(2\pi vt) \quad (48)$$

Dividing both sides by the sin gives

$$-4\pi^2 v^2 m A = -k A \quad (49)$$

In other words, the equation applies to the time dependence of the vibration and also to the amplitude of the vibration separately. Therefore Eqs 12-14 and 17-19 allow us to solve for the amplitudes of the vibrations, where x_i, y_i, z_i can be read as the amplitudes of the waves in the x, y, and z directions for atom i. Similarly, $\tilde{x}_i, \tilde{y}_i, \tilde{z}_i$ can be considered to be the corresponding mass weighted amplitudes. The time dependent values are then:

$$\tilde{x}_i(t) = \tilde{x}_i \sin(2\pi vt) \quad \tilde{y}_i(t) = \tilde{y}_i \sin(2\pi vt) \quad \tilde{z}_i(t) = \tilde{z}_i \sin(2\pi vt) \quad (50)$$

Dropping the "(t)" for convenience and converting back into non-mass weighted coordinates gives:

$$x_i = \frac{\tilde{x}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad y_i = \frac{\tilde{y}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad z_i = \frac{\tilde{z}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad (51)$$

Converting from extensions into final coordinates using Eq 8 gives Eq 33.

Now you may have noted that Eqs 17-19 involve four unknowns ($v, \tilde{x}_i, \tilde{y}_i, \text{ and } \tilde{z}_i$) but only three equations. So to obtain unique solutions, some more information is necessary. We must add the requirement that the center of mass can't move:

$$m_1 x_1 + m_2 x_2 + m_3 x_3 = 0 \quad (52)$$

or equivalently in mass weighted coordinates:

$$\sqrt{m_1} \tilde{x}_1 + \sqrt{m_2} \tilde{x}_2 + \sqrt{m_3} \tilde{x}_3 = 0 \quad (53)$$

As we solve for each successive normal mode we also need to ensure that the vibrations don't interact. Mathematically this requires that the normal modes are orthogonal. For each pair of normal modes A and B, with normal coordinates \tilde{x}_{iA} and \tilde{x}_{iB} , respectively:

$$\tilde{x}_{1A} \tilde{x}_{1B} + \tilde{x}_{2A} \tilde{x}_{2B} + \tilde{x}_{3A} \tilde{x}_{3B} = 0 \quad (54)$$

Taken together, Eqs 17-19 and Eq 53 and 54 provide the unique set of normal modes satisfying the desired characteristics set out in the introduction. Solving these equations as a linear set of simultaneous equations is difficult. Luckily, solving the problem as an eigenvalue-eigenvector equation using Eq 21 automatically satisfies the requirement for orthogonality.

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Section 10

Partial Atomic Charges

No issue in molecular mechanics is more problematic or contentious than the determination of partial atomic charges. Atomic charges enter the force field through the Coulomb potential (see Section 1 Eq. 9)

$$E_{qq,ij} = \frac{k Q_i Q_j}{4\pi\epsilon r_{ij}} \quad 1$$

Partial atomic charges also are critical in continuum electrostatic solvation treatments. Partial atomic charges assigned by different methods and force fields vary widely. Most force fields assign charges based on tabular values. Molecular orbital treatments calculate partial atomic charges using several different charge models. To appreciate the problem, Table 1 lists the charges assigned by force fields or calculated by molecular orbital methods for the chlorines in 1,1,1-trichloroethane. Chemical intuition would argue that the Cl partial charges should be rather negative. The table shows that even the sign of the partial charge on Cl, a very electronegative atom, is in dispute.

Table 1. Partial atomic charge on Cl in 1,1,1-trichloroethane. The force field based charges are derived from MOE, the semi-empirical charges are from MOPAC, the *ab initio* charges are from Spartan, and the DFT and AMBER charges are from Gaussian.

Level	Method	Phase	Cl Charge
MMFF94	Tabular, empirical	gas	-0.290
CHARMM2.2	Tabular, empirical	aq	-0.153
OPLS	Tabular, empirical	aq	-0.154
AMBER (6-31G(d))	ESP(Merz-Kollman/Singh)	gas	0.016
AM1	Mulliken	gas	-0.049
PM3	Mulliken	gas	0.014
PM3-ESP	ESP	gas	-0.09
3-21G(*)	Mulliken	gas	0.06
3-21G(*)-ESP	ESP	gas	-0.14
6-31G*	Mulliken	gas	0.03
6-31G*-ESP	ESP	gas	-0.14
DFT (B3LYP/6-31G(d))	ESP	gas	-0.029
Gasteiger, PEOE	Empirical	gas	-0.084

So what's the problem? Why are partial charges so hard to calculate? The problem is that while partial atomic charges are very intuitive, they don't really exist. Partial charges are simply models of the true electrostatic potential energy in molecules. The partial charge is an effective charge placed on the nucleus of each atom that approximates the electrostatic potential around the molecule. In real molecules the electrostatic potential energy is determined by the localized positive charges on the nuclei and the very delocalized negative charge of the electrons as they occupy their molecular orbitals. Therefore, partial charges cannot be determined experimentally. There is no model possible that uniquely determines the best set of partial charges¹.

Molecular Orbital Partial Charge Methods

There are two general ways to calculate partial charges from molecular orbital calculations, population analysis and electrostatic potential fit (ESP) calculations. The Mulliken procedure is the most common population analysis technique. In population analysis, the electrons in each molecular orbital are partitioned to each atom based on the probability that the electron is in an orbital on that atom. At the end of the calculation the fractional occupation for each molecular orbital is summed to get a total atomic electron population for each atom. As can be seen from Table 1, Mulliken population analysis can give results that are "unintuitive." That is, since there is no unique method for calculating partial charge, we can't say that the Mulliken values are wrong, we can simply state that in some circumstances the Mulliken values don't look like they will be useful. As an alternative, the careful analysis of electrostatic interactions can be used.

In molecular orbital calculations, the electrostatic potential field of a molecule is determined by moving a positive test charge around the molecule and calculating the potential energy of interaction based on the molecular orbitals. Electrostatic potential fits assume that the real electrostatic field of the molecule can be modeled by partial charges placed on each nucleus. The fitting procedure uses a least squares approach to adjust the partial charges to get the best agreement with the molecular orbital-based electrostatic potential field. ESP calculations usually give results that are in agreement with chemical intuition, Table 1.

Unlike other force fields, AMBER was designed to use explicit molecular orbital calculations to derive charges instead of tabular values.² The charges in AMBER are to be calculated for each specific problem at the HF 6-31G* level using a modified ESP procedure (In Gaussian Pop=MK). However, the results in Table 1 show that sometimes the modified ESP procedure used for AMBER charges can give "unintuitive" results, similar to Mulliken population analysis. AMBER has been very successful for studies on proteins. This ESP based approach is awkward to implement in a general-purpose program because it requires a preliminary molecular orbital calculation. General-purpose programs get around this problem by supplying a table of charges. MOE uses PEOE charges for AMBER by default.

Partial Equalization of Orbital Electronegativity (PEOE)

The calculation of ESP based partial charges is very time intensive. Many authors have developed empirical procedures that seek to reproduce molecular orbital based charges but in a much shorter period of time. In addition, like ESP calculations, a measure of partial charge that is not entangled in the details of a specific force field is also desirable. The most popular of these techniques is called Partial Equalization of Orbital Electronegativity (PEOE) or the Gasteiger method.³ One of the important failings of any tabular based approach is that the assigned charges will not be sensitive to the molecular environment of the atoms in a given functional group. The PEOE method was designed to take the molecular environment into account by allowing atoms many bonds apart to influence each other. PEOE charges are very popular and are widely used as QSAR descriptors.

In General Chemistry, the electronegativity of an atom is taken as fixed. However, shouldn't the electronegativity, the "hungriness of an atom for electrons", vary as electron density is donated to or withdrawn from an atom in polar covalent bonds? Shouldn't electronegativity also depend on the hybridization of the atom? The answer to both of these questions is yes. The basic model in PEOE is that the electronegativity of an atom i for valance v is charge dependent:

$$\chi_{iv}(q) = a_{iv} + b_{iv} Q + c_{iv} Q^2 \quad 2$$

where a_{iV} is the electronegativity of the neutral atom, while b_{iV} and c_{iV} are fit coefficients to reproduce the experimental values of the electronegativity for positive ions ($Q = +1$) and negative ions ($Q = -1$). For example, the electronegativity for an sp^3 hybridized carbon is:

$$\chi^{C(sp^3)} = 7.98 + 9.18 Q + 1.88 Q^2 \quad 3$$

and for an sp^2 carbon:

$$\chi^{C(sp^2)} = 8.79 + 9.32 Q + 1.51 Q^2 \quad 4$$

In other words a carbon with a positive partial charge is more electronegative than a neutral carbon. Also sp^2 hybridized carbons are more electronegative than sp^3 . The units of electronegativity in Eqs. 3 and 4 are in kcal/mol and are not scaled to match the Pauling scale of 4 for fluorine.

The tug-of-war for electrons between atoms in polar covalent bonds will tend to equalize the electronegativity of the two interacting atoms. For example, in a C=O bond, the O will withdraw electron density from the C. A partial positive charge will develop on the C and a negative charge on the O. The positive charge on the C will increase the electronegativity of the C making it harder for the O atom to withdraw more electron density, while the negative charge on the O will decrease its electronegativity making the O less capable of attracting more electron density. At first it was expected that the final charges would equalize the electronegativity on the two atoms. In other words both atoms would end up with the same electronegativity so there would be no impetus for further transfer of electrons. However, it was found that this complete equalization overestimates the charges. Complete equalization of electronegativity overlooks the parallel changes in the size of the atomic orbitals and their overlap.

The key to the PEOE approach is to calculate in an iterative way the final charge on each atom based on the partial equalization of electronegativity. The method is designed to correlate with experimental measurements that depend on charge and Mulliken population analysis. In the first iteration the charge transferred between two atoms i and j is

$$q = \frac{\chi_i - \chi_i^+}{\chi_j^+} \left(\frac{1}{2}\right) \quad 5$$

where we assume that i is more electronegative than j and χ_j^+ is the electronegativity of the positive ion of j . The factor of $1/2$ is called the damping factor, which prevents the total equalization. The electronegativities of the atoms are then recalculated with the new charge. In the second iteration the additional charge transferred is calculated from

$$q = \frac{\chi_i - \chi_i}{\chi_j^+} \left(\frac{1}{2}\right)^2 \quad 5$$

This time the damping factor is increased to $1/4$ dampen the transfer of electrons even more. This process is continued for five total iterations, each time decreasing the damping factor by another factor of two. For iteration α the additional charge transferred is calculated as

$$q = \frac{\chi_i - \chi_i}{\chi_j^+} \left(\frac{1}{2}\right)^\alpha \quad 6$$

This procedure is done at each iteration for all atoms bonded to the atom of interest. Each iteration brings in the influence of all atoms one bond further away. So after five iterations atoms five bonds apart have an influence on each other. The principle advantage of the PEOE procedure is this ability to more fully take into account the bonding environment of an atom. Another important advantage is speed. PEOE charges correlate well with chemical intuition, see Table 1 and Figure 1 for examples. PEOE charges are a big improvement over Mulliken based values. However, PEOE values are smaller than ESP values and the charges used in force fields like CHARMM and OPLS that are designed to be used for aqueous simulations (see below).

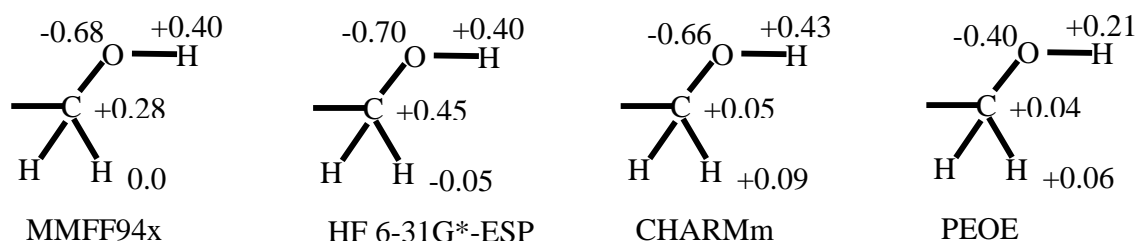


Figure 1. Partial charges for ethanol assigned by MMFF, HF 6-31G*-ESP, CHARMM, and PEOE. The methylene H's are equivalent

Aqueous Based Charges for Biomolecular Simulation

Population analysis and ESP based methods don't take intermolecular-interaction energies into account.² So not surprisingly, the Mulliken and ESP approaches fail in reproducing solvation energetics and interaction energies. Several newer force fields take a completely empirical approach based on experimental measurements of solvation energetics and careful molecular orbital (HF 6-31G* level) calculations on intermolecular interaction energies. CHARMM and OPLS force fields are examples. CHARMM and OPLS are parameterized to be useful for inclusion of solvation energetics in aqueous systems. The effect of aqueous solvation is to stabilize partial charges through charge compensation in the bulk of the solvent (see Section 8). Therefore, it is not surprising that CHARMM and OPLS based charges tend to be larger than gas phase methods. These charges, however, are not as useful for gas phase or nonaqueous solvents. These force fields are tailored to proteins and nucleic acids and are not as good at the varied functionality found in small organic molecules. For small organics MMFF excels.

The charges used in MMFF are also completely empirical and are essentially tabular in style, which once again lacks flexibility for considering through-bond environment effects.⁴ The MMFF charges are also not optimized using solvation energetics, and so are essentially gas phase.

What's a modeler to do?

OK, why is this important? Historically the first molecular mechanics calculations on proteins used partial charges calculated by Del Re based on Mulliken population analysis.^{5,6} These charges were tabulated by Del Re and widely used in a variety of programs. The charges used by some modern force fields are closely related to the original Del Re values, at least in spirit. These force fields do a good job of predicting molecular structure. However, the partial charges are not the best values for studying molecular recognition or for solvation energetics. So why not use better partial charges within these force fields? All of the parameters are interdependent in a force field. So changing the partial charge assignments will also change the optimal values for the other parameters in the force field. With altered charges, the force field may not reproduce experimental geometries well.

AMBER uses a better charge model, but requires an initial long molecular orbital calculation. Newer force fields like CHARMM and OPLS are really geared to aqueous simulations of proteins. What do you do about gas phase or nonaqueous solvents?

People will continue to argue about the best approach for years to come. Some practitioners argue that ESP or PEOE based charges should always be used in molecular mechanics and dynamics. On the other hand, Halgren, the author of MMFF, cautions that using PEOE charges with the MMFF force field will tend to underestimate intermolecular interactions and in general PEOE charges don't work well for the MMFF force field⁵. In general it is probably best to stick with the native charge assignments when doing structure studies or explicit solvation studies. However, it is probably advisable to use ESP charges for continuum dielectric solvation treatments. Donald Truhlar's recent advances in continuum solvation in the molecular orbital context are a case in point. The major differences in the various levels of theory for continuum dielectric calculations, e.g. SM5.4 versus SM3, is in the development of better partial charge models. PEOE will continue to be an important tool for QSAR studies and has the advantage of being based on an appealing intuitive model.

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