

## T6.2 Molecular Mechanics

We have seen that Benson group additivities are capable of giving heats of formation of molecules with accuracies comparable to those of the best *ab initio* procedures. However, non-quantum-mechanical procedures are not reliable for transition states or many kinds of reactive intermediates where bonding is often far from the Lewis electron-pair approximation. Nevertheless, the remarkable simplicity of group-additivity methods in comparison to any quantum mechanical procedure makes them appealing candidates for dealing with the energetics of large “normal” molecules. The principal barrier to wide application is the difficulty of dealing with angle strain and non-bonded interactions such as steric and dipole-dipole effects. The purpose of molecular mechanics is to provide a solution to this problem through, as its name implies, the use of purely mechanical models.

Given that group additivity can provide good estimates of heats of formation for strain-free molecules, what one wants to be able to estimate are the various strain contributions in any given molecular structure. These contributions are generally treated as additive, although, as we will see, it is sometimes necessary to include interaction terms.

For bond stretches and angle deformations, a minimal model could be based on Hooke's law.

$$E = \frac{1}{2}k(l - l^\circ)^2$$

$E$	= strain energy
$k$	= force constant
$l$	= bond length
$l^\circ$	= optimum bond length

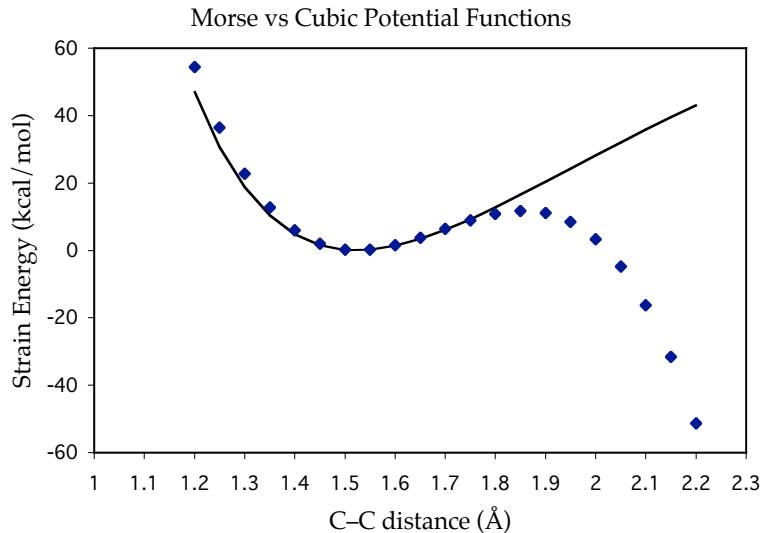
Assuming similar behavior for stretches and bends, and assuming too that the effects in different parts of a molecule are additive, one would write:

$$E_s = \frac{1}{2} \sum_i k_{si} (l_i - l_i^\circ)^2$$
$$E_\theta = \frac{1}{2} \sum_i k_{\theta i} (\theta_i - \theta_i^\circ)^2$$

However, these quadratic terms turn out not to be good enough to describe the strain energy for large displacements from the equilibrium values. It is thus common to add higher order polynomial terms to correct for anharmonicity. Even these have limited ranges of application, as the graph on the next page shows. The best empirical function for describing bond stretching over larger distances is the Morse potential:

$$E_s = D \left[ 1 + e^{-2a(l-l^\circ)} - 2e^{-a(l-l^\circ)} \right]$$

where  $D$  is the bond dissociation energy and  $a$  is an empirical parameter (often the 1 in the square brackets is omitted, in which case the energy at  $l = l^\circ$  becomes  $-D$  and that at infinity is zero; including the 1 makes the energy zero at  $l = l^\circ$  and  $+D$  at infinity).

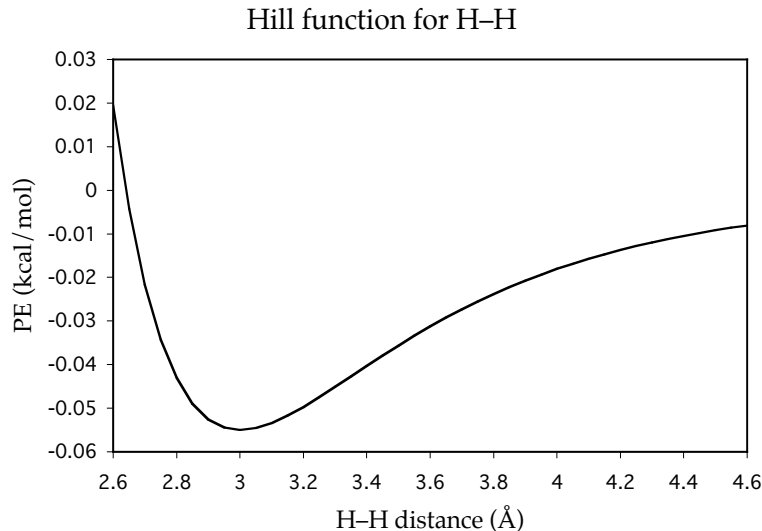


The reason that polynomial expressions are usually used in place of the Morse potential in molecular mechanics programs is that they are much faster for computers to evaluate.

Van der Waals forces are generally included for atoms that are not directly bonded (in which case they are included in the value of  $k_s$ ) or are not bonded to a common third atom (in which case they are included in the value of  $k_\theta$ ). The function that most accurately represents such forces is the Hill function:

$$E_{vdw} = \epsilon \left[ -c_1 \left( \frac{r^*}{r} \right)^6 + c_2 e^{-c_3 \frac{r^*}{r}} \right]$$

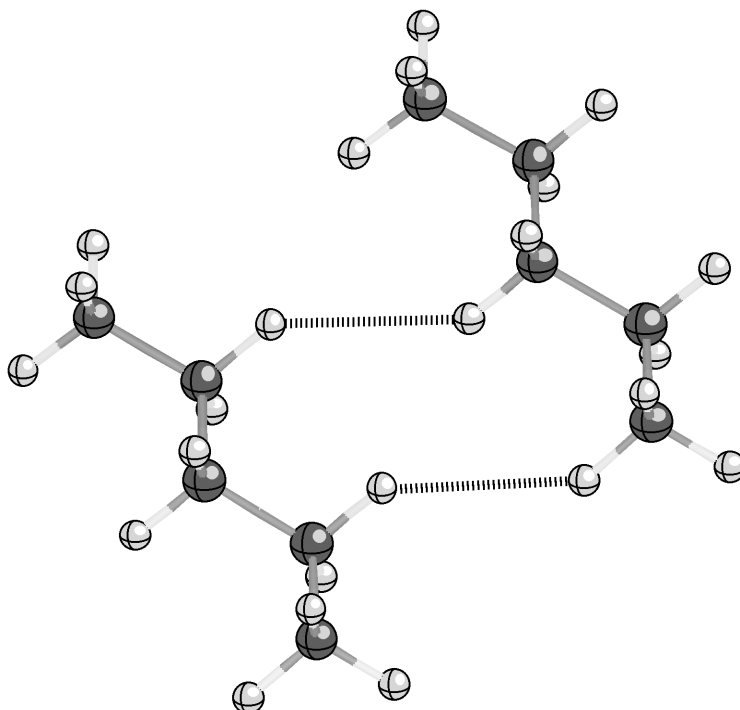
where  $c_1$ - $c_3$  are taken to be universal constants and the parameters  $\epsilon$  and  $r^*$  are atom-pair specific. The distance between the nonbonded atoms is  $r$ .



Again because of the relatively large computational cost of evaluating the exponential, the Hill function is sometimes replaced with the Leonard-Jones potential:

$$E_{vdw} = \epsilon \left[ -c_1 \left( \frac{r^*}{r} \right)^6 + c_2 \left( \frac{r^*}{r} \right)^{12} \right]$$

There is a problem with assigning sums of “standard” van der Waals radii from Pauling and Bondi to  $r^*$ . These values for the van der Waals radii came from X-ray crystallography. It was assumed that the distances of closest approach between atoms in different molecules would be the sum of their van der Waals radii.



However, this gives values for the atomic van der Waals radii that are too small, because atoms that are slightly further apart than the closest-approach pairs are in the attractive parts of their van der Waals potentials, and so they act to bring the closest-approach pairs inside their own minimum-energy distances. Because there are typically a large number of these not-quite-closest-approach atom pairs, their total effect can be quite large. Thus Pauling and Bondi thought that the van der Waals radius of hydrogen was 1.2 Å, whereas values of 1.5 Å or larger work best in molecular mechanics calculations.

Torsional contributions to the strain energy in symmetrical  $sp^3$ - $sp^3$  rotors, such as ethane, can be represented by functions such as:

$$E_{\omega} = \frac{V_0}{2} (1 + \cos 3\omega)$$

(where  $\omega$  is the dihedral angle, and  $V_0$  is the barrier height). For less symmetrical cases, the torsional potential is generally expanded in a Fourier series:

$$E_{\omega} = \frac{1}{2}[V_1(1 + \cos \omega) + V_2(1 + \cos 2\omega) + V_3(1 + \cos 3\omega) + \dots]$$

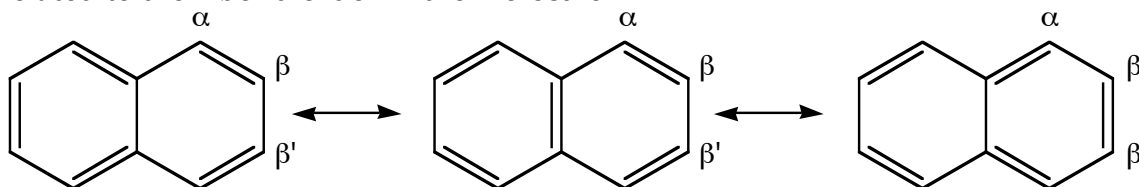
A force field consisting of a sum of the  $E_{s\theta}$ ,  $E_{\theta}$ ,  $E_{vdw}$ , and  $E_{\omega}$  terms just discussed does quite well in reproducing the structures and relative energies of relatively unstrained alkanes. However, it does not do well in reproducing the geometries and strain energies of small rings. For example, cyclobutane is predicted to have C–C bonds like those of cyclohexane (1.535 Å) and to be planar, whereas in reality it has longer C–C bonds (1.548 Å) and is puckered. In order to correct for problems of this kind, interaction terms between bond length and bond angle, and between torsion and bond angle can be introduced. They take forms such as:

$$E_{s\theta} = k_{s\theta}(l - l^{\circ})(\theta - \theta^{\circ})$$

$$E_{\omega\theta} = k_{\omega\theta}(\omega - \omega^{\circ})(\theta - \theta^{\circ})$$

A force field including these terms can correctly describe most alkanes and unconjugated alkenes and alkynes. However, another problem arises for conjugated systems. The molecular mechanics model, in treating bonds as localized mechanical objects, is in some ways like the Lewis electron-pair-bond model. Like the Lewis model, molecular mechanics has difficulty dealing with electron delocalization and its consequences for the energy and structure of molecules.

The problem can be illustrated by naphthalene, whose C–C bond lengths are related to the  $\pi$  bond order in the molecule:



One sees that the  $\alpha$ - $\beta$  bond is double in two resonance structures and single in one, whereas the  $\beta$ - $\beta'$  bond is double in one and single in two. One might consequently expect the  $\alpha$ - $\beta$  bond to have the higher bond order and to be shorter. That expectation is consistent with the experimental fact that the  $\alpha$ - $\beta$  bond length is 1.371 Å whereas the  $\beta$ - $\beta'$  bond length is 1.422 Å. This kind of phenomenon cannot be described by simple mechanical functions. Consequently, most molecular mechanics procedures get around it by doing something like a PPP calculation (effectively a HF on just the  $\pi$  electrons), and then correcting the bond length on the basis of the calculated bond order. For example, the MM2 force field uses the empirical relationship:

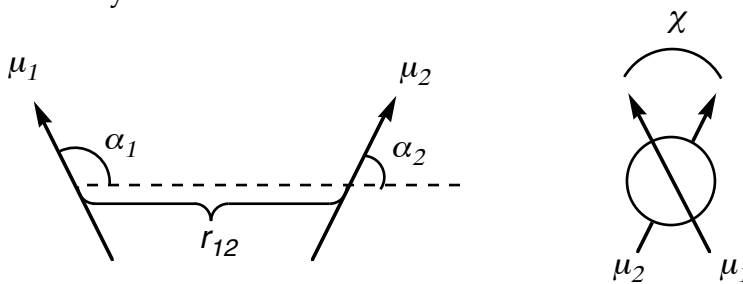
$$l_{ij} = 1.525 - 0.191\rho_{ij}$$

where  $l_{ij}$  is the length of a bond between carbons  $i$  and  $j$  and  $\rho_{ij}$  is the  $\pi$  bond order between them. An empirical correction to the calculated  $\Delta H_f^\circ$  for the molecule also has to be made on the basis of the computed  $\pi$ -electron energy.

Once heteroatoms are added, it is commonly necessary to include some method of handling dipole-dipole interactions. A typical expression is:

$$E_{\mu\mu} = c \frac{\mu_1 \mu_2}{D r_{12}^2} (\cos \chi - 3 \cos \alpha_1 \cos \alpha_2)$$

where  $c$  is a constant,  $\mu_1$  and  $\mu_2$  are the magnitudes of the two dipole moments, and  $D$  is the effective dielectric constant. The definitions of  $r_{12}$ ,  $\chi$ ,  $\alpha_1$ , and  $\alpha_2$  are shown diagrammatically below:



### The MM2 Force Field

(Allinger, N.L. *JACS* **1977**, 99, 8127)

$$E_s = 71.94 k_s (l - l^\circ)^2 [1 - 2(l - l^\circ)]$$

$$\text{C} - \text{C}: k_s = 4.4 \text{ mdyne/\AA}, l^\circ = 1.523 \text{ \AA}$$

$$\text{C} - \text{H}: k_s = 4.6 \text{ mdyne/\AA}, l^\circ = 1.113 \text{ \AA}$$

$$E_\theta = 0.02191418 k_\theta (\theta - \theta^\circ)^2 [1 + 7.0 \times 10^{-8} (\theta - \theta^\circ)^4]$$

$$E_{s\theta} = 2.51124 k_{s\theta} (\theta - \theta^\circ) [(l - l^\circ)_a + (l - l^\circ)_b]$$

(where bonds  $a$  and  $b$  are attached to a common atom with angle  $\theta$ .)

$$E_{vdw} = \epsilon (-2.25 P^6 + 2.90 \times 10^5 e^{-\frac{12.50}{P}}) \quad P = \frac{r^*}{r}$$

$$\text{C} | \text{C}: r^* = 3.80 \text{ \AA}, \epsilon = 0.044 \text{ kcal/mol}$$

$$\text{C} | \text{H}: r^* = 3.34 \text{ \AA}, \epsilon = 0.046 \text{ kcal/mol}$$

$$\text{H} | \text{H}: r^* = 3.00 \text{ \AA}, \epsilon = 0.047 \text{ kcal/mol}$$

$$E_\omega = \frac{1}{2} [V_1(1 + \cos \omega) + V_2(1 + \cos 2\omega) + V_3(1 + \cos 3\omega)]$$

$$E_{\mu\mu} = -14.388 \frac{\mu_1 \mu_2}{D r_{12}^2} (\cos \chi - 3 \cos \alpha_1 \cos \alpha_2)$$

### The MM3 Force Field

(Allinger, N.L.; Yuh, Y.H.; Lii, J.-H. *JACS* **1989**, *111*, 8551.)

$$E_s = 71.94k_s(l - l^\circ)^2[1 - 2.55(l - l^\circ) + 0.5833(l - l^\circ)^2]$$

$$E_\theta = 0.02191418k_\theta(\theta - \theta^\circ)^2[1 - 0.014(\theta - \theta^\circ) + 5.6 \times 10^{-5}(\theta - \theta^\circ)^2 - 7.0 \times 10^{-7}(\theta - \theta^\circ)^3 + 9.0 \times 10^{-10}(\theta - \theta^\circ)^4]$$

$$E_{s\theta} = 2.51118k_{s\theta}(\theta - \theta^\circ)[(l - l^\circ)_a + (l - l^\circ)_b]$$

(where bonds *a* and *b* are attached to a common atom with angle  $\theta$ .)

$$E_{s\omega} = 5.9975k_{s\omega}(l - l^\circ)(1 + \cos 3\omega) \quad (\text{where the bond length is for the } 2 - 3 \text{ bond and the torsion angle is for the } 1 - 2 - 3 - 4 \text{ dihedral.})$$

$$E_{\theta\theta'} = -0.02191418k_{\theta\theta'}(\theta - \theta^\circ)(\theta' - \theta'^\circ)$$

$$E_{vdw} = \epsilon(-2.25P^6 + 1.84 \times 10^5 e^{-\frac{12.00}{P}}) \quad P = \frac{r^*}{r}$$

$$E_\omega = \frac{1}{2}[V_1(1 + \cos \omega) + V_2(1 + \cos 2\omega) + V_3(1 + \cos 3\omega)]$$

$$E_{\mu\mu} = -14.388 \frac{\mu_1 \mu_2}{Dr_{12}^2} (\cos \chi - 3 \cos \alpha_1 \cos \alpha_2)$$

Hydrogen bonding and anomeric effects were subsequently added (Allinger, N.L.; Rahman, M.; Lii, J.-H. *JACS* **1990**, *112*, 8293.)