Molecular Mechanics

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Introduction

Molecular Mechanics uses classical type models to predict the energy of a molecule as a function of its conformation (or nuclear configuration, $\mathbf{R}$). This allows one to predict relative energies between different conformations or between different molecules, as well as equilibrium geometries and transition states, which correspond to potential energy surface local minima and first-order saddle points. This family of methods uses Taylor and Fourier series type expansions and additional terms, all of which involve empirically fitted parameters. The computational cost of molecular mechanics is the lowest of any detailed computational chemistry method.

Recall the ro-vibrational energy levels of a diatomic are given by

$$E \approx U(R_e)+h\nu_e(v+\frac{1}{2})-h\nu_e x_e(v+\frac{1}{2})^2+hB_e J(J+1)-h\alpha_e(v+\frac{1}{2})J(J+1)-h\tilde{D}_e J^2(J+1)^2+Y_{00}. \quad (1)$$

This gives the ro-vibrational energy as a function of several parameters (the *spectroscopic constants*, R_e, ν_e, $\nu_e x_e$, B_e, $\tilde{D}_e$, α_e, Y_{00}) and quantum numbers (v, J). High-resolution spectra can be fit to such expressions to deduce the spectroscopic constants.

Molecular mechanics starts with much simpler (classical) expressions for the energy as a function of nuclear coordinates, and applies to *ground states only* (does not directly account for electronic, vibrational, or rotational excitation, although the atoms can be given initial velocities). In a classical picture, there are no special quantized energy levels v and J, and we go back to a Taylor-series expansion of the potential energy as a function of nuclear coordinates. For a diatomic molecule, we have simply:

$$E(R) = U(R_e) + \frac{dE}{dR}(R-R_e) + \frac{1}{2}\frac{d^2E}{dR^2}(R-R_e)^2 + \frac{1}{3!}\frac{d^3E}{dR^3}(R-R_e)^3 + \cdots \quad (2)$$

where we have already identified the second derivative at $R = R_e$ as the harmonic oscillator force constant k, and the third derivative would be related to the anharmonic constant $\omega_e x_e$ (which includes a fourth-derivative term, also). The derivatives could therefore be treated as parameters which could be found by experiment:

$$E(R) = k_2(R - R_e)^2 + k_3(R - R_e)^3 + \cdots \tag{3}$$

where the first derivative term drops out because the expansion is about $R = R_e$, where the gradient is zero, and the arbitrary zero of energy $U(R_e)$ has been set to zero. The constants $1/n!$ have been absorbed into the k_n constants.

Of course, finding parameters like k_2, k_3, R_e from experiment is useless for modeling the diatomic! *The central idea of molecular mechanics is that these constants are* **transferrable** *to other molecules.* Most C–H bond lengths are 1.06 to 1.10 Å in just about any molecule, with stretching frequencies between 2900 and 3300 cm^{-1}. This means a C–H bond has a similar R_e and ν_e for any molecule. This strategy is refined by considering, e.g., sp^3 carbons as different from sp^2 carbons. Some example atom types are given in Fig. 1.

Molecular mechanics expresses the total energy as a sum of Taylor series expansions for *stretches* for every pair of bonded atoms, and adds additional potential energy terms coming from *bending*, *torsional energy*, *van der Waals energy*, *electrostatics*, and *cross terms*:

$$E = E_{str} + E_{bend} + E_{tors} + E_{vdw} + E_{el} + E_{cross}. \tag{4}$$

By separating out the van der Waals and electrostatic terms, molecular mechanics attempts to make the remaining constants more transferrable among molecules than they would be in a spectroscopic force field.

History

- D. H. Andrews (*Phys. Rev.*, 1930) proposed extending spectroscopic force field ideas to doing molecular mechanics
- F. H. Westheimer (1940) performed the only molecular mechanics calculation done by hand to determine the transition state of a tetrasubstituted biphenyl
- Census bureau receives first commercial supercomputer (1950)
- J. B. Hendrickson (1961) performs conformational analysis of larger than 6 membered rings
- K. B. Wiberg (1965) publishes first *general* molecular mechanics type program with ability to find energy minimum
- N. L. Allinger [*Adv. Phys. Org. Chem.* **13**, 1 (1976)] publishes the first (MM1) in a series of highly popular force fields; the second, MM2, follows in 1977
- Many other force field methods have been developed over the years

Figure 1: Atom Types for MM2

Table 2.1 MM2(91) atom types

Type	Symbol	Description	Type	Symbol	Description
1	C	sp^3-carbon	28	H	enol or amide
2	C	sp^2-carbon, alkene	48	H	ammonium
3	C	sp^2-carbon, carbonyl, imine	36	D	deuterium
4	C	sp-carbon	20	lp	lone pair
22	C	cyclopropane	15	S	sulfide (R_2S)
29	C·	radical	16	S+	sulfonium (R_3S^+)
30	C+	carbocation	17	S	sulfoxide (R_2SO)
38	C	sp^2-carbon, cyclopropene	18	S	sulfone (R_2SO_2)
50	C	sp^2-carbon, aromatic	42	S	sp^2-sulfur, thiophene
56	C	sp^3-carbon, cyclobutane	11	F	fluoride
57	C	sp^2-carbon, cyclobutene	12	Cl	chloride
58	C	carbonyl, cyclobutanone	13	Br	bromide
67	C	carbonyl, cyclopropanone	14	I	iodide
68	C	carbonyl, ketene	26	B	boron, trigonal
71	C	ketonium carbon	27	B	boron, tetrahedral
8	N	sp^3-nitrogen	19	Si	silane
9	N	sp^2-nitrogen, amide	25	P	phosphine (R_3P)
10	N	sp-nitrogen	60	P	phosphor, pentavalent
37	N	azo or pyridine (–N=)	51	He	helium
39	N+	sp^3-nitrogen, ammonium (R_4N^+)	52	Ne	neon
40	N	sp^2-nitrogen, pyrrole	53	Ar	argon
43	N	azoxy (–N=N–O)	54	Kr	krypton
45	N	azide, central atom	55	Xe	xenon
46	N	nitro ($-NO_2$)	31	Ge	germanium
72	N	imine, oxime (=N–)	32	Sn	tin
6	O	sp^3-oxygen	33	Pb	lead (R_4Pb)
7	O	sp^2-oxygen, carbonyl	34	Se	selenium
41	O	sp^2-oxygen, furan	35	Te	tellurium
47	O^-	carboxylate	59	Mg	magnesium
49	O	epoxy	61	Fe	iron(II)
69	O	amine oxide	62	Fe	iron(III)
70	O	ketonium oxygen	63	Ni	nickel(II)
5	H	hydrogen, except on N or O	64	Ni	nickel(III)
21	H	alcohol (OH)	65	Co	cobalt (II)
23	H	amine (NH)	66	Co	cobalt (III)
24	H	carboxyl (COOH)			

Note that special atom types are defined for carbon atoms involved in small rings, like cyclopropane and cyclobutane. The reason for this will be discussed in Section 2.2.2.

From Jensen's Introduction to Computational Chemistry

Stretch Energy

The stretching energy has been discussed above. The stretching potential for a bond between atoms A and B is given by the Taylor series

$$E(R^{AB}) = k_2^{AB}(R^{AB} - R_0^{AB})^2 + k_3^{AB}(R^{AB} - R_0^{AB})^3 + k_4^{AB}(R^{AB} - R_0^{AB})^4 + \cdots \tag{5}$$

and different force field methods retain different numbers of terms in this expansion. Such expansions have incorrect limiting behavior: at large distances, higher powers of $(R^{AB} - R_0^{AB})$ dominate, leading $E(R^{AB})$ to go to positive or negative infinity, depending on the sign of k_n^{AB}.

A simple function with correct limiting behavior is the Morse potential

$$E_{\mathrm{str}}(R - R_0) = D[1 - e^{\sqrt{k/2D}(R-R_0)}]^2, \tag{6}$$

where D is the dissociation energy. However, this potential gives very small restoring forces for large R and therefore causes slow convergence in geometry optimization. For this reason, the truncated polynomial expansion is usually preferred. Figure 2 compares the exact C–H stretching potential for CH_4 to a Morse potential and to second and fourth order polynomials.

Bend Energy

Bending energy potentials are usually treated very similarly to stretching potentials; the energy is assumed to increase quadratically with displacement of the bond angle from equilibrium.

$$E_{\mathrm{bend}}(\theta^{ABC} - \theta_0^{ABC}) = k^{ABC}(\theta^{ABC} - \theta_0^{ABC})^2 \tag{7}$$

An unusual thing happens for $\theta^{ABC} = 180^{\circ}$: the derivative of the potential needs to go to zero. This is sometimes enforced (Fig. 3).

The potential for moving an atom out of a plane is sometimes treated separately from bending (although it also involves bending). An out-of-plane coordinate (either χ or d) is displayed in Fig. 4). The potential is usually taken quadratic in this out-of-plane bend,

$$E_{\mathrm{bend-oop}}(\chi^B) = k^B(\chi^B)^2. \tag{8}$$

Torsional Energy

The torsional energy term attempts to capture some of the steric and electrostatic nonbonded interactions between two atoms A and D which are connected through an intermediate bond B–C

Figure 2: Stretching Potential for CH_4 (from Jensen)

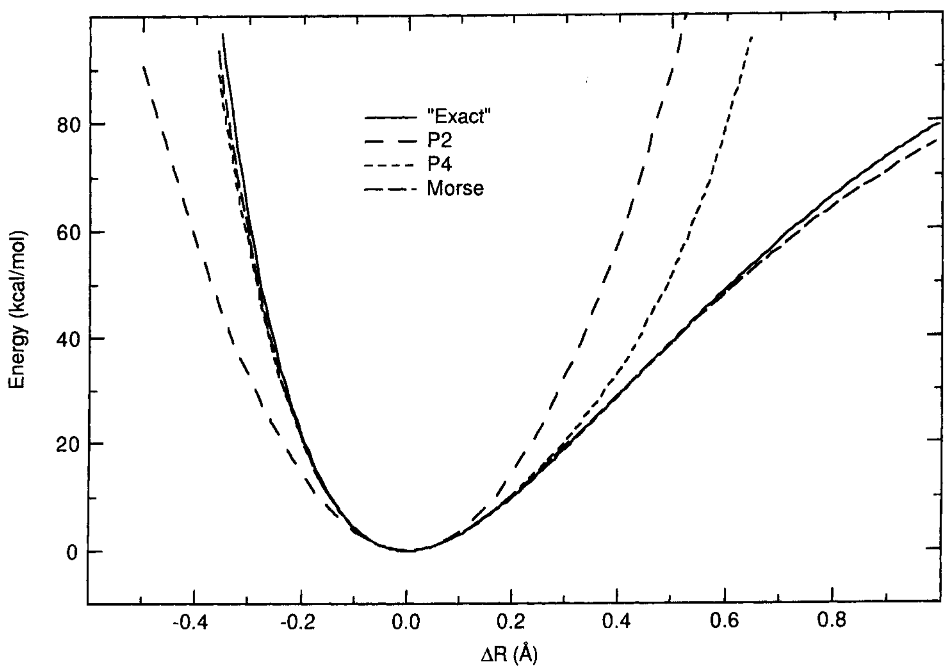

Figure 2.1 The stretch energy for CH_4

Figure 3: Bending Potential for H_2O (from Jensen)

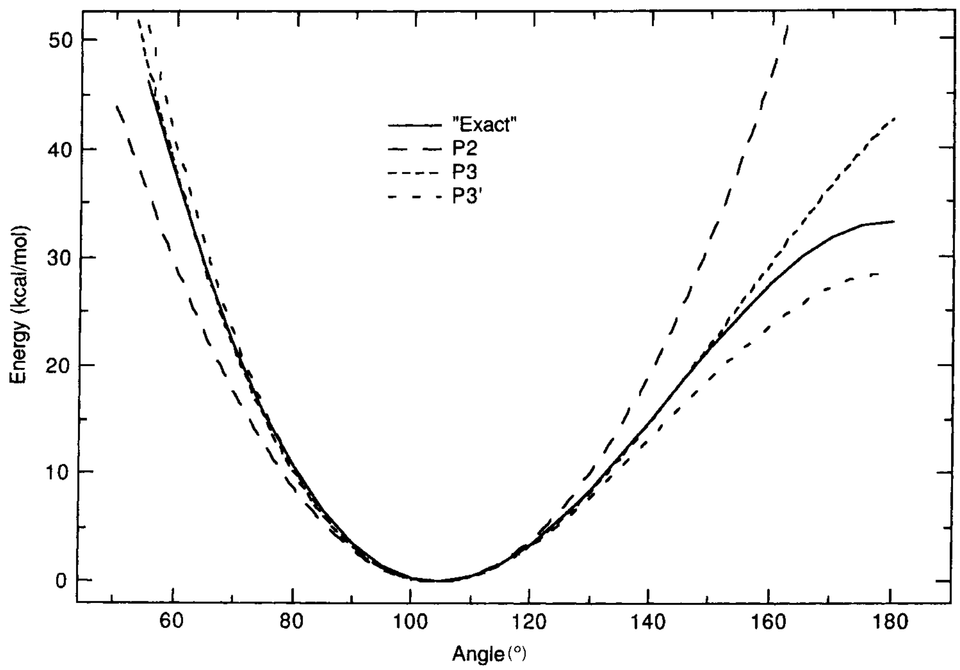

Figure 2.5 The bending energy for H_2O

Figure 4: Out-of-plane Coordinate (from Jensen)

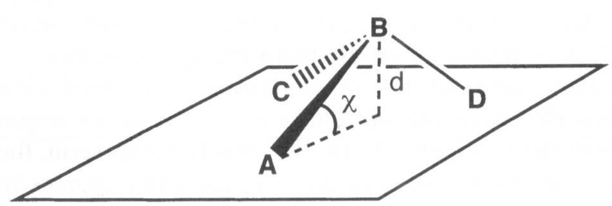

Figure 2.6 Out-of-plane variable definitions

Figure 5: Torsion Angle (from Jensen)

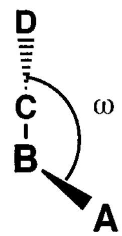

Figure 2.7 Torsional angle definition

as A–B–C–D. The torsional angle ω (also often denoted τ) is depicted in Fig. 5. It is the angle betwen the two planes defined by atoms A, B, and C and by B, C, and D.

The torsional potential is not expanded as a Taylor series because the torsional angle can go far from equilibrium. Fourier series are used instead:

$$E_{\text{tors}}(\omega^{ABCD}) = \sum_{n=1} V_n^{ABCD} cos(n\omega^{ABCD}). \tag{9}$$

Often this is rewritten to make sure the energy is non-negative, and typically the number of terms is 3 (bad for inorganic chemists who need $n = 4$ for octahedral complexes!):

$$E_{\text{tors}}(\omega^{ABCD}) = \frac{1}{2}V_1^{ABCD}[1+cos(\omega^{ABCD})]+\frac{1}{2}V_2^{ABCD}[1-cos(2\omega^{ABCD})]+\frac{1}{2}V_3^{ABCD}[1+cos(3\omega^{ABCD})]. \tag{10}$$

For a molecule like ethylene, rotation about the C=C bond must be periodic by 180^o, so only even terms $n = 2, 4, \ldots$ can occur. For a molecule like ethane, only terms $n = 3, 6, 9, \ldots$ can occur.

van der Waals Energy

The van der Waals energy arises from the interactions between electron clouds around two non-bonded atoms. At short range, this interaction is strongly repulsive, while at intermediate range, the interaction is attractive. As $R \to \infty$, the interaction of course dies off to zero. The attraction is due to *electron correlation*: a fluctuation of the electrons on one atom produces a temporary dipole which induces a complementary dipole on the other atom. The resulting attractive force is called a “dispersion” or “London” force.

van der Waals energies are usually computed for atoms which are connected by no less than

Figure 6: Example Torsional Potentials (from Jensen)

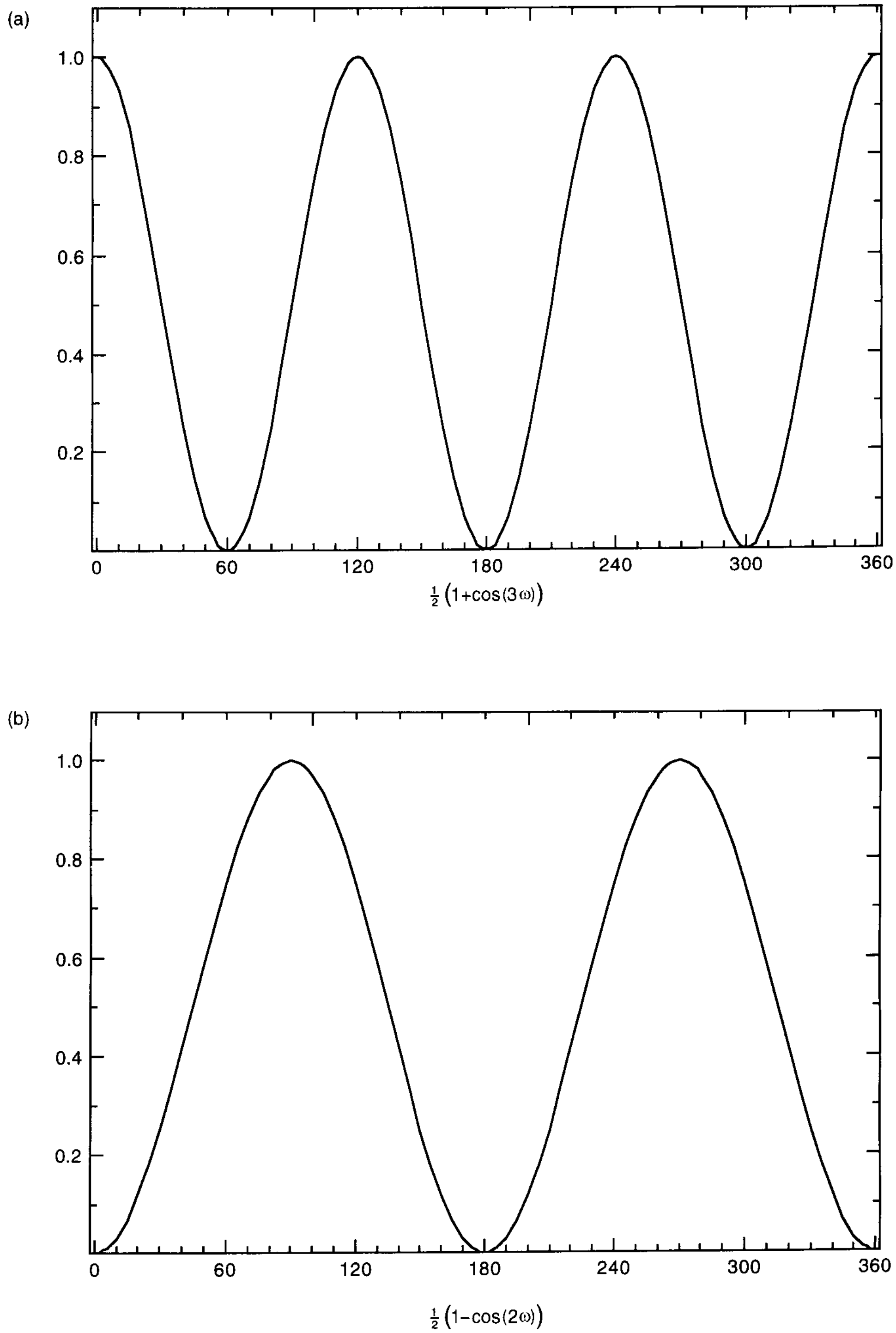

Figure 2.8 Torsional energy functions

Figure 7: Example Torsional Potential (from Jensen)

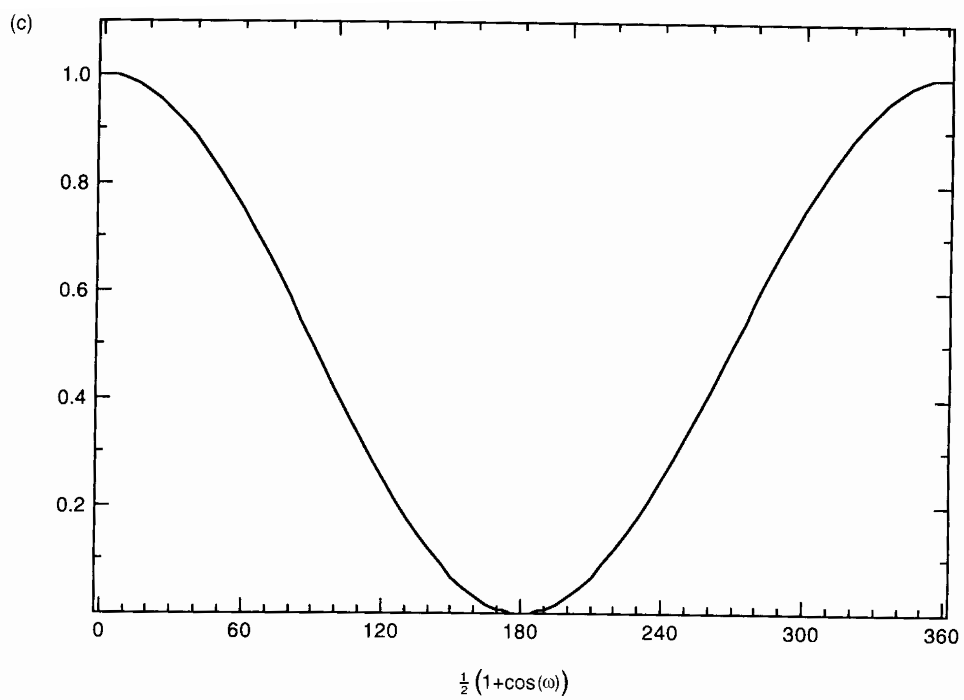

Figure 2.8 (*contd.*)

two atoms (e.g., 1-4 interactions between A and D in A-B-C-D and higher). Interactions betwen atoms closer than this are already accounted for by stretching and/or bending terms.

At intermediate to long ranges, the attraction is proportional to $1/R^6$. At short ranges, the repulsion is close to exponential. Hence, an appropriate model of the van der Waals interaction is

$$E_{\mathrm{vdw}}(R^{AB}) = Ce^{-DR} - \frac{E}{R^6}. \tag{11}$$

One technical problem with the above "Buckingham" or "Hill" potential is that it goes to negative infinity for very small R. Since the van der Walls interaction is long range, it becomes the dominant cost of a force-field computation. It can be speeded up substantially by a more economical expression, the Lennard-Jones potential

$$E_{\mathrm{vdw}}(R^{AB}) = \epsilon \left[\left(\frac{R_0}{R} \right)^{12} - 2 \left(\frac{R_0}{R} \right)^{6} \right]. \tag{12}$$

The R^{-12} term is easier to compute than the exponential because no square roots need to be taken to get R. It is also possible to use the form of a Morse potential with much smaller D and α parameters (and a larger R_0) than used for stretches. Figure 8 presents a comparison of various van der Waals potentials.

Nonbonded interactions between hydrogen and nitrogen or oxygen are much stronger (1-5 kcal/mol) than normal van der Waals interactions (0.1-0.2 kcal/mol) and can be treated by special hydrogen bonding terms.

Electrostatic Energy

Electrostatic terms describe the Coulomb interaction between atoms A and B with partial charges, according to

$$E_{\mathrm{el}}(R^{AB}) = \frac{Q^A Q^B}{\epsilon R^{AB}}, \tag{13}$$

where ϵ is an effective dialectric constant which is 1 in vacuum but higher when there are intermediate atoms or solvent. Usually ϵ is picked fairly arbitrarily; higher values or so-called "distance-dependent dialectrics" ($\epsilon = \epsilon_0 R^{AB}$) account for "screening" and kill off the electrostatic contributions faster, making them easier to compute.

Electrostatic terms are important in, e.g., carbonyls, where the carbon has a partial positive charge and oxygen is partially negative. Hydrogen bonding is also sometimes accounted for by partial charges. (Of course, quantum mechanically, it is hard to rigorously and unambiguously define an atomic charge).

Figure 8: Example van der Waals Potentials (from Jensen)

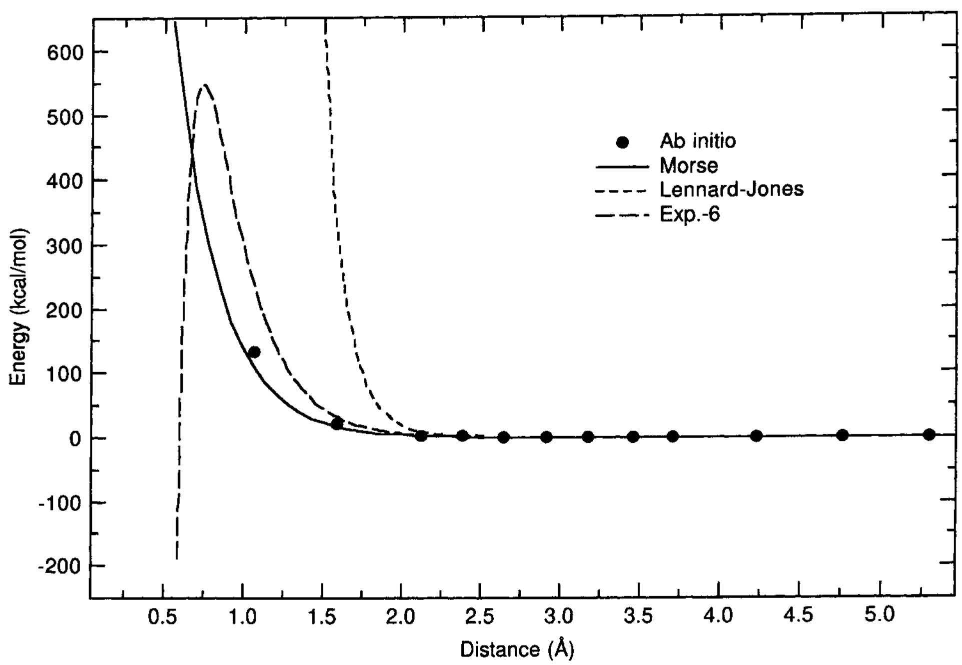

Figure 2.9 Comparison of E_{vdw} functionals for the H_2–He potential

A slightly different approach to partial charges is to consider polarized bonds as dipoles, and compute the electrostatic interaction between these dipoles (e.g., MM2 and MM3):

$$E_{\mathrm{el}}(R^{AB}) = \frac{\mu^A \mu^B}{\epsilon (R^{AB})^3} \left(cos\chi - 3\cos\alpha_A cos\alpha_B \right), \tag{14}$$

where χ is the angle between the dipoles and α_A and α_B are the angles each dipole makes with the line joining atoms A and B.

Like van der Waals terms, electrostatic terms are typically computed for nonbonded atoms in a 1,4 relationship or further apart. Like van der Waals interactions, these are also long range interactions and dominate the computation time. While the number of bonding interactions grows linearly with molecule size, the number of nonbonded interactions grows *quadratically* with molecule size. The computation time can be reduced by cutting off the interactions after a certain distance. The van der Waals terms die off relatively quickly ($\propto R^{-6}$) and can be cut off around 10 Å. The electrostatic terms die off slower ($\propto R^{-1}$, although sometimes faster in practice), and are much harder to treat with cutoffs. Economical computation of long-range terms is a challenging research area where recent progress has been made.

Cross Terms

Cross terms are required to account for some interactions affecting others. For example, a strongly bent H_2O molecule brings the two H atoms closer together than they would like; this strain can be partially alleviated by the O–H bonds stretching a little longer than normal. Hence, the bend can affect the stretch. This can be modeled by cross terms such as

$$E_{\mathrm{str/bend}} = k^{ABC}(\theta^{ABC} - \theta_0^{ABC}) \left[(R^{AB} - R_0^{AB}) + (R^{BC} - R_0^{BC}) \right] \tag{15}$$

Other cross terms might include stretch-stretch, bend-bend, stretch-torsion, bend-torsion, etc. Force field models vary in what types of cross terms they use.

Parameterizing from Experiment

It is clear that molecular mechanics requires many parameters, e.g., R_0^{AB}, k^{AB}, θ_0^{ABC}, k^{ABC}, V_n^{ABCD}, etc. The number of potential parameters is staggering — assuming there are 30 atoms which form bonds with each other, there are $30^4/2$ torsional parameters for each V_n^{ABCD} term, or 1 215 000 parameters for V_1 through V_3! Only the 2466 "most useful" torsional parameters are present in MM2, meaning that certain torsions cannot be described. Lack of parameters is a serious drawback of all force field methods. Some programs use a set of "generic" parameters when the proper ones are unavailable — this can lead to inaccurate results!

Moreover, it can be difficult to extract the necessary parameters from experiment, especially because experiment most directly probes molecules at their eqilibrium geometries. *Ab initio* electronic structure methods are being used more commonly to determine some of the parameters. Unfortunately van der Waals interactions are hard to get reliably from any but the largest *ab initio* computations, and are usually fit to experimental data for solids or liquids instead.

Obtaining parameters from experiment is not straightforward, because experiments measure subtly different things. For example, different types of experiments can give many types of bond lengths: r_a, r_g, r_0, r_z, r_s, r_e, $\cdots$.

Electron diffraction: Samples are hit with an electron beam in a vacuum, giving a diffraction pattern which is Fourier tranformed to yield an intensity vs. distance radial distribution function. Distances between pairs of atoms can be determined this way. The distance measured is r_g, the *average distance between atoms*. Older literature (around 1960 and before) used a quantity r_a which is about 0.002 Å smaller than r_g.

X-ray and neutron diffraction: Measures the distance between the average atomic positions, r_α, which is not the same as the average distance between atoms r_g. The difference between the two increases with increasing temperature.

$$\begin{array}{rl} \text{He(l)} & r_g = r_\alpha + 0.004 \text{ Å} \\ \text{N}_2\text{(l)} & r_g = r_\alpha + 0.005 \text{ Å} \\ \text{R.T.} & r_g = r_\alpha + 0.007 \text{ Å} \end{array}$$

Microwave spectroscopy: Can deduce moments of inertia from rotational levels (recall rotational constant B includes I). This only gives three pieces of data; need to use isotopic substitution to get more information. Yields distances called r_z.

High-resolution spectroscopy and ab initio theory: Can deduce the equilibrium distance r_e, defined as the bottom of the potential well. Can also get r_0, which is the *average distance* at absolute zero. Usually r_0 is very slightly larger than r_e because the potential is softer to the right.

Molecular mechanics methods typically work from r_0, but are often based on other types of data. Hence, agreement to better than a few thousandths of an Ångstrom is not possible. Likewise, it should be remembered that *ab initio* computations which provide r_e will not exactly match x-ray or electron diffraction data, etc.

Table 1: Average errors in heat of formations (kcal/mol) by MM2[a]

Compound type	Avg error ΔH_f
Hydrocarbons	0.42
Ethers and alcohols	0.50
Carbonyls	0.81
Aliphatic amines	0.46
Aromatic amines	2.90
Silanes	1.08

[a]Table 2.6 from Jensen's *Introduction to Computational Chemistry.*

Heats of Formation

ΔH_f is the heat conent relative to the elements at standard state at 25° C (g). This is a useful quantity for comparing the energies of two conformers of a molecule or two different molecules.

Bond energy schemes estimate the overall ΔH_f by adding tabulated contributions from each type of bond. This works acceptably well for strainless systems.

Molecular mechanics adds steric energy to the bond/structure increments to obtain better estimates of ΔH_f. Each bond is assigned a ΔH_f value, and corrections are added for larger groups (functional groups). The force field energy, which represents the steric energy, is added to this. Additionally, to go from bare energies to enthalpies, one needs to add PV $(=RT)$ and $(1/2)RT$ for each translational and rotational degree of freedom, for an overall enthalpy correction of $4RT$.

The bare molecular mechanics energy is not a meaningful quantity, because the zero of energy of each individual term was chosen as zero for convenience. Therefore different molecules have different zeros of energy until they are normalized by converting to ΔH_f.

In principle, other corrections should be added (but usually aren't): population increments (for low-lying conformers), torsional increments (for shallow wells), and corrections for low (<7 kcal/mol) barriers other than methyl rotation (already included in group increment).

The performance of the MM2 force field for typical molecules is given in Table 1. Overall, these results are rather good; however, unusual molecules can exhibit far larger errors.

Different Force Field Methods

There are many different force field methods. Some of these contain high order terms (e.g., quartic terms in stretching potentials) and several types of cross terms. These "Class I" force fields have higher accuracy and are generally applied to small/medium sized molecules. Examples include Allinger's MM1-4, EFF, and CFF.

For very large molecules (e.g., proteins), it is not possible to afford Class I level computations. The force field methods can be made cheaper by using only quadratic Taylor expansions and neglecting cross terms. This leads to "Class II" force field methods such as AMBER, CHARMM, GROMOS, etc. These force fields are made even cheaper by considering CH_2 units as a single "CH_2 atom."

Hybrid Force Field/Electronic Structure Methods

These methods, such as Morokuma's ONIOM method, treat "uninteresting" parts of the molecule by force field methods and "interesting" parts by high-accuracy electronic structure methods. This approach is useful for systems where part of the molecule is needed at high accuracy or for which no force field parameters exist (e.g., metal centers in metalloenzymes). The challenge of these methods is meshing the force field description with the electronic structure description. Such methods are also called "quantum mechanics/molecular mechanics" (or QM/MM) methods.