Chapter 3

Molecular Mechanics Models

This chapter describes the basis of molecular mechanics models and introduces the SYBYL and MMFF force fields. It also compares and contrasts molecular mechanics and quantum chemical models.

Introduction

Molecular mechanics describes molecules in terms of "bonded atoms", which have been distorted from some idealized geometry due to non-bonded van der Waals and Coulombic interactions.[1] This is fundamentally different from quantum chemical models, which make no reference whatsoever to chemical bonding. The success of molecular mechanics models depends on a high degree of transferability of geometrical parameters from one molecule to another, as well as predictable dependence of the parameters on atomic hybridization. For example, carbon-carbon single bond lengths generally fall in the small range from 1.45 to 1.55Å, and increase in length with increasing "p character" of the carbon hybrids. Thus, it is possible to provide a fairly accurate "guess" at molecular geometry in terms of bond lengths, bond angles and torsion angles, provided that the molecule has already been represented in terms of a particular valence structure. The majority of organic molecules fall into this category.

The molecular mechanics "energy" of a molecule is described in terms of a sum of contributions arising from distortions from "ideal" bond distances ("stretch contributions"), bond angles ("bend contributions") and torsion angles ("torsion contributions"), together with contributions due to "non-bonded" (van der Waals and Coulombic) interactions. It is commonly referred to as a "strain energy", meaning that it reflects the "strain" inherent to a "real" molecule relative to some idealized form.

$$E^{\text{strain}} = \sum_{A}^{\text{bonds}} E_{A}^{\text{stretch}} + \sum_{A}^{\text{bond angles}} E_{A}^{\text{bend}} + \sum_{A}^{\text{torsion angles}} E_{A}^{\text{torsion}} + \sum_{A}^{\text{non-bonded atoms}}\sum_{B} E_{AB}^{\text{non-bonded}} \tag{1}$$

The first three summations in equation 1 are over all “bonds”, all “bond angles” and all “torsion angles”, respectively. Thus, information about bonding is “part of the input” to a molecular mechanics calculation, in contrast to a quantum chemical calculation where it is “part of the output”. The last summation in equation 1 is over all pairs of atoms which are not bonded.

Stretch and bend terms are most simply given in terms of quadratic (“Hook’s law”) forms.

$$E^{\text{stretch}}\ (r) = \frac{1}{2}\ k^{\text{stretch}}\ (r - r^{\text{eq}})^2 \tag{2}$$

$$E^{\text{bend}}\ (\alpha) = \frac{1}{2}\ k^{\text{bend}}\ (\alpha - \alpha^{\text{eq}})^2 \tag{3}$$

r and α are the bond distance and angle, respectively, r^{eq} and α^{eq} are the “ideal” (equilibrium) bond length and bond angle, respectively, taken either from experiment or from accurate quantum chemical calculations, and k^{stretch} and k^{bend}, so-called stretch and bend “force constants”, respectively, are parameters. Molecular mechanics models may also include cubic and higher-order contributions, as well as “cross terms” to account for correlations between stretch and bend components. The degree of complexity depends on the availability of data on which to base parameters.

Proper description of the torsional potential requires a form that reflects its inherent periodicity. For example, the three-fold periodicity of rotation about the carbon-carbon bond in ethane may be described by the simple functional form.

$$E^{\text{torsion}}\ (\omega) = k^{\text{torsion3}}\ [1 - \cos 3\ (\omega - \omega^{\text{eq}})] \tag{4}$$

ω is the torsion angle, ω^{eq} is the ideal torsion angle and k^{torsion3} is treated as a parameter. Bond torsion contributions to the overall energy may also need to include terms which are one-fold and two-fold periodic.

$$E^{torsion}(\omega) = k^{torsion1}[1 - \cos(\omega - \omega^{eq})] + k^{torsion2}[1 - \cos 2(\omega - \omega^{eq})] + k^{torsion3}[1 - \cos 3(\omega - \omega^{eq})] \qquad (5)$$

$k^{torsion1}$ and $k^{torsion2}$ are additional parameters. Equation 5 is a truncated Fourier series. The one-fold term accounts for the difference in energy between *cis* (0°) and *trans* (180°) conformers, and the two-fold term accounts for the difference in energy between planar (0°, 180°) and perpendicular (90°, 270°) conformers. (Further discussion is provided in **Chapter 14**.) Molecular mechanics models may also include higher-order terms and cross terms, as well as terms to account for asymmetrical environments. As with stretch and bend components, the degree of complexity depends on the availability of data on which to base parameters.

Non-bonded interactions typically involve a sum of van der Waals (VDW) interactions and Coulombic interactions.

$$E^{non\text{-}bonded}(r) = E^{VDW}(r) + E^{Coulombic}(r) \qquad (6)$$

Additional non-bonded terms may be included to account explicitly for such interactions as hydrogen bonding.

Most commonly, van der Waals interactions are represented as a sum of a repulsive and attractive terms.

$$E^{VDW}(r) = \varepsilon\left[\left(\frac{r^o}{r}\right)^{12} - 2\left(\frac{r^o}{r}\right)^{6}\right] \qquad (7)$$

r is the non-bonded distance, and ε and r^o are parameters. This functional form provides a very steep energy barrier inside the sum of van der Waals radii for the two atoms involved, and a shallow energy well at larger separations, and as such accounts both for the inherent size requirements of atoms, as well as for weak attractive forces between separated atoms.

The Coulombic term takes account of the interaction of charges.

$$E^{Coulombic}(r) = \frac{qq'}{r} \qquad (8)$$

r is the non-bonded distance, and the atomic charges, q, may either be treated as parameters or be taken from quantum chemical calculations. The sum of atomic charges needs to be equal the total molecular charge, 0 in the case of a neutral molecule.

SYBYL and MMFF Force Fields

Molecular mechanics models differ both in the number and specific nature of the terms which they incorporate, as well as in the details of their parameterization. Taken together, functional form and parameterization, constitute what is termed a force field. Very simple force fields such as SYBYL[2], developed by Tripos, Inc., may easily be extended to diverse systems but would not be expected to yield quantitatively accurate results. On the other hand, a more complex force field such as MMFF94[3] (or more simply MMFF), developed at Merck Pharmaceuticals, while limited in scope to common organic systems and biopolymers, is better able to provide quantitative accounts of molecular geometry and conformation. Both SYBYL and MMFF are incorporated into Spartan.

Limitations of Molecular Mechanics Models

The primary advantage of molecular mechanics models (over any of the quantum chemical models described in the previous chapter) is their simplicity. Except for very small systems, computation cost is completely dominated by evaluation of non-bonded van der Waals and Coulombic terms, the number of which is given by the square of the number of atoms. However, the magnitude of these terms falls off rapidly with increasing interatomic distance and, in practice, computation cost scales linearly with molecular size for sufficiently large molecules. Molecular mechanics calculations may easily be performed on molecules comprising several thousand atoms. Additionally, molecular mechanics calculations are sufficiently rapid to permit extensive conformational searching on molecules containing upwards of 100-200 atoms. Conformational analysis is perhaps the single most important application of molecular mechanics.

The fact that molecular mechanics models are parameterized may also be seen as providing an advantage over quantum chemical models. It is possible, at least in principle, to construct molecular mechanics models which will accurately reproduce known experimental data, and hopefully will anticipate (unknown) data on closely-related systems.

There are important limitations of molecular mechanics models. First, they are limited to the description of equilibrium geometries and equilibrium conformations. Because the mechanics "strain energy" is specific to a given molecule (as a measure of how far this molecule deviates from its "ideal arrangement"), strain energies cannot be used in thermochemical calculations. Two important exceptions are calculations involving isomers with exactly the same bonding, e.g., comparison of *cis* and *trans*-2-butene, and conformational energy comparisons, where different conformers necessarily have exactly the same bonding.

Second, molecular mechanics calculations reveal nothing about bonding or, more generally, about electron distributions in molecules. As will become evident later, information about electron distributions is key to modeling chemical reactivity and selectivity. There are, however, important situations where purely steric effects are responsible for trends in reactivity and selectivity, and here molecular mechanics would be expected to be of some value.

Third, currently available force fields have not been parameterized to handle non-equilibrium forms, in particular, reaction transition states. Note, however, that there is no fundamental reason why this could not be done (using results from quantum chemical calculations rather than experiment as a basis for parameterization).

Finally, it needs to be noted that molecular mechanics is essentially an interpolation scheme, the success of which depends not only on good parameters, but also on systematics among related molecules. Molecular mechanics models would not be expected to be highly successful in describing the structures and conformations of "new" (unfamiliar) molecules outside the range of parameterization.

References

1. Reviews: (a) U. Burkert and N.L. Allinger, ***Molecular Mechanics***, ACS Monograph no. 177, American Chemical Society, Washington D.C., 1982; (b) A.K. Rappe´ and C.J. Casewit, ***Molecular Mechanics Across Chemistry***, University Science Books, Sausalito, CA, 1997.
2. M. Clark, R.D. Cramer III and N. van Opdensch, *J. Computational Chem.,* **10**, 982 (1989).
3. T.A. Halgren, *J. Computational Chem*., **17**, 490 (1996), and following papers in this issue. Two different variations of MMFF have been published. The default choice in Spartan is the one in which nitrogen attached to an unsaturated carbon, e.g., the nitrogen in aniline, is allowed to pucker. The other variation assumes that the nitrogen attached to unsaturated carbon is planar.