

2

Molecular Mechanics

2.1 History and Fundamental Assumptions

Let us return to the concept of the PES as described in Chapter 1. To a computational chemist, the PES is a surface that can be generated point by point by use of some computational method which determines a molecular energy for each point's structure. However, the concept of the PES predates any serious efforts to "compute" such surfaces. The first PESs (or slices thereof) were constructed by molecular spectroscopists.

A heterodiatomic molecule represents the simplest case for study by vibrational spectroscopy, and it also represents the simplest PES, since there is only the single degree of freedom, the bond length. Vibrational spectroscopy measures the energy separations between different vibrational levels, which are quantized. Most chemistry students are familiar with the simplest kind of vibrational spectroscopy, where allowed transitions from the vibrational ground state ($\nu = 0$) to the first vibrationally excited state ($\nu = 1$) are monitored by absorption spectroscopy; the typical photon energy for the excitation falls in the infrared region of the optical spectrum. More sensitive experimental apparatus are capable of observing other allowed absorptions (or emissions) between more highly excited vibrational states, and/or forbidden transitions between states differing by more than 1 vibrational quantum number. Isotopic substitution perturbs the vibrational energy levels by changing the reduced mass of the molecule, so the number of vibrational transitions that can be observed is arithmetically related to the number of different isotopomers that can be studied. Taking all of these data together, spectroscopists are able to construct an extensive ladder of vibrational energy levels to a very high degree of accuracy (tenths of a wavenumber in favorable cases), as illustrated in Figure 2.1.

The spacings between the various vibrational energy levels depend on the potential energy associated with bond stretching (see Section 9.3.2). The data from the spectroscopic experiments thus permit the derivation of that potential energy function in a straightforward way.

Let us consider for the moment the potential energy function in an abstract form. A useful potential energy function for a bond between atoms A and B should have an analytic form. Moreover, it should be continuously differentiable. Finally, assuming the dissociation energy for the bond to be positive, we will define the minimum of the function to have a potential energy of zero; we will call the bond length at the minimum r_{eq} . We can determine the value

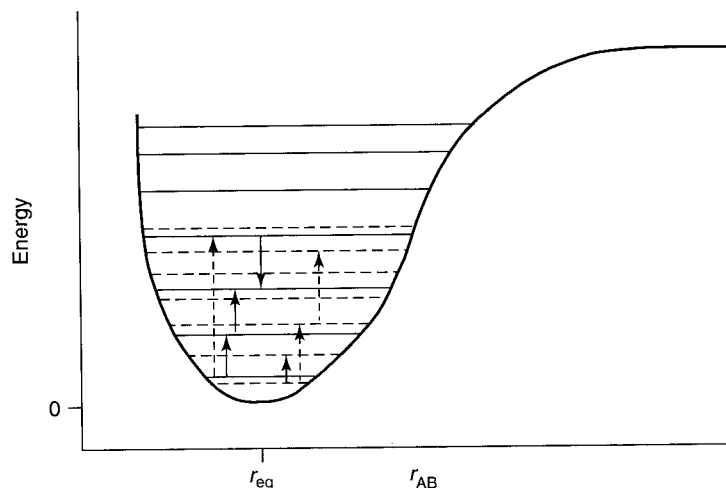


Figure 2.1 The first seven vibrational energy levels for a lighter (solid horizontal lines) and heavier (horizontal dashed lines) isotopomer of diatomic AB. Allowed vibrational transitions are indicated by solid vertical arrows, forbidden transitions are indicated by dashed vertical arrows

of the potential energy at an arbitrary point by taking a Taylor expansion about r_{eq}

$$U(r) = U(r_{eq}) + \left. \frac{dU}{dr} \right|_{r=r_{eq}} (r - r_{eq}) + \frac{1}{2!} \left. \frac{d^2U}{dr^2} \right|_{r=r_{eq}} (r - r_{eq})^2 + \frac{1}{3!} \left. \frac{d^3U}{dr^3} \right|_{r=r_{eq}} (r - r_{eq})^3 + \dots \quad (2.1)$$

Note that the first two terms on the r.h.s. of Eq. (2.1) are zero, the first by arbitrary choice, the second by virtue of r_{eq} being the minimum. If we truncate after the first non-zero term, we have the simplest possible expression for the vibrational potential energy

$$U(r_{AB}) = \frac{1}{2} k_{AB} (r_{AB} - r_{AB,eq})^2 \quad (2.2)$$

where we have replaced the second derivative of U by the symbol k . Equation (2.2) is Hooke's law for a spring, where k is the 'force constant' for the spring; the same term is used for k in spectroscopy and molecular mechanics. Subscripts have been added to emphasize that force constants and equilibrium bond lengths may vary from one pair of atoms to another.

Indeed, one might expect that force constants and equilibrium lengths might vary substantially even when A and B remain constant, but the bond itself is embedded in different molecular frameworks (i.e., surroundings). However, as more and more spectroscopic data became available in the early 20th century, particularly in the area of organic chemistry, where hundreds or thousands of molecules having similar bonds (e.g., C-C single bonds)

could be characterized, equilibrium bond lengths came to be called

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could be characterized, it became empirically evident that the force constants and equilibrium bond lengths were largely the same from one molecule to the next. This phenomenon came to be called 'transferability'.

Concomitant with these developments in spectroscopy, thermochemists were finding that, to a reasonable approximation, molecular enthalpies could be determined as a sum of bond enthalpies. Thus, assuming transferability, if two different molecules were to be composed of identical bonds (i.e., they were to be isomers of one kind or another), the sum of the differences in the 'strains' of those bonds from one molecule to the other (which would arise from different bond lengths in the two molecules – the definition of strain in this instance is the positive deviation from the zero of energy) would allow one to predict the difference in enthalpies. Such prediction was a major goal of the emerging area of organic conformational analysis.

One might ask why any classical mechanical bond would deviate from its equilibrium bond length, insofar as that represents the zero of energy. The answer is that in polyatomic molecules, other energies of interaction must also be considered. For instance, repulsive van der Waals interactions between nearby groups may force some bonds connecting them to lengthen. The same argument can be applied to bond angles, which also have transferable force constants and optimal values (vide infra). Energetically unfavorable non-bonded, non-angle-bending interactions have come to be called 'steric effects' following the terminology suggested by Hill (1946), who proposed that a minimization of overall steric energy could be used to predict optimal structures. The first truly successful reduction of this general idea to practice was accomplished by Westheimer and Mayer (1946), who used potential energy functions to compute energy differences between twisted and planar substituted biphenyls and were able to rationalize racemization rates in these molecules.

The rest of this chapter examines the various components of the molecular energy and the force-field approaches taken for their computation. The discussion is, for the most part, general. At the end of the chapter, a comprehensive listing of reported/available force fields is provided with some description of their form and intended applicability.

2.2 Potential Energy Functional Forms

2.2.1 Bond Stretching

Before we go on to consider functional forms for all of the components of a molecule's total steric energy, let us consider the limitations of Eq. (2.2) for bond stretching. Like any truncated Taylor expansion, it works best in regions near its reference point, in this case r_{eq} . Thus, if we are interested primarily in molecular structures where no bond is terribly distorted from its optimal value, we may expect Eq. (2.2) to have reasonable utility. However, as the bond is stretched to longer and longer r , Eq. (2.2) predicts the energy to become infinitely positive, which is certainly not chemically realistic. The practical solution to such inaccuracy is to include additional terms in the Taylor expansion. Inclusion of the cubic term provides a potential energy function of the form

$$U(r_{AB}) = \frac{1}{2}[k_{AB} + k_{AB}^{(3)}(r_{AB} - r_{AB,eq})](r_{AB} - r_{AB,eq})^2 \quad (2.3)$$

where we have added the superscript '(3)' to the cubic force constant (also called the 'anharmonic' force constant) to emphasize that it is different from the quadratic one. The cubic force constant is negative, since its function is to reduce the overly high stretching energies predicted by Eq. (2.2). This leads to an unintended complication, however; Eq. (2.3) diverges to *negative* infinity with increasing bond length. Thus, the lowest possible energy for a molecule whose bond energies are described by functions having the form of Eq. (2.3) corresponds to all bonds being dissociated, and this can play havoc with automated minimization procedures.

Again, the simple, practical solution is to include the next term in the Taylor expansion, namely the quartic term, leading to an expression of the form

$$U(r_{AB}) = \frac{1}{2}[k_{AB} + k_{AB}^{(3)}(r_{AB} - r_{AB,eq}) + k_{AB}^{(4)}(r_{AB} - r_{AB,eq})^2](r_{AB} - r_{AB,eq})^2 \quad (2.4)$$

Such quartic functional forms are used in the general organic force field, MM3 (a large taxonomy of existing force fields appears at the end of the chapter). Many force fields that are designed to be used in reduced regions of chemical space (e.g., for specific biopolymers), however, use quadratic bond stretching potentials because of their greater computational simplicity.

The alert reader may wonder, at this point, why there has been no discussion of the Morse function

$$U(r_{AB}) = D_{AB}[1 - e^{-\alpha_{AB}(r_{AB} - r_{AB,eq})}]^2 \quad (2.5)$$

where D_{AB} is the dissociation energy of the bond and α_{AB} is a fitting constant. The hypothetical potential energy curve shown in Figure 2.1 can be reproduced over a much wider range of r by a Morse potential than by a quartic potential. Most force fields decline to use the Morse potential because it is computationally much less efficient to evaluate the exponential function than to evaluate a polynomial function (vide infra). Moreover, most force fields are designed to study the energetics of molecules whose various degrees of freedom are all reasonably close to their equilibrium values, say within 10 kcal/mol. Over such a range, the deviation between the Morse function and a quartic function is usually negligible.

Even in these instances, however, there is some utility to considering the Morse function. If we approximate the exponential in Eq. (2.5) as its infinite series expansion truncated at the cubic term, we have

$$U(r_{AB}) = D_{AB} \left\{ 1 - \left[1 - \alpha_{AB}(r_{AB} - r_{AB,eq}) + \frac{1}{2}\alpha_{AB}^2(r_{AB} - r_{AB,eq})^2 - \frac{1}{6}\alpha_{AB}^3(r_{AB} - r_{AB,eq})^3 \right] \right\}^2 \quad (2.6)$$

Squaring the quantity in braces and keeping only terms through quartic gives

$$U(r_{AB}) = D_{AB} \left[\alpha_{AB}^2 - \alpha_{AB}^3(r_{AB} - r_{AB,eq}) + \frac{7}{12}\alpha_{AB}^4(r_{AB} - r_{AB,eq})^2 \right] (r_{AB} - r_{AB,eq})^2 \quad (2.7)$$

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where comparison of Eqs. (2.4) and (2.7) makes clear the relationship between the various force constants and the parameters D and α of the Morse potential. In particular,

$$k_{AB} = 2\alpha_{AB}^2 D_{AB} \quad (2.8)$$

Typically, the simplest parameters to determine from experiment are k_{AB} and D_{AB} . With these two parameters available, α_{AB} can be determined from Eq. (2.8), and thus the cubic and quartic force constants can also be determined from Eqs. (2.4) and (2.7). Direct measurement of cubic and quartic force constants requires more spectral data than are available for many kinds of bonds, so this derivation facilitates parameterization. We will discuss parameterization in more detail later in the chapter, but turn now to consideration of other components of the total molecular energy.

2.2.2 Valence Angle Bending

Vibrational spectroscopy reveals that, for small displacements from equilibrium, energy variations associated with bond angle deformation are as well modeled by polynomial expansions as are variations associated with bond stretching. Thus, the typical force field function for angle strain energy is

$$U(\theta_{ABC}) = \frac{1}{2} [k_{ABC} + k_{ABC}^{(3)}(\theta_{ABC} - \theta_{ABC,eq}) + k_{ABC}^{(4)}(\theta_{ABC} - \theta_{ABC,eq})^2 + \dots] (\theta_{ABC} - \theta_{ABC,eq})^2 \quad (2.9)$$

where θ is the valence angle between bonds AB and BC (note that in a force field, a bond is *defined* to be a vector connecting two atoms, so there is no ambiguity about what is meant by an angle between two bonds), and the force constants are now subscripted ABC to emphasize that they are dependent on three atoms. Whether Eq. (2.9) is truncated at the quadratic term or whether more terms are included in the expansion depends entirely on the balance between computational simplicity and generality that any given force field chooses to strike. Thus, to note two specific examples, the general organic force field MM3 continues the expansion through to the sextic term for some ABC combinations, while the biomolecular force field of Cornell *et al.* (see Table 2.1, first row) limits itself to a quadratic expression in all instances. (Original references to all the force fields discussed in this chapter will be found in Table 2.1.)

While the above prescription for angle bending seems useful, certain issues do arise. First, note that no power expansion having the form of Eq. (2.9) will show the appropriate chemical behavior as the bond angle becomes linear, i.e., at $\theta = \pi$. Another flaw with Eq. (2.9) is that, particularly in inorganic systems, it is possible to have *multiple* equilibrium values; for instance, in the trigonal bipyramidal system PCl_5 there are stable Cl-P-Cl angles of $\pi/2$, $\pi/3$, and π for axial/equatorial, equatorial/equatorial, and axial/axial combinations of chlorine atoms, respectively. Finally, there is another kind of angle bending that is sometimes discussed in molecular systems, namely 'out-of-plane' bending. Prior to addressing these

various issues, it is instructive to consider the manner in which force fields typically handle potential energy variations associated with torsional motion.

2.2.3 Torsions

If we consider four atoms connected in sequence, ABCD, Figure 1.2 shows that a convenient means to describe the location of atom D is by means of a CD bond length, a BCD valence angle, and the torsional angle (or dihedral angle) associated with the ABCD linkage. As depicted in Figure 2.2, the torsional angle is defined as the angle between bonds AB and CD when they are projected into the plane bisecting the BC bond. The convention is to define the angle as positive if one must rotate the bond in front of the bisecting plane in a clockwise fashion to eclipse the bond behind the bisecting plane. By construction, the torsion angle is periodic. An obvious convention would be to use only the positive angle, in which case the torsion period would run from 0 to 2π radians (0 to 360°). However, the minimum energy for many torsions is for the antiperiplanar arrangement, i.e., $\omega = \pi$. Thus, the convention that $-\pi < \omega \leq \pi$ ($-180^\circ \leq \omega \leq 180^\circ$) also sees considerable use.

Since the torsion itself is periodic, so too must be the torsional potential energy. As such, it makes sense to model the potential energy function as an expansion of periodic functions, e.g., a Fourier series. In a general form, typical force fields use

$$U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD} [1 + (-1)^{j+1} \cos(j\omega_{ABCD} + \psi_{j,ABCD})] \quad (2.10)$$

where the values of the signed term amplitudes V_j and the set of periodicities $\{j\}$ included in the sum are specific to the torsional linkage ABCD (note that deleting a particular value of j from the evaluated set is equivalent to setting the term amplitude for that value of j

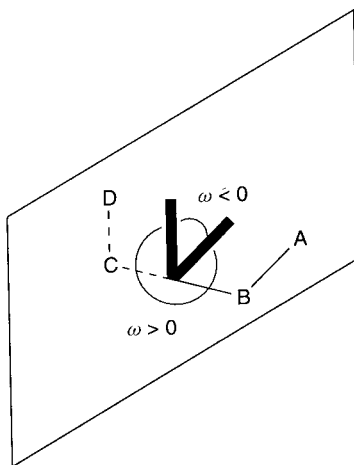


Figure 2.2 Definition and sign convention for dihedral angle ω . Note that the sign of ω is independent of whether one chooses to view the bisecting plane from the AB side or the CD side

equal to zero) which is included in the term can contribute within the sum. The choice is motivated by the fact that the energy is minimized when the torsion angle is zero. The coordinate, which is the stereoelectronic

While the minimum energy sense, because the overall rotation of all phase angles is minimized. The individual fit of the overall rotation of fluoromethane (Radom, Hehre) is the complete profile, and the antiperiplanar is instructive to the profile, and the

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Figure 2.3 Force field for methanol (because of the onefold (\diamond), two the molecule, the

equal to zero). Other features of Eq. (2.10) meriting note are the factor of $1/2$ on the r.h.s., which is included so that the term amplitude V_j is equal to the maximum the particular term can contribute to U . The factor of $(-1)^{j+1}$ is included so that the function in brackets within the sum is zero for all j when $\omega = \pi$, if the phase angles ψ are all set to 0. This choice is motivated by the empirical observation that most (but not all) torsional energies are minimized for antiperiplanar geometries; the zero of energy for U in Eq. (2.10) thus occurs at $\omega = \pi$. Choice of phase angles ψ other than 0 permits a fine tuning of the torsional coordinate, which can be particularly useful for describing torsions in systems exhibiting large stereoelectronic effects, like the anomeric linkages in sugars (see, for instance, Woods 1996).

While the mathematical utility of Eq. (2.10) is clear, it is also well founded in a chemical sense, because the various terms can be associated with particular physical interactions when all phase angles ψ are taken equal to 0. Indeed, the magnitudes of the terms appearing in an individual fit can be informative in illuminating the degree to which those terms influence the overall rotational profile. We consider as an example the rotation about the C–O bond in fluoromethanol, the analysis of which was first described in detail by Wolfe *et al.* (1971) and Radom, Hehre and Pople (1971). Figure 2.3 shows the three-term Fourier decomposition of the complete torsional potential energy curve. Fluoromethanol is somewhat unusual insofar as the antiperiplanar structure is *not* the global minimum, although it is a local minimum. It is instructive to note the extent to which each Fourier term contributes to the overall torsional profile, and also to consider the physical factors implicit in each term.

One physical effect that would be expected to be onefold periodic in the case of fluoromethanol is the dipole–dipole interaction between the C–F bond and the O–H bond. Because of differences in electronegativity between C and F and O and H, the bond dipoles

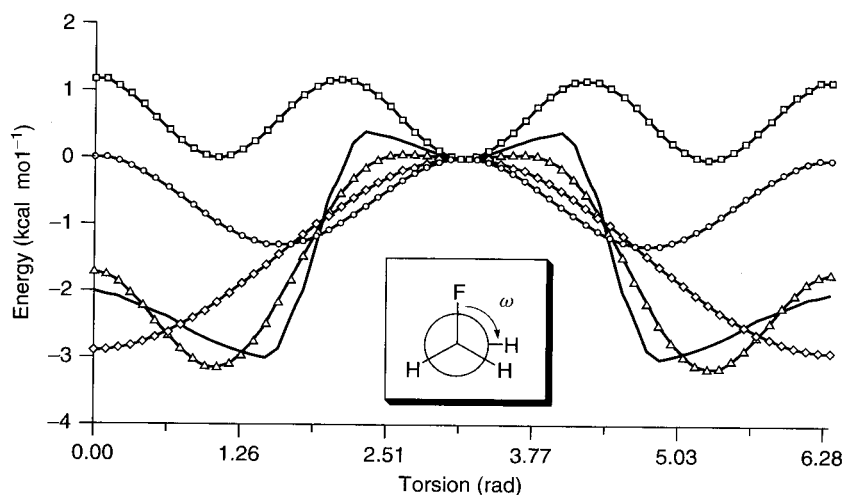


Figure 2.3 Fourier decomposition of the torsional energy for rotation about the C–O bond of fluoromethanol (bold black curve, energetics approximate). The Fourier sum (Δ) is composed of the onefold (\diamond), twofold (\circ), and threefold (\square) periodic terms, respectively. In the Newman projection of the molecule, the oxygen atom lies behind the carbon atom at center

for these bonds point from C to F and from H to O, respectively. Thus, at $\omega = 0$, the dipoles are antiparallel (most energetically favorable) while at $\omega = \pi$ they are parallel (least energetically favorable). Thus, we would expect the V_1 term to be a minimum at $\omega = 0$, implying V_1 should be negative, and that is indeed the case. This term makes the largest contribution to the full rotational profile, having a magnitude roughly double either of the other two terms.

Twofold periodicity is associated with hyperconjugative effects. Hyperconjugation is the favorable interaction of a filled or partially filled orbital, typically a σ orbital, with a nearby empty orbital (hyperconjugation is discussed in more detail in Appendix D within the context of natural bond orbital (NBO) analysis). In the case of fluoromethanol, the filled orbital that is highest in energy is an oxygen lone pair orbital, and the empty orbital lowest in energy (and thus best able to interact in a resonance fashion with the oxygen lone pair) is the C–F σ^* antibonding orbital. Resonance between these orbitals, which is sometimes called negative hyperconjugation to distinguish it from resonance involving filled σ orbitals as donors, is favored by maximum overlap; this takes place for torsion angles of roughly $\pm\pi/2$. The contribution of this V_2 term to the overall torsional potential of fluoromethanol is roughly half that of the V_1 term, and of the expected sign.

The remaining V_3 term is associated with unfavorable bond–bond eclipsing interactions, which, for a torsion involving sp^3 -hybridized carbon atoms, would be expected to show threefold periodicity. To be precise, true threefold periodicity would only be expected were each carbon atom to bear all identical substituents. Experiments suggest that fluorine and hydrogen have similar steric behavior, so we will ignore this point for the moment. As expected, the sign of the V_3 term is positive, and it has roughly equal weight to the hyperconjugative term.

[Note that, following the terminology introduced earlier, we refer to the unfavorable eclipsing of chemical bonds as a steric interaction. Since molecular mechanics in essence treats molecules as classical atomic balls (possibly charged balls, as discussed in more detail below) connected together by springs, this terminology is certainly acceptable. It should be borne in mind, however, that real atoms are most certainly not billiard balls bumping into one another with hard shells. Rather, the unfavorable steric interaction derives from exchange-repulsion between filled molecular orbitals as they come closer to one another, i.e., the effect is electronic in nature. Thus, the bromide that all energetic issues in chemistry can be analyzed as a combination of electronic and steric effects is perhaps overly complex. . . *all* energetic effects in chemistry, at least if we ignore nuclear chemistry, are *exclusively* electronic/electrical in nature.]

While this analysis of fluoromethanol is instructive, it must be pointed out that a number of critical issues have been either finessed or ignored. First, as can be seen in Figure 2.3, the actual rotational profile of fluoromethanol cannot be perfectly fit by restricting the Fourier decomposition to only three terms. This may sound like quibbling, since the ‘perfect’ fitting of an arbitrary periodic curve takes an infinite number of Fourier terms, but the poorness of the fit is actually rather severe from a chemical standpoint. This may be most readily appreciated by considering simply the four symmetry-unique stationary points – two minima and two rotational barriers. We are trying to fit their energies, but we also want their nature as stationary points to be correct, implying that we are trying to fit their first derivatives as

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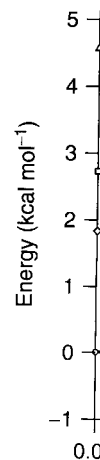


Figure 2.4 Four (bold black curve) of the onefold (\diamond)

well (making the first derivative equal to zero defines them as stationary points). Thus, we are trying to fit eight constraints using only three variables (namely, the term amplitudes). By construction, we are actually guaranteed that 0 and π will have correct first derivatives, and that the energy value for π will be correct (since it is required to be the relative zero), but that still leaves five constraints on three variables. If we add non-zero phase angles ψ , we can do a better (but still not perfect) job.

Another major difficulty is that we have biased the system so that we can focus on a single dihedral interaction (FCOH) as being dominant, i.e., we ignored the HCOH interactions, and we picked a system where one end of the rotating bond had only a single substituent. To illustrate the complexities introduced by more substitution, consider the relatively simple case of *n*-butane (Figure 2.4). In this case, the three-term Fourier fit is in very good agreement with the full rotational profile, and certain aspects continue to make very good chemical sense. For instance, the twofold periodic term is essentially negligible, as would be expected since there are no particularly good donors or acceptors to interact in a hyperconjugative fashion. The onefold term, on the other hand, makes a very significant contribution, and this clearly cannot be assigned to some sort of dipole-dipole interaction, since the magnitude of a methylene-methyl bond dipole is very near zero. Rather, the magnitudes of the one- and threefold symmetric terms provide information about the relative steric strains associated with the two possible eclipsed structures, the lower energy of which has one H/H and two H/CH₃ eclipsing interactions, while the higher energy structure has two H/H and one CH₃/CH₃ interactions. While one might be tempted to try to derive some sort of linear combination rule for this still highly symmetric case, it should be clear that by the time one tries to analyze the torsion about a C-C bond bearing six different substituents, one's ability

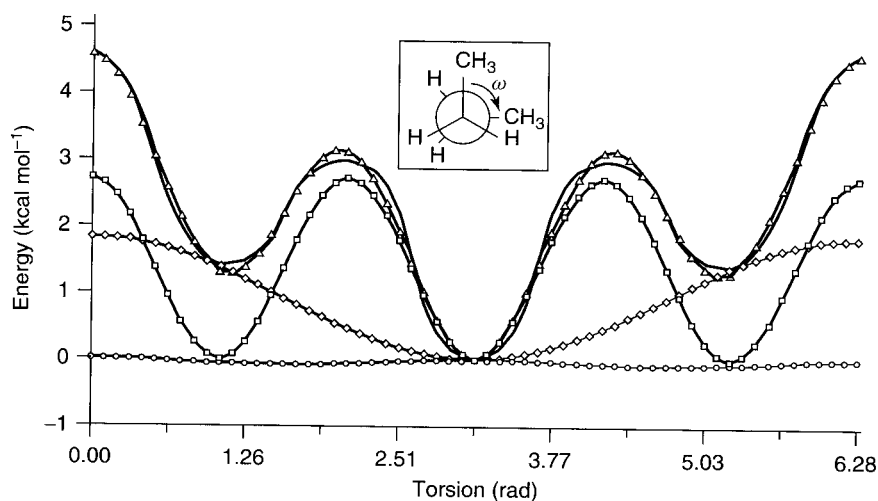


Figure 2.4 Fourier decomposition of the torsional energy for rotation about the C-C bond of *n*-butane (bold black curve, energetics approximate). The Fourier sum (Δ) has a close overlap, and is composed of the onefold (\diamond), twofold (\circ), and threefold (\square) periodic terms, respectively

to provide a physically meaningful interpretation of the many different term amplitudes is quite limited.

Moreover, as discussed in more detail later, force field parameters are not statistically orthogonal, so optimized values can be skewed by coupling with other parameters. With all of these caveats in mind, however, there are still instances where valuable physical insights derive from a term-by-term analysis of the torsional coordinate.

Let us return now to a question raised above, namely, how to handle the valence angle bending term in a system where multiple equilibrium angles are present. Such a case is clearly analogous to the torsional energy, which also presents multiple minima. Thus, the inorganic SHAPES force field uses the following equations to compute angle bending energy

$$U(\theta_{ABC}) = \sum_{\{j\}_{ABC}} k_{j,ABC}^{\text{Fourier}} [1 + \cos(j\theta_{ABC} + \psi)] \quad (2.11)$$

$$k_{j,ABC}^{\text{Fourier}} = \frac{2k_{ABC}^{\text{harmonic}}}{j^2} \quad (2.12)$$

where ψ is a phase angle. Note that this functional form can also be used to ensure appropriate behavior in regions of bond angle inversion, i.e., where $\theta = \pi$. [As a digression, in metal coordination force fields an alternative formulation designed to handle multiple ligand-metal-ligand angles is simply to remove the angle term altogether. It is replaced by a non-bonded term specific to 1,3-interactions (a so-called 'Urey-Bradley' term) which tends to be repulsive. Thus, a given number of ligands attached to a central atom will tend to organize themselves so as to maximize the separation between any two. This 'points-on-a-sphere' (POS) approach is reminiscent of the VSEPR model of coordination chemistry.]

A separate situation, also mentioned in the angle bending discussion, arises in the case of four-atom systems where a central atom is bonded to three otherwise unconnected atoms, e.g., formaldehyde. Such systems are good examples of the second case of step IV of Figure 1.2, i.e., systems where a fourth atom is more naturally defined by a bond length to the central atom and its two bond angles to the other two atoms. However, as Figure 2.5 makes clear, one *could* define the final atom's position using the first case of step IV of Figure 1.2, i.e., by assigning a length to the central atom, an angle to a third atom, and *then a dihedral angle to the fourth atom even though atoms three and four are not defined as connected*. Such an

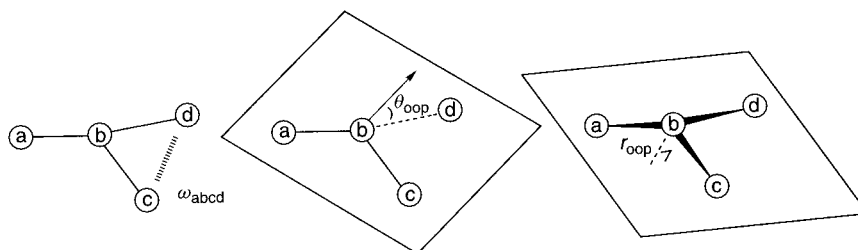


Figure 2.5 Alternative molecular coordinates that can be used to compute the energetics of distortions from planarity about a triply substituted central atom

assignment is not unique, but it can be derived from a chemical description. The 'improper' torsion angle might have a value of π , or it might have a value of 0 , depending on the direction of the decreasing torsion angle. The torsion angle is defined by the direction of the rotation, and any other torsion angle description of the same rotation might choose a different direction. One substitution is to define the torsion angle by the three atoms, and the direction of rotation to angle bending energy, respectively.

Let us return to the discussion of energy barriers in the torsional coordinate. The energy barriers in the torsional coordinate are determined by the atoms/groups attached to the central atom. The molecule is not a rigid body, and the 'space-filling' model is not a 'test' metric of the molecule's shape. The atoms remain intact, and the torsion angle is small about π . The torsional function is periodic, and the torsion angle is periodic. The torsion angle is periodic, and the torsion angle is periodic. Such a prescription is not unique, but it is one which we now

2.2.4 van der Waals

Consider the interaction between two atoms, spherically symmetric, as they approach each other. The force F in a

In this one-dimensional case, the slope of the energy remains constant, and our classical description of the energy when the bond

assignment makes perfect sense from a geometric standpoint, even though it may seem odd from a chemical standpoint. Torsion angles defined in this manner are typically referred to as 'improper torsions'. In a system like formaldehyde, an improper torsion like OCHH would have a value of π radians (180°) in the planar, minimum energy structure. Increasing or decreasing this value would have the effect of moving the oxygen atom out of the plane defined by the remaining three atoms. Many force fields treat such improper torsions like any other torsion, i.e., they use Eq. (2.10). However, as Figure 2.5 indicates, the torsional description for this motion is only one of several equally reasonable coordinates that one might choose. One alternative is to quantify deviations from planarity by the angle $\theta_{\text{o.o.p.}}$ that one substituent makes with the plane defined by the other three (o.o.p. = 'out of plane'). Another is to quantify the elevation $r_{\text{o.o.p.}}$ of the central atom above/below the plane defined by the three atoms to which it is attached. Both of these latter modes have obvious connections to angle bending and bond stretching, respectively, and typically Eqs. (2.9) and (2.4), respectively, are used to model the energetics of their motion.

Let us return to the case of the butane rotational potential. As noted previously, the barriers in this potential are primarily associated with steric interactions between eclipsing atoms/groups. Anyone who has ever built a space-filling model of a sterically congested molecule is familiar with the phenomenon of steric congestion – some atomic balls in the space-filling model push against one another, creating strain (leading to the apocryphal 'drop test' metric of molecular stability: how great a height can the model be dropped from and remain intact?) Thus, in cases where dipole–dipole and hyperconjugative interactions are small about a rotating bond, one might question whether there is a need to parameterize a torsional function at all. Instead, one could represent atoms as balls, each having a characteristic radius, and develop a functional form quantifying the energetics of ball–ball interactions. Such a prescription provides an intuitive model for more distant 'non-bonded' interactions, which we now examine.

2.2.4 van der Waals Interactions

Consider the mutual approach of two noble gas atoms. At infinite separation, there is no interaction between them, and this defines the zero of potential energy. The isolated atoms are spherically symmetric, lacking any electric multipole moments. In a classical world (ignoring the chemically irrelevant gravitational interaction) there is no attractive force between them as they approach one another. When there are no dissipative forces, the relationship between force F in a given coordinate direction q and potential energy U is

$$F_q = -\frac{\partial U}{\partial q} \quad (2.13)$$

In this one-dimensional problem, saying that there is no force is equivalent to saying that the slope of the energy curve with respect to the 'bond length' coordinate is zero, so the potential energy remains zero as the two atoms approach one another. Associating non-zero size with our classical noble gas atoms, we might assign them hard-sphere radii r_{vdw} . In that case, when the bond length reaches twice the radius, the two cannot approach one another more

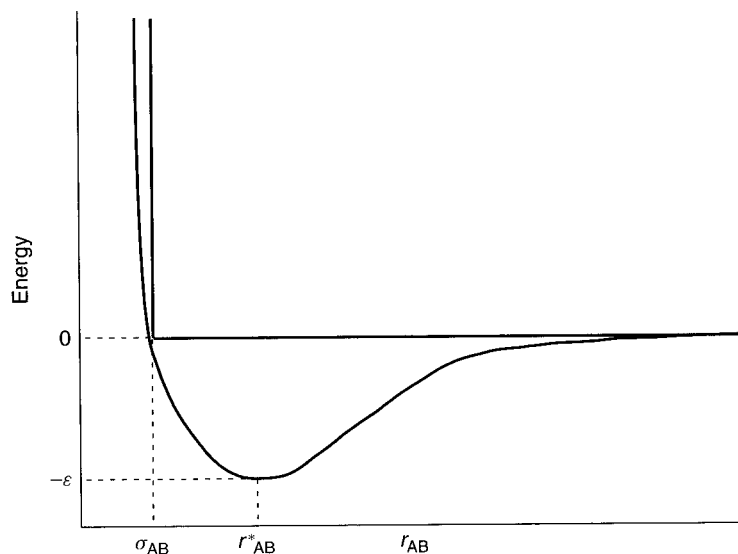


Figure 2.6 Non-attractive hard-sphere potential (straight lines) and Lennard-Jones potential (curve). Key points on the energy and bond length axes are labeled

closely, which is to say the potential energy discontinuously becomes infinite for $r < 2r_{vdw}$. This potential energy curve is illustrated in Figure 2.6.

One of the more profound manifestations of quantum mechanics is that this curve does *not* accurately describe reality. Instead, because the ‘motions’ of electrons are correlated (more properly, the electronic wave functions are correlated), the two atoms simultaneously develop electrical moments that are oriented so as to be mutually attractive. The force associated with this interaction is referred to variously as ‘dispersion’, the ‘London’ force, or the ‘attractive van der Waals’ force. In the absence of a permanent charge, the strongest such interaction is a dipole–dipole interaction, usually referred to as an ‘induced dipole–induced dipole’ interaction, since the moments in question are not permanent. Such an interaction has an inverse sixth power dependence on the distance between the two atoms. Thus, the potential energy becomes increasingly negative as the two noble gas atoms approach one another from infinity.

Dispersion is a fascinating phenomenon. It is sufficiently strong that even the dimer of He is found to have one bound vibrational state (Luo *et al.* 1993; with a vibrationally averaged bond length of 55 Å it is a remarkable member of the molecular bestiary). Even for molecules with fairly large *permanent* electric moments in the gas phase, dispersion is the dominant force favoring condensation to the liquid state at favorable temperatures and pressures (Reichardt 1990).

However, as the two atoms continue to approach one another, their surrounding electron densities ultimately begin to interpenetrate. In the absence of opportunities for bonding interactions, Pauli repulsion (or ‘exchange repulsion’) causes the energy of the system to rise rapidly with decreasing bond length. The sum of these two effects is depicted in Figure 2.6;

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the contrasts with the classical hard-sphere model are that (i) an attractive region of the potential energy curve exists and (ii) the repulsive wall is not infinitely steep. [Note that at $r = 0$ the potential energy is that for an isolated atom having an atomic number equal to the sum of the atomic numbers for the two separated atoms; this can be of interest in certain formal and even certain practical situations, but we do no modeling of nuclear chemistry here.]

The simplest functional form that tends to be used in force fields to represent the combination of the dispersion and repulsion energies is

$$U(r_{AB}) = \frac{a_{AB}}{r_{AB}^{12}} - \frac{b_{AB}}{r_{AB}^6} \quad (2.14)$$

where a and b are constants specific to atoms A and B. Equation (2.14) defines a so-called 'Lennard-Jones' potential.

The inverse 12th power dependence of the repulsive term on interatomic separation has no theoretical justification – instead, this term offers a glimpse into the nuts and bolts of the algorithmic implementation of computational chemistry. Formally, one can more convincingly argue that the repulsive term in the non-bonded potential should have an exponential dependence on interatomic distance. However, the evaluation of the exponential function (and the log, square root, and trigonometric functions, *inter alia*) is roughly a factor of five times more costly in terms of central processing unit (cpu) time than the evaluation of the simple mathematical functions of addition, subtraction, or multiplication. Thus, the evaluation of r^{12} requires only that the theoretically justified r^6 term be multiplied by itself, which is a very cheap operation. Note moreover the happy coincidence that all terms in r involve *even* powers of r . The relationship between the internal coordinate r and Cartesian coordinates, which are typically used to specify atomic positions (see Section 2.4), is defined by

$$r_{AB} = \sqrt{(x_A - x_B)^2 + (y_A - y_B)^2 + (z_A - z_B)^2} \quad (2.15)$$

If only even powers of r are required, one avoids having to compute a square root. While quibbling over relative factors of five with respect to an operation that takes a tiny fraction of a second in absolute time may seem like overkill, one should keep in mind how many times the function in question may have to be evaluated in a given calculation. In a formal analysis, the number of non-bonded interactions that must be evaluated scales as N^2 , where N is the number of atoms. In the process of optimizing a geometry, or of searching for many energy minima for a complex molecule, hundreds or thousands of energy evaluations may need to be performed for interim structures. Thus, seemingly small savings in time can be multiplied so that they are of practical importance in code development.

The form of the Lennard-Jones potential is more typically written as

$$U(r_{AB}) = 4\epsilon_{AB} \left[\left(\frac{\sigma_{AB}}{r_{AB}} \right)^{12} - \left(\frac{\sigma_{AB}}{r_{AB}} \right)^6 \right] \quad (2.16)$$

where the constants a and b of Eq. (2.14) are here replaced by the constants ε and σ . Inspection of Eq. (2.16) indicates that σ has units of length, and is the interatomic separation at which repulsive and attractive forces exactly balance, so that $U = 0$. If we differentiate Eq. (2.16) with respect to r_{AB} , we obtain

$$\frac{dU(r_{AB})}{dr_{AB}} = \frac{4\varepsilon_{AB}}{r_{AB}} \left[-12 \left(\frac{\sigma_{AB}}{r_{AB}} \right)^{12} + 6 \left(\frac{\sigma_{AB}}{r_{AB}} \right)^6 \right] \quad (2.17)$$

Setting the derivative equal to zero in order to find the minimum in the Lennard-Jones potential gives, after rearrangement

$$r_{AB}^* = 2^{1/6} \sigma_{AB} \quad (2.18)$$

where r^* is the bond length at the minimum. If we use this value for the bond length in Eq. (2.16), we obtain $U = -\varepsilon_{AB}$, indicating that the parameter ε is the Lennard-Jones well depth (Figure 2.6).

The Lennard-Jones potential continues to be used in many force fields, particularly those targeted for use in large systems, e.g., biomolecular force fields. In more general force fields targeted at molecules of small to medium size, slightly more complicated functional forms, arguably having more physical justification, tend to be used (computational times for small molecules are so short that the efficiency of the Lennard-Jones potential is of little consequence). Such forms include the Morse potential [Eq. (2.5)] and the 'Hill' potential

$$U(r_{AB}) = \varepsilon_{AB} \left[\frac{6}{\beta_{AB} - 6} \exp \left(\beta_{AB} \frac{1 - r_{AB}}{r_{AB}^*} \right) - \frac{\beta_{AB}}{\beta_{AB} - 6} \left(\frac{r_{AB}^*}{r_{AB}} \right)^6 \right] \quad (2.19)$$

where β is a new parameter and all other terms have the same meanings as in previous equations.

Irrespective of the functional form of the van der Waals interaction, some force fields reduce the energy computed for 1,4-related atoms (i.e., torsionally related) by a constant scale factor.

Our discussion of non-bonded interactions began with the example of two noble gas atoms having no permanent electrical moments. We now turn to a consideration of non-bonded interactions between atoms, bonds, or groups characterized by non-zero local electrical moments.

2.2.5 Electrostatic Interactions

Consider the case of two molecules A and B interacting at a reasonably large distance, each characterized by classical, non-polarizable, permanent electric moments. Classical electrostatics asserts the energy of interaction for the system to be

$$U_{AB} = \mathbf{M}^{(A)} \mathbf{V}^{(B)} \quad (2.20)$$

where $\mathbf{M}^{(A)}$ is the dipole moment, etc. Equation (2.20) is, we may

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where $\mathbf{M}^{(A)}$ is an ordered vector of the multipole moments of A, e.g., charge (zeroth moment), x , y , and z components of the dipole moment, then the nine components of the quadrupole moment, etc., and $\mathbf{V}^{(B)}$ is a similarly ordered row vector of the electrical potentials deriving from the multipole moments of B. Both expansions are about single centers, e.g., the centers of mass of the molecules. At long distances, one can truncate the moment expansions at reasonably low order and obtain useful interaction energies.

Equation (2.20) can be used to model the behavior of a large collection of individual molecules efficiently because the electrostatic interaction energy is pairwise additive. That is, we may write

$$U = \sum_A \sum_{B>A} \mathbf{M}^{(A)} \mathbf{V}^{(B)} \quad (2.21)$$

However, Eq. (2.21) is not very convenient in the context of *intramolecular* electrostatic interactions. In a protein, for instance, how can one derive the electrostatic interactions between spatially adjacent amide groups (which have large local electrical moments)? In principle, one could attempt to define moment expansions for functional groups that recur with high frequency in molecules, but such an approach poses several difficulties. First, there is no good experimental way in which to measure (or even define) such local moments, making parameterization difficult at best. Furthermore, such an approach would be computationally quite intensive, as evaluation of the moment potentials is tedious. Finally, the convergence of Eq. (2.20) at short distances can be quite slow with respect to the point of truncation in the electrical moments.

Let us pause for a moment to consider the fundamental constructs we have used thus far to define a force field. We have introduced van der Waals balls we call atoms, and we have defined bonds, angles, and torsional linkages between them. What would be convenient would be to describe electrostatic interactions in some manner that is based on these available entities (this convenience derives in part from our desire to be able to optimize molecular geometries efficiently, as described in more detail below). The simplest approach is to assign to each van der Waals atom a partial charge, in which case the interaction energy between atoms A and B is simply

$$U_{AB} = \frac{q_A q_B}{\epsilon_{AB} r_{AB}} \quad (2.22)$$

This assignment tends to follow one of three formalisms, depending on the intent of the modeling endeavor. In the simplest case, the charges are 'permanent', in the sense that all atoms of a given type are defined to carry that charge in all situations. Thus, the atomic charge is a fixed parameter.

Alternatively, the charge can be determined from a scheme that depends on the electronegativity of the atom in question, and also on the electronegativities of those atoms to which it is defined to be connected. Thus, the atomic electronegativity becomes a parameter and some functional form is adopted in which it plays a role as a variable. In a force field with a reduced number of atomic 'types' (see below for more discussion of atomic types) this preserves flexibility in the recognition of different chemical environments. Such flexibility is critical for the charge because the electrostatic energy can be so large compared to other

components of the force field: Eq. (2.22) is written in a.u.; the conversion to energy units of kilocalories per mole and distance units of ångströms involves multiplication of the r.h.s. by a factor of 332. Thus, even at 100 Å separation, the interaction energy between two unit charges in a vacuum would be more than 3 kcal/mol, which is of the same order of energy we expect for distortion of an individual stretching, bending, or torsional coordinate.

Finally, in cases where the force field is designed to study a particular molecule (i.e., generality is not an issue), the partial charges are often chosen to accurately reproduce some experimental or computed electrostatic observable of the molecule. Various schemes in common use are described in Chapter 9.

If, instead of the atom, we define charge polarization for the chemical bonds, the most convenient bond moment is the dipole moment. In this case, the interaction energy is defined between bonds AB and CD as

$$U_{AB/CD} = \frac{\mu_{AB}\mu_{CD}}{\epsilon_{AB/CD}r_{AB/CD}^3} (\cos \chi_{AB/CD} - 3 \cos \alpha_{AB}\alpha_{CD}) \quad (2.23)$$

where the bond moment vectors having magnitude μ are centered midway along the bonds and are collinear with them. The orientation vectors χ and α are defined in Figure 2.7.

Note that in Eqs. (2.22) and (2.23) the dielectric constant ϵ is subscripted. Although one might expect the best dielectric constant to be that for the permittivity of free space, such an assumption is not necessarily consistent with the approximations introduced by the use of atomic point charges. Instead, the dielectric constant must be viewed as a parameter of the model, and it is moreover a parameter that can take on multiple values. For use in Eq. (2.22),

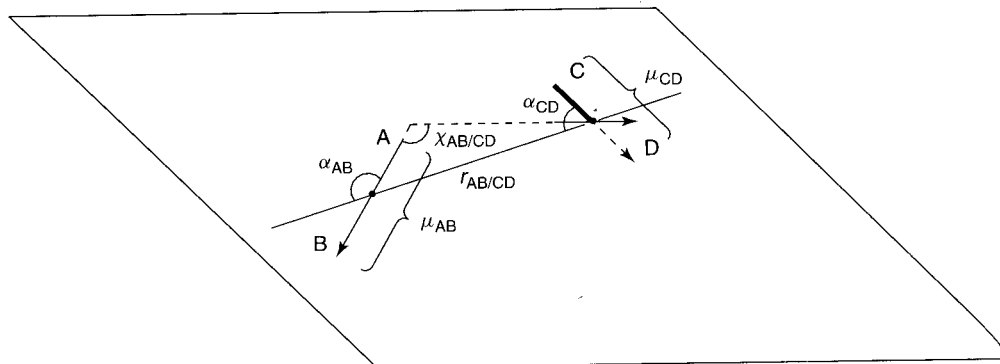


Figure 2.7 Prescription for evaluating the interaction energy between two dipoles. Each angle α is defined as the angle between the positive end of its respective dipole and the line passing through the two dipole centroids. The length of the line segment connecting the two centroids is r . To determine χ , the AB dipole and the centroid of the CD dipole are used to define a plane, and the CD dipole is projected into this plane. If the AB dipole and the projected CD dipole are parallel, χ is defined to be 0; if they are not parallel, they are extended as rays until they intersect. If the extension is from the same signed end of both dipoles, χ is the interior angle of the intersection (as illustrated), otherwise it is the exterior angle of the intersection

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$$\epsilon_{AB} = \begin{cases} \infty & \text{if A and B are 1,2- or 1,3-related} \\ 3.0 & \text{if A and B are 1,4-related} \\ 1.5 & \text{otherwise} \end{cases} \quad (2.24)$$

which dictates that electrostatic interactions between bonded atoms or between atoms sharing a common bonded atom are not evaluated, interactions between torsionally related atoms *are* evaluated, but are reduced in magnitude by a factor of 2 relative to all other interactions, which are evaluated with a dielectric constant of 1.5. Dielectric constants can also be defined so as to have a continuous dependence on the distance between the atoms. Although one might expect the use of high dielectric constants to mimic to some extent the influence of a surrounding medium characterized by that dielectric (e.g., a solvent), this is rarely successful – more accurate approaches for including condensed-phase effects are discussed in Chapters 3, 11, and 12.

Bonds between heteroatoms and hydrogen atoms are amongst the most polar found in non-ionic systems. This polarity is largely responsible for the well-known phenomenon of hydrogen bonding, which is a favorable interaction (usually ranging from 3 to 10 kcal/mol) between a hydrogen and a heteroatom to which it is *not* formally bonded. Most force fields account for hydrogen bonding implicitly in the non-bonded terms, van der Waals and electrostatic. In some instances an additional non-bonded interaction term, in the form of a 10–12 potential, is added

$$U(r_{XH}) = \frac{a'_{XH}}{r_{XH}^{12}} - \frac{b'_{XH}}{r_{XH}^{10}} \quad (2.25)$$

where X is a heteroatom to which H is not bound. This term is analogous to a Lennard–Jones potential, but has a much more rapid decay of the attractive region with increasing bond length. Indeed, the potential well is so steep and narrow that one may regard this term as effectively forcing a hydrogen bond to deviate only very slightly from its equilibrium value.

Up to now, we have considered the interactions of *static* electric moments, but actual molecules have their electric moments *perturbed* under the influence of an electrical field (such as that deriving from the electrical moments of another molecule). That is to say, molecules are polarizable. To extend a force field to include polarizability is conceptually straightforward. Each atom is assigned a polarizability tensor. In the presence of the permanent electric field of the molecule (i.e., the field derived from the atomic charges or the bond–dipole moments), a dipole moment will be induced on each atom. Following this, however, the total electric field is the *sum* of the permanent electric field and that created by the induced dipoles, so the determination of the ‘final’ induced dipoles is an iterative process that must be carried out to convergence (which may be difficult to achieve). The total electrostatic energy can then be determined from the pairwise interaction of all moments and moment potentials (although the energy is determined in a pairwise fashion, note that many-body effects are incorporated by the iterative determination of the induced dipole moments). As a rough rule, computing the electrostatic interaction energy for a polarizable force field is about an order of magnitude more costly than it is for a static force field. Moreover, except for

the most accurate work in very large systems, the benefits derived from polarization appear to be small. Thus, with the possible exception of solvent molecules in condensed-phase models (see Section 12.4.1), most force fields tend to avoid including polarization.

2.2.6 Cross Terms

Bonds, angles, and torsions are not isolated molecular coordinates: they couple with one another. To appreciate this from a chemical point of view, consider BeH_2 . In its preferred, linear geometry, one describes the Be hybridization as sp, i.e., each Be hybrid orbital used to bond with hydrogen has 50% 2s character and 50% 2p character. If we now decrease the bond angle, the p contribution increases until we stop at, say, a bond angle of $\pi/3$, which is the value corresponding to sp^2 hybridization. With more p character in the Be bonding hybrids, the bonds should grow longer. While this argument relies on rather basic molecular orbital theory, even from a *mechanical* standpoint, one would expect that as a bond angle is compressed, the bond lengths to the central atom will lengthen to decrease the non-bonded interactions between the terminal atoms in the sequence.

We can put this on a somewhat clearer mathematical footing by expanding the full molecular potential energy in a multi-dimensional Taylor expansion, which is a generalization of the one-dimensional case presented as Eq. (2.1). Thus

$$\begin{aligned}
 U(\mathbf{q}) = & U(\mathbf{q}_{\text{eq}}) + \sum_{i=1}^{3N-6} (q_i - q_{i,\text{eq}}) \left. \frac{\partial U}{\partial q_i} \right|_{\mathbf{q}=\mathbf{q}_{\text{eq}}} \\
 & + \frac{1}{2!} \sum_{i=1}^{3N-6} \sum_{j=1}^{3N-6} (q_i - q_{i,\text{eq}})(q_j - q_{j,\text{eq}}) \left. \frac{\partial^2 U}{\partial q_i \partial q_j} \right|_{\mathbf{q}=\mathbf{q}_{\text{eq}}} \\
 & + \frac{1}{3!} \sum_{i=1}^{3N-6} \sum_{j=1}^{3N-6} \sum_{k=1}^{3N-6} (q_i - q_{i,\text{eq}})(q_j - q_{j,\text{eq}})(q_k - q_{k,\text{eq}}) \left. \frac{\partial^3 U}{\partial q_i \partial q_j \partial q_k} \right|_{\mathbf{q}=\mathbf{q}_{\text{eq}}} + \dots
 \end{aligned} \quad (2.26)$$

where \mathbf{q} is a molecular geometry vector of $3N - 6$ internal coordinates and the expansion is taken about an equilibrium structure. Again, the first two terms on the r.h.s. are zero by definition of U for \mathbf{q}_{eq} and by virtue of all of the first derivatives being zero for an equilibrium structure. Up to this point, we have primarily discussed the 'diagonal' terms of the remaining summations, i.e., those terms for which all of the summation indices are equal to one another. However, if we imagine that index 1 of the double summation corresponds to a bond stretching coordinate, and index 2 to an angle bending coordinate, it is clear that our force field will be more 'complete' if we include energy terms like

$$U(r_{\text{AB}}, \theta_{\text{ABC}}) = \frac{1}{2} k_{\text{AB,ABC}} (r_{\text{AB}} - r_{\text{AB,eq}})(\theta_{\text{ABC}} - \theta_{\text{ABC,eq}}) \quad (2.27)$$

where $k_{\text{AB,ABC}}$ is the mixed partial derivative appearing in Eq. (2.26). Typically, the mixed partial derivative will be negligible for degrees of freedom that do not share common atoms

In general force fields by π conjugation. stretching has been force constants (F useful in highly st Chapter 9). Stretch lead to high degree

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2.2.7 Parameters

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In general force fields, stretch–stretch terms can be useful in modeling systems characterized by π conjugation. In amides, for instance, the coupling force constant between CO and CN stretching has been found to be roughly 15% as large as the respective diagonal bond-stretch force constants (Fogarasi and Balázs, 1985). Stretch–bend coupling terms tend to be most useful in highly strained systems, and for the computation of vibrational frequencies (see Chapter 9). Stretch–torsion coupling can be useful in systems where eclipsing interactions lead to high degrees of strain. The coupling has the form

$$U(r_{BC}, \omega_{ABCD}) = \frac{1}{2} k_{BC,ABCD} (r_{BC} - r_{BC,eq}) [1 + \cos(j\omega + \psi)] \quad (2.28)$$

where j is the periodicity of the torsional term and ψ is a phase angle. Thus, if the term were designed to capture extra strain involving eclipsing interactions in a substituted ethane, the periodicity would require $j = 3$ and the phase angle would be 0. Note that the stretching bond, BC, is the *central* bond in the torsional linkage.

Other useful coupling terms include stretch–stretch coupling (typically between two adjacent bonds) and bend–bend coupling (typically between two angles sharing a common central atom). In force fields that aim for spectroscopic accuracy, i.e., the reproduction of vibrational spectra, still higher order coupling terms are often included. However, for purposes of general molecular modeling, they are typically not used.

2.2.7 Parameterization Strategies

At this stage, it is worth emphasizing the possibly obvious point that a force field is nothing but a (possibly very large) collection of functional forms and associated constants. With that collection in hand, the energy of a given molecule (whose atomic connectivity must in general be specified) can be evaluated by computing the energy associated with every defined type of interaction occurring in the molecule. Because there are typically a rather large number of such interactions, the process is facilitated by the use of a digital computer, but the mathematics is really extraordinarily simple and straightforward.

Thus, we have detailed how to construct a molecular PES as a sum of energies from chemically intuitive functional forms that depend on internal coordinates and on atomic (and possibly bond-specific) properties. However, we have not paid much attention to the individual parameters appearing in those functional forms (force constants, equilibrium coordinate values, phase angles, etc.) other than pointing out the relationship of many of them to certain spectroscopically measurable quantities. Let us now look more closely at the ‘Art and Science’ of the parameterization process.

In an abstract sense, parameterization can be a very well-defined process. The goal is to develop a model that reproduces experimental measurements to as high a degree as possible. Thus, step 1 of parameterization is to assemble the experimental data. For molecular mechanics, these data consist of structural data, energetic data, and, possibly, data on molecular electric moments. We will discuss the issues associated with each kind of datum further below, but for the moment let us proceed abstractly. We next need to define a ‘penalty function’, that is, a function that provides a measure of how much deviation there is between

$$\left. \frac{\partial^3 U}{\partial q_i \partial q_j \partial q_k} \right|_{q=q_{eq}} + \dots \quad (2.26)$$

minates and the expansion terms on the r.h.s. are zero derivatives being zero for an and the ‘diagonal’ terms of summation indices are equal the summation corresponds coordinate, it is clear that s like

$$\theta_{ABC,eq} \quad (2.27)$$

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our predicted values and our experimental values. Our goal will then be to select force-field parameters that minimize the penalty function. Choice of a penalty function is necessarily completely arbitrary. One example of such a function is

$$Z = \left[\sum_i^{\text{Observables}} \sum_j^{\text{Occurrences}} \frac{(\text{calc}_{i,j} - \text{expt}_{i,j})^2}{w_i^2} \right]^{1/2} \quad (2.29)$$

where observables might include bond lengths, bond angles, torsion angles, heats of formation, neutral molecular dipole moments, etc., and the weighting factors w carry units (so as to make Z dimensionless) and take into account not only possibly different numbers of data for different observables, but also the degree of tolerance the penalty function will have for the deviation of calculation from experiment for those observables. Thus, for instance, one might choose the weights so as to tolerate equally 0.01 Å deviations in bond lengths, 1° deviations in bond angles, 5° deviations in dihedral angles, 2 kcal/mol deviations in heats of formation, and 0.3 D deviations in dipole moment. Note that Z is evaluated using optimized geometries for all molecules; geometry optimization is discussed in Section 2.4. Minimization of Z is a typical problem in applied mathematics, and any number of statistical or quasi-statistical techniques can be used (see, for example, Schlick 1992). The minimization approach taken, however, is rarely able to remove the chemist and his or her intuition from the process.

To elaborate on this point, first consider the challenge for a force field designed to be general over the periodic table – or, for ease of discussion, over the first 100 elements. The number of unique bonds that can be formed from any two elements is 5050. If we were to operate under the assumption that bond-stretch force constants depend only on the atomic numbers of the bonded atoms (e.g., to make no distinction between so-called single, double, triple, etc. bonds), we would require 5050 force constants and 5050 equilibrium bond lengths to complete our force field. Similarly, we would require 100 partial atomic charges, and 5050 each values of σ and ε if we use Coulomb's law for electrostatics and a Lennard–Jones formalism for van der Waals interactions. If we carry out the same sort of analysis for bond angles, we need on the order of 10^6 parameters to complete the force field. Finally, in the case of torsions, somewhere on the order of 10^8 different terms are needed. If we include coupling terms, yet more constants are introduced.

Since one is unlikely to have access to 100 000 000+ relevant experimental data, minimization of Z is an underdetermined process, and in such a case there will be many different combinations of parameter values that give similar Z values. What combination is optimal? Chemical knowledge can facilitate the process of settling on a single set of parameters. For instance, a set of parameters that involved fluorine atoms being assigned a partial positive charge would seem chemically unreasonable. Similarly, a quick glance at many force constants and equilibrium coordinate values would rapidly eliminate cases with abnormally large or small values. Another approach that introduces the chemist is making the optimization process stepwise. One optimizes some parameters over a smaller data set, then holds those parameters frozen while optimizing others over a larger data set, and this process goes on until all parameters have been chosen. The process of choosing which parameters

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to optimize in which order is as arbitrary as the choice of a penalty function, but may be justified with chemical reasoning.

Now, one might argue that no one would be foolish enough to attempt to design a force field that would be completely general over the first 100 elements. Perhaps if we were to restrict ourselves to organic molecules composed of {H, C, N, O, F, Si, P, Cl, Br, and I} – which certainly encompasses a large range of interesting molecules – then we could ameliorate the data sparsity problem. In principle, this is true, but in practice, the results are not very satisfactory. When large quantities of data are in hand, it becomes quite clear that atomic ‘types’ cannot be defined by atomic number alone. Thus, for instance, bonds involving two C atoms fall into at least four classes, each one characterized by its own particular stretching force constant and equilibrium distance (e.g., single, aromatic, double, and triple). A similar situation obtains for any pair of atoms when multiple bonding is an option. Different atomic hybridizations give rise to different angle bending equilibrium values. The same is true for torsional terms. If one wants to include metals, usually different oxidation states give rise to differences in structural and energetic properties (indeed, this segregation of compounds based on similar, discrete properties is what inorganic chemists sometimes use to *assign* oxidation state).

Thus, in order to improve accuracy, a given force field may have a very large number of atom types, even though it includes only a relatively modest number of nuclei. The primarily organic force fields MM3 and MMFF have 153 and 99 atom types, respectively. The two general biomolecular force fields (proteins, nucleic acids, carbohydrates) OPLS (optimized potentials for liquid simulations) and of Cornell *et al.* have 41 atoms types each. The completely general (i.e., most of the periodic table) universal force field (UFF) has 126 atom types. So, again, the chemist typically faces an underdetermined optimization of parameter values in finalizing the force field.

So, what steps can be taken to decrease the scope of the problem? One approach is to make certain parameters that depend on more than one atom themselves functions of single-atom-specific parameters. For instance, for use in Eq. (2.16), one usually defines

$$\sigma_{AB} = \sigma_A + \sigma_B \quad (2.30)$$

and

$$\varepsilon_{AB} = (\varepsilon_A \varepsilon_B)^{1/2} \quad (2.31)$$

thereby reducing in each case the need for $N(N+1)/2$ diatomic parameters to only N atomic parameters. [Indeed, truly general force fields, like DREIDING, UFF, and VALBOND attempt to reduce almost all parameters to being derivable from a fairly small set of atomic parameters. In practice, these force fields are not very robust, but as their limitations continue to be addressed, they have good long-range potential for broad, general utility.]

Another approach that is conceptually similar is to make certain constants depend on bond order or bond hybridization. Thus, for instance, in the VALBOND force field, angle bending energies at metal atoms are computed from orbital properties of the metal–ligand bonds; in the MM2 and MM3 force fields, stretching force constants, equilibrium bond lengths, and two-fold torsional terms depend on computed π bond orders between atoms.

Such additions to the force field somewhat strain the limits of a 'classical' model, since references to orbitals or computed bond orders necessarily introduce quantum mechanical aspects to the calculation. There is, of course, nothing wrong with moving the model in this direction – aesthetics and accuracy are orthogonal concepts – but such QM enhancements add to model complexity and increase the computational cost.

Yet another way to minimize the number of parameters required is to adopt a so-called 'united-atom' (UA) model. That is, instead of defining only atoms as the fundamental units of the force field, one also defines certain functional groups, usually hydrocarbon groups, e.g., methyl, methylene, aryl CH, etc. The group has its own single set of non-bonded and other parameters – effectively, this reduces the total number of atoms by one less than the total number incorporated into the united atom group.

Even with the various simplifications one may envision to reduce the number of parameters needed, a vast number remain for which experimental data may be too sparse to permit reliable parameterization (thus, for example, the MMFF94 force field has about 9000 defined parameters). How does one find the best parameter values? There are three typical responses to this problem.

The most common response nowadays is to supplement the experimental data with the highest quality *ab initio* data that can be had (either from molecular orbital or density functional calculations). A pleasant feature of using theoretical data is that one can compare regions on a PES that are far from equilibrium structures by direct computation rather than by trying to interpret vibrational spectra. Furthermore, one can attempt to make force-field energy derivatives correspond to those computed *ab initio*. The only limitation to this approach is the computational resources that are required to ensure that the *ab initio* data are sufficiently accurate.

The next most sensible response is to do nothing, and accept that there will be some molecules whose connectivity places them outside the range of chemical space to which the force field can be applied. While this can be very frustrating for the general user (typically the software package delivers a message to the effect that one or more parameters are lacking and then quits), if the situation merits, the necessary new parameters can be determined in relatively short order. Far more objectionable, when not well described, is the third response, which is to estimate missing parameter values and then carry on. The estimation process can be highly suspect, and unwary users can be returned nonsense results with no indication that some parameters were guessed at. If one suspects that a particular linkage or linkages in one's molecule may be outside the well-parameterized bounds of the force field, it is always wise to run a few test calculations on structures having small to moderate distortions of those linkages so as to evaluate the quality of the force constants employed.

It is worth noting that sometimes parameter estimation takes place 'on-the-fly'. That is, the program is designed to guess without human intervention parameters that were not explicitly coded. This is a somewhat pernicious aspect of so-called graphical user interfaces (GUIs), while they make the submission of a calculation blissfully simple – all one has to do is draw the structure – one is rather far removed from knowing what is taking place in the process of the calculation. Ideally, prominent warnings from the software should accompany any results derived from such calculations.

2.3 Force

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2.3 Force-field Energies and Thermodynamics

We have alluded above that one measure of the accuracy of a force field can be its ability to predict heats of formation. A careful inspection of all of the formulas presented thus far, however, should make it clear that we have not yet established any kind of connection between the force-field energy and any kind of thermodynamic quantity.

Let us review again the sense of Eqs. (2.4) and (2.9). In both instances, the minimum value for the energy is zero (assuming positive force constants and sensible behavior for odd power terms). An energy of zero is obtained when the bond length or angle adopts its equilibrium value. Thus, a 'strain-free' molecule is one in which every coordinate adopts its equilibrium value. Although we accepted a negative torsional term in our fluoromethanol example above, because it provided some chemical insight, by proper choice of phase angles in Eq. (2.10) we could also require this energy to have zero as a minimum (although not necessarily for the dihedral angle $\omega = \pi$). So, neglecting non-bonded terms for the moment, we see that the raw force-field energy can be called the 'strain energy', since it represents the positive deviation from a hypothetical strain-free system.

The key point that must be noted here is that strain energies for two different molecules *cannot be meaningfully compared unless the zero of energy is identical*. This is probably best illustrated with a chemical example. Consider a comparison of the molecules ethanol and dimethyl ether using the MM2(91) force field. Both have the chemical formula C_2H_6O . However, while ethanol is defined by the force field to be composed of two sp^3 carbon atoms, one sp^3 oxygen atom, five carbon-bound hydrogen atoms, and one alcohol hydrogen atom, dimethyl ether differs in that all six of its hydrogen atoms are of the carbon-bound type. Each strain energy will thus be computed relative to a different hypothetical reference system, and there is no *a priori* reason that the two hypothetical systems should be thermodynamically equivalent.

What is necessary to compute a heat of formation, then, is to define the heat of formation of each hypothetical, unstrained atom type. The molecular heat of formation can then be computed as the sum of the heats of formation of all of the atom types plus the strain energy. Assigning atom-type heats of formation can be accomplished using additivity methods originally developed for organic functional groups (Cohen and Benson 1993). The process is typically iterative in conjunction with parameter determination.

Since the assignment of the atomic heats of formation is really just an aspect of parameterization, it should be clear that the possibility of a negative force-field energy, which could derive from addition of net negative non-bonded interaction energies to small non-negative strain energies, is not a complication. Thus, a typical force-field energy calculation will report any or all of (i) a strain energy, which is the energetic consequence of the deviation of the internal molecular coordinates from their equilibrium values, (ii) a force-field energy, which is the sum of the strain energy and the non-bonded interaction energies, and (iii) a heat of formation, which is the sum of the force-field energy and the reference heats of formation for the constituent atom types (Figure 2.8).

For some atom types, thermodynamic data may be lacking to assign a reference heat of formation. When a molecule contains one or more of these atom types, the force field cannot

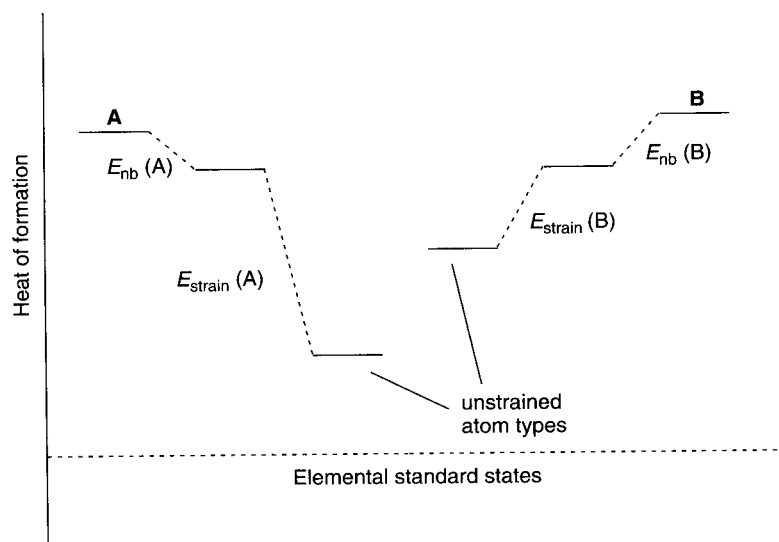


Figure 2.8 Molecules **A** and **B** are chemical isomers but are composed of different atomic types (atomic typomers?). Thus, the sums of the heats of formation of their respective unstrained atom types, which serve as their zeroes of force-field energy, are different. To each zero, strain energy and non-bonded energy (the sum of which are force-field energy) are added to determine heat of formation. In this example, note that **A** is predicted to have a lower heat of formation than **B** even though it has a substantially larger strain energy (and force-field energy); this difference is more than offset by the difference in the reference zeroes.

compute a molecular heat of formation, and energetic comparisons are necessarily limited to conformers, or other isomers that can be formed without any change in atom types.

2.4 Geometry Optimization

One of the key motivations in early force-field design was the development of an energy functional that would permit facile optimization of molecular geometries. While the energy of an arbitrary structure can be interesting, real molecules vibrate thermally about their equilibrium structures, so finding minimum energy structures is key to describing equilibrium constants, comparing to experiment, etc. Thus, as emphasized above, one priority in force-field development is to adopt reasonably simple functional forms so as to facilitate geometry optimization. We now examine the optimization process in order to see how the functional forms enter into the problem.

2.4.1 Optimization Algorithms

Note that, in principle, geometry optimization could be a separate chapter of this text. In essence, geometry optimization is a problem in applied mathematics. How does one find a minimum in an arbitrary function of many variables? [Indeed, we have already discussed the

problem once, in however, it is not on any given variable of geometry optimization (of freedom) and depends on the variable. The problem is generally functional. However, merit discussion, and then examining

Because this text is on computational chemistry, the most basic principles are available (see

For pedagogical reasons, how our energy function is defined for geometry, all we need is that we have found a minimum with force fields, it is indeed the only different geometries

It is easiest to optimize the bond length and the energy. One typically computes the energy in that direction, as a function of length). If the energy we should take a step to adjacent points with non-collinear points to a minimum (since the energy for the computed energy how nearly harmonic the bond stretching is smaller) and repeated are satisfied that the defining convergence this theme. One can solve equations, step size

In the multi-dimensional process iterative for the OH bond, t