

1

What are Theory, Computation, and Modeling?

1.1 Definition of Terms

A clear definition of terms is critical to the success of all communication. Particularly in the area of computational chemistry, there is a need to be careful in the nomenclature used to describe predictive tools, since this often helps clarify what approximations have been made in the course of a modeling ‘experiment’. For the purposes of this textbook, we will adopt a specific convention for what distinguishes theory, computation, and modeling.

In general, ‘theory’ is a word with which most scientists are entirely comfortable. A theory is one or more rules that are postulated to govern the behavior of physical systems. Often, in science at least, such rules are quantitative in nature and expressed in the form of a mathematical equation. Thus, for example, one has the theory of Einstein that the energy of a particle, E , is equal to its relativistic mass, m , times the speed of light in a vacuum, c , squared,

$$E = mc^2 \quad (1.1)$$

The quantitative nature of scientific theories allows them to be tested by experiment. This testing is the means by which the applicable range of a theory is elucidated. Thus, for instance, many theories of classical mechanics prove applicable to macroscopic systems but break down for very small systems, where one must instead resort to quantum mechanics. The observation that a theory has limits in its applicability might, at first glance, seem a sufficient flaw to warrant discarding it. However, if a sufficiently large number of ‘interesting’ systems falls within the range of the theory, practical reasons tend to motivate its continued use. Of course, such a situation tends to inspire efforts to find a more *general* theory that is not subject to the limitations of the original. Thus, for example, classical mechanics can be viewed as a special case of the more general quantum mechanics in which the presence of macroscopic masses and velocities leads to a simplification of the governing equations (and concepts).

Such simplifications of general theories under special circumstances can be key to getting anything useful done! One would certainly *not* want to design the pendulum for a mechanical

clock using the fairly complicated mathematics of quantal theories, for instance, although the process would ultimately lead to the same result as that obtained from the simpler equations of the more restricted classical theories. Furthermore, at least at the start of the twenty-first century, a generalized ‘theory of everything’ does not yet exist. For instance, efforts to link theories of quantum electromagnetics and theories of gravity continue to be pursued.

Occasionally, a theory has proven so robust over time, even if only within a limited range of applicability, that it is called a ‘law’. For instance, Coulomb’s law specifies that the energy of interaction (in arbitrary units) between two point charges is given by

$$E = \frac{q_1 q_2}{\epsilon r_{12}} \quad (1.2)$$

where q is a charge, ϵ is the dielectric constant of a homogeneous medium (possibly vacuum) in which the charges are embedded, and r_{12} is the distance between them. However, the term ‘law’ is best regarded as honorific – indeed, one might regard it as hubris to imply that experimentalists *can* discern the laws of the universe within a finite span of time.

Theory behind us, let us now move on to ‘model’. The difference between a theory and a model tends to be rather subtle, and largely a matter of intent. Thus, the goal of a theory tends to be to achieve as great a generality as possible, irrespective of the practical consequences. Quantum theory, for instance, has breathtaking generality, but the practical consequence is that the equations that govern quantum theory are intractable for all but the most ideal of systems. A model, on the other hand, typically involves the deliberate introduction of simplifying approximations into a more general theory so as to extend its practical utility. Indeed, the approximations sometimes go to the extreme of rendering the model deliberately qualitative. Thus, one can regard the valence-shell-electron-pair repulsion (VSEPR; an acronym glossary is provided as Appendix A of this text) model familiar to most students of inorganic chemistry as a drastic simplification of quantum mechanics to permit discrete choices for preferred conformations of inorganic complexes. (While serious theoreticians may shudder at the empiricism that often governs such drastic simplifications, and mutter gloomily about lack of ‘rigor’, the value of a model is not in its intrinsic beauty, of course, but in its ability to solve practical problems; for a delightful cartoon capturing the hubris of theoretical dogmatism, see Ghosh 2003.)

Another feature sometimes characteristic of a *quantitative* ‘model’ is that it incorporates certain constants that are derived wholly from experimental data, i.e., they are empirically determined. Again, the degree to which this distinguishes a model from a theory can be subtle. The speed of light and the charge of the electron are fundamental constants of the universe that appear either explicitly or implicitly in Eqs. (1.1) and (1.2), and we know these values only through experimental measurement. So, again, the issue tends to be intent. A model is often designed to apply specifically to a restricted volume of what we might call chemical space. For instance, we might imagine developing a model that would predict the free energy of activation for the hydrolysis of substituted β -lactams in water. Our motivation, obviously, would be the therapeutic utility of these species as antibiotics. Because we are limiting ourselves to consideration of only very specific kinds of bond-making and bond-breaking, we may be able to construct a model that takes advantage of a few experimentally known free energies of activation and correlates them with some other measured or predicted

clock using the fairly complicated mathematics of quantal theories, for instance, although the process would ultimately lead to the same result as that obtained from the simpler equations of the more restricted classical theories. Furthermore, at least at the start of the twenty-first century, a generalized ‘theory of everything’ does not yet exist. For instance, efforts to link theories of quantum electromagnetics and theories of gravity continue to be pursued.

Occasionally, a theory has proven so robust over time, even if only within a limited range of applicability, that it is called a ‘law’. For instance, Coulomb’s law specifies that the energy of interaction (in arbitrary units) between two point charges is given by

$$E = \frac{q_1 q_2}{\epsilon r_{12}} \quad (1.2)$$

where q is a charge, ϵ is the dielectric constant of a homogeneous medium (possibly vacuum) in which the charges are embedded, and r_{12} is the distance between them. However, the term ‘law’ is best regarded as honorific – indeed, one might regard it as hubris to imply that experimentalists *can* discern the laws of the universe within a finite span of time.

Theory behind us, let us now move on to ‘model’. The difference between a theory and a model tends to be rather subtle, and largely a matter of intent. Thus, the goal of a theory tends to be to achieve as great a generality as possible, irrespective of the practical consequences. Quantum theory, for instance, has breathtaking generality, but the practical consequence is that the equations that govern quantum theory are intractable for all but the most ideal of systems. A model, on the other hand, typically involves the deliberate introduction of simplifying approximations into a more general theory so as to extend its practical utility. Indeed, the approximations sometimes go to the extreme of rendering the model deliberately qualitative. Thus, one can regard the valence-shell-electron-pair repulsion (VSEPR; an acronym glossary is provided as Appendix A of this text) model familiar to most students of inorganic chemistry as a drastic simplification of quantum mechanics to permit discrete choices for preferred conformations of inorganic complexes. (While serious theoreticians may shudder at the empiricism that often governs such drastic simplifications, and mutter gloomily about lack of ‘rigor’, the value of a model is not in its intrinsic beauty, of course, but in its ability to solve practical problems; for a delightful cartoon capturing the hubris of theoretical dogmatism, see Ghosh 2003.)

Another feature sometimes characteristic of a *quantitative* ‘model’ is that it incorporates certain constants that are derived wholly from experimental data, i.e., they are empirically determined. Again, the degree to which this distinguishes a model from a theory can be subtle. The speed of light and the charge of the electron are fundamental constants of the universe that appear either explicitly or implicitly in Eqs. (1.1) and (1.2), and we know these values only through experimental measurement. So, again, the issue tends to be intent. A model is often designed to apply specifically to a restricted volume of what we might call chemical space. For instance, we might imagine developing a model that would predict the free energy of activation for the hydrolysis of substituted β -lactams in water. Our motivation, obviously, would be the therapeutic utility of these species as antibiotics. Because we are limiting ourselves to consideration of only very specific kinds of bond-making and bond-breaking, we may be able to construct a model that takes advantage of a few experimentally known free energies of activation and correlates them with some other measured or predicted

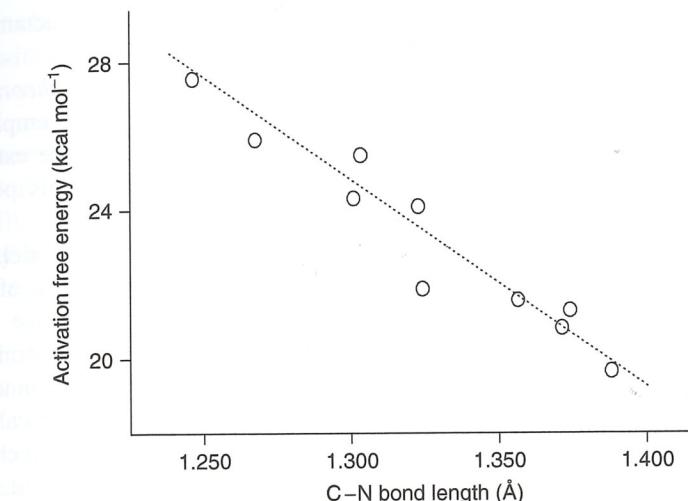


Figure 1.1 Correlation between activation free energy for aqueous hydrolysis of β -lactams and lactam C–N bond lengths as determined from X-ray crystallography (data entirely fictitious)

quantity. For example, we might find from comparison with X-ray crystallography that there is a linear correlation between the aqueous free energy of activation, ΔG^\ddagger , and the length of the lactam C–N bond in the crystal, r_{CN} (Figure 1.1). Our ‘model’ would then be

$$\Delta G^\ddagger = ar_{CN} + b \quad (1.3)$$

where a would be the slope (in units of energy per length) and b the intercept (in units of energy) for the empirically determined correlation.

Equation (1.3) represents a very simple model, and that simplicity derives, presumably, from the small volume of chemical space over which it appears to hold. As it is hard to imagine deriving Eq. (1.3) from the fundamental equations of quantum mechanics, it might be more descriptive to refer to it as a ‘relationship’ rather than a ‘model’. That is, we make some attempt to distinguish between correlation and causality. For the moment, we will not parse the terms too closely.

An interesting question that arises with respect to Eq. (1.3) is whether it may be more broadly applicable. For instance, might the model be useful for predicting the free energies of activation for the hydrolysis of γ -lactams? What about amides in general? What about imides? In a statistical sense, these chemical questions are analogous to asking about the degree to which a correlation may be trusted for extrapolation vs. interpolation. One might say that we have derived a correlation involving two axes of multi-dimensional chemical space, activation free energy for β -lactam hydrolysis and β -lactam C–N bond length. Like any correlation, our model is expected to be most robust when used in an interpolative sense, i.e., when applied to newly measured β -lactam C–N bonds with lengths that fall within the range of the data used to derive the correlation. Increasingly less certain will be application of Eq. (1.3) to β -lactam bond lengths that are *outside* the range used to derive the correlation,

or assumption that other chemical axes, albeit qualitatively similar (like γ -lactam C–N bond lengths), will be coincident with the abscissa.

Thus, a key question in one's mind when evaluating any application of a theoretical model should be, 'How similar is the system being studied to systems that were employed in the development of the model?' The generality of a given model can only be established by comparison to experiment for a wider and wider variety of systems. This point will be emphasized repeatedly throughout this text.

Finally, there is the definition of ‘computation’. While theories and models like those represented by Eqs. (1.1), (1.2), and (1.3), are not particularly taxing in terms of their mathematics, many others can only be efficiently put to use with the assistance of a digital computer. Indeed, there is a certain synergy between the development of chemical theories and the development of computational hardware, software, etc. If a theory cannot be tested, say because solution of the relevant equations lies outside the scope of practical possibility, then its utility cannot be determined. Similarly, advances in computational technology can permit existing theories to be applied to increasingly complex systems to better gauge the degree to which they are robust. These points are expanded upon in Section 1.4. Here we simply close with the concise statement that ‘computation’ is the use of digital technology to solve the mathematical equations defining a particular theory or model.

With all these definitions in hand, we may return to a point raised in the preface, namely, what is the difference between ‘Theory’, ‘Molecular Modeling’, and ‘Computational Chemistry’? To the extent members of the community make distinctions, ‘theorists’ tend to have as their greatest goal the development of new theories and/or models that have improved performance or generality over existing ones. Researchers involved in ‘molecular modeling’ tend to focus on target systems having particular chemical relevance (e.g., for economic reasons) and to be willing to sacrifice a certain amount of theoretical rigor in favor of getting the right answer in an efficient manner. Finally, ‘computational chemists’ may devote themselves not to chemical aspects of the problem, *per se*, but to computer-related aspects, e.g., writing improved algorithms for solving particularly difficult equations, or developing new ways to encode or visualize data, either as input to or output from a model. As with any classification scheme, there are no distinct boundaries recognized either by observers or by individual researchers, and certainly a given research endeavor may involve significant efforts undertaken within all three of the areas noted above. In the spirit of inclusiveness, we will treat the terms as essentially interchangeable.

1.2 Quantum Mechanics

The postulates and theorems of quantum mechanics form the rigorous foundation for the prediction of observable chemical properties from first principles. Expressed somewhat loosely, the fundamental postulates of quantum mechanics assert that microscopic systems are described by ‘wave functions’ that completely characterize all of the physical properties of the system. In particular, there are quantum mechanical ‘operators’ corresponding to each physical observable that, when applied to the wave function, allow one to predict the probability of finding the system to exhibit a particular value or range of values (scalar, vector,

etc.)
famil
Ho
conn
intuit
mode
tions
more
than
blush

The
of thi
headi
menta
appro

1.3

What
it, on
than
studie

1.3.1

Let u
pure
is its
those
requi
or ‘be
the ‘b
under
possi
the at
in mo

The
single
equil
In th
stere
system
in suc

ilar (like γ -lactam C–N bond

lication of a theoretical model
ns that were employed in the
I can only be established by
systems. This point will be

ories and models like those
axing in terms of their math-
with the assistance of a digital
lopment of chemical theories
If a theory cannot be tested,
scope of practical possibility,
computational technology can
systems to better gauge the
pon in Section 1.4. Here we
the use of digital technology
or model.

aised in the preface, namely,
, and ‘Computational Chem-
is, ‘theorists’ tend to have as
s that have improved perfor-
n ‘molecular modeling’ tend
(e.g., for economic reasons)
in favor of getting the right
may devote themselves not
related aspects, e.g., writing
or developing new ways to
el. As with any classifica-
y observers or by individual
ve significant efforts under-
inclusiveness, we will treat

igorous foundation for the
ples. Expressed somewhat
t that microscopic systems
1 of the physical properties
tors’ corresponding to each
ow one to predict the prob-
e of values (scalar, vector,

etc.) for that observable. This text assumes prior exposure to quantum mechanics and some familiarity with operator and matrix formalisms and notation.

However, many successful chemical models exist that do not necessarily have obvious connections with quantum mechanics. Typically, these models were developed based on intuitive concepts, i.e., their forms were determined inductively. In principle, any successful model *must* ultimately find its basis in quantum mechanics, and indeed *a posteriori* derivations have illustrated this point in select instances, but often the form of a good model is more readily grasped when rationalized on the basis of intuitive chemical concepts rather than on the basis of quantum mechanics (the latter being desperately non-intuitive at first blush).

Thus, we shall leave quantum mechanics largely unreviewed in the next two chapters of this text, focusing instead on the intuitive basis for classical models falling under the heading of ‘molecular mechanics’. Later in the text, we shall see how some of the fundamental approximations used in molecular mechanics can be justified in terms of well-defined approximations to more complete quantum mechanical theories.

1.3 Computable Quantities

What predictions can be made by the computational chemist? In principle, if one can measure it, one can predict it. In practice, some properties are more amenable to accurate computation than others. There is thus some utility in categorizing the various properties most typically studied by computational chemists.

1.3.1 Structure

Let us begin by focusing on isolated molecules, as they are the fundamental unit from which pure substances are constructed. The minimum information required to specify a molecule is its molecular formula, i.e., the atoms of which it is composed, and the manner in which those atoms are connected. Actually, the latter point should be put more generally. What is required is simply to know the relative positions of all of the atoms in space. Connectivity, or ‘bonding’, is itself a property that is open to determination. Indeed, the determination of the ‘best’ structure from a chemically reasonable (or unreasonable) guess is a very common undertaking of computational chemistry. In this case ‘best’ is defined as having the lowest possible energy given an overall connectivity roughly dictated by the starting positions of the atoms as chosen by the theoretician (the process of structure optimization is described in more detail in subsequent chapters).

This sounds relatively simple because we are talking about the modeling of an isolated, single molecule. In the laboratory, however, we are much more typically dealing with an equilibrium mixture of a very large number of molecules at some non-zero temperature. In that case, *measured* properties reflect thermal averaging, possibly over multiple discrete stereoisomers, tautomers, etc., that are structurally quite different from the idealized model system, and great care must be taken in making comparisons between theory and experiment in such instances.

1.3.2 Potential Energy Surfaces

The first step to making the theory more closely mimic the experiment is to consider not just one structure for a given chemical formula, but all possible structures. That is, we fully characterize the potential energy surface (PES) for a given chemical formula (this requires invocation of the Born–Oppenheimer approximation, as discussed in more detail in Chapters 4 and 15). The PES is a hypersurface defined by the potential energy of a collection of atoms over all possible atomic arrangements; the PES has $3N - 6$ coordinate dimensions, where N is the number of atoms ≥ 3 . This dimensionality derives from the three-dimensional nature of Cartesian space. Thus each structure, which is a point on the PES, can be defined by a vector \mathbf{X} where

$$\mathbf{X} \equiv (x_1, y_1, z_1, x_2, y_2, z_2, \dots, x_N, y_N, z_N) \quad (1.4)$$

and x_i , y_i , and z_i are the Cartesian coordinates of atom i . However, this expression of \mathbf{X} does not *uniquely* define the structure because it involves an arbitrary origin. We can reduce the dimensionality without affecting the structure by removing the three dimensions associated with translation of the structure in the x , y , and z directions (e.g., by insisting that the molecular center of mass be at the origin) and removing the three dimensions associated with rotation about the x , y , and z axes (e.g., by requiring that the principal moments of inertia align along those axes in increasing order).

A different way to appreciate this reduced dimensionality is to imagine constructing a structure vector atom by atom (Figure 1.2), in which case it is most convenient to imagine the dimensions of the PES being internal coordinates (i.e., bond lengths, valence angles, etc.). Thus, choice of the first atom involves no degrees of geometric freedom – the atom defines the origin. The position of the second atom is specified by its distance from the first. So, a two-atom system has a single degree of freedom, the bond length; this corresponds to $3N - 5$ degrees of freedom, as should be the case for a linear molecule. The third atom must be specified either by its distances to each of the preceding atoms, or by a distance to one and an angle between the two bonds thus far defined to a common atom. The three-atom system, if collinearity is not enforced, has 3 total degrees of freedom, as it should. Each additional atom requires three coordinates to describe its position. There are several ways to envision describing those coordinates. As in Figure 1.2, they can either be a bond length, a valence angle, and a dihedral angle, or they can be a bond length and two valence angles. Or, one can imagine that the first three atoms have been used to create a fixed Cartesian reference frame, with atom 1 defining the origin, atom 2 defining the direction of the positive x axis, and atom 3 defining the upper half of the xy plane. The choice in a given calculation is a matter of computational convenience. Note, however, that the *shapes* of particular surfaces necessarily depend on the choice of their coordinate systems, although they will map to one another in a one-to-one fashion.

Particularly interesting points on PESs include local minima, which correspond to optimal molecular structures, and saddle points (i.e., points characterized by having no slope in any direction, downward curvature for a single coordinate, and upward curvature for all of the other coordinates). Simple calculus dictates that saddle points are lowest energy barriers

Figure
of free
freed
freed
ways
be sp

on p
trans
info
nect
U
they
surf
and
that
coo
coo
the
the
a s
ass
act
of

The experiment is to consider not possible structures. That is, we given chemical formula (this, as discussed in more detail in potential energy of a collection $3N - 6$ coordinate dimensions, gives from the three-dimensional point on the PES, can be defined

$$v, z_N) \quad (1.4)$$

ever, this expression of \mathbf{X} does not have a physical origin. We can reduce the number of degrees of freedom associated with the molecule by insisting that the principal moments of

is to imagine constructing a molecular model. It is most convenient to imagine specifying bond lengths, valence angles, and dihedral angles. Geometric freedom – the atom can rotate about its bond – is specified by its distance from the first atom, which is the bond length; this corresponds to one degree of freedom per bond. The third atom must be specified either by a distance to one and a valence angle, or by a distance to one and a dihedral angle. The three-atom system, as it should be, has three degrees of freedom. Each additional atom adds one degree of freedom. There are several ways to envision the nature of the fourth atom. It can be a bond length, a valence angle, or a dihedral angle. Or, one can use a fixed Cartesian reference frame. In this frame, the direction of the positive x axis, for example, in a given calculation is a fixed coordinate. The shapes of particular surfaces depend on the choice of axes, though they will map to one another.

which correspond to optimal structures. This is achieved by having no slope in any coordinate dimension for all of the atoms except those at the lowest energy barriers.

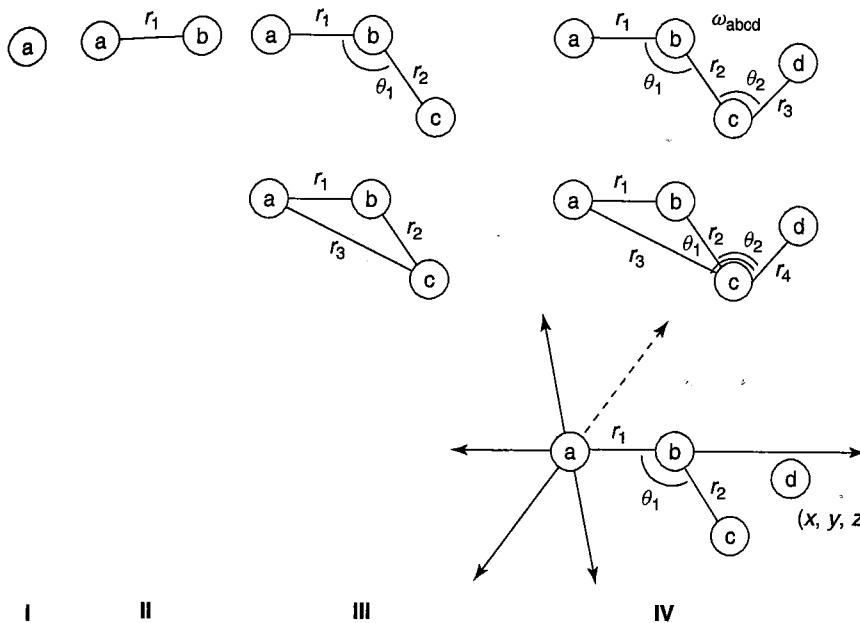


Figure 1.2 Different means for specifying molecular geometries. In frame **I**, there are no degrees of freedom as only the nature of atom 'a' has been specified. In frame **II**, there is a single degree of freedom, namely the bond length. In frame **III**, location of atom 'c' requires two additional degrees of freedom, either two bond lengths or a bond length and a valence angle. Frame **IV** illustrates various ways to specify the location of atom 'd'; note that in every case, three new degrees of freedom must be specified, either in internal or Cartesian coordinates

on paths connecting minima, and thus they can be related to the chemical concept of a transition state. So, a complete PES provides, for a given collection of atoms, complete information about all possible chemical structures and all isomerization pathways interconnecting them.

Unfortunately, complete PESs for polyatomic molecules are very hard to visualize, since they involve a large number of dimensions. Typically, we take slices through potential energy surfaces that involve only a single coordinate (e.g., a bond length) or perhaps two coordinates, and show the relevant reduced-dimensionality energy curves or surfaces (Figure 1.3). Note that some care must be taken to describe the nature of the slice with respect to the other coordinates. For instance, was the slice a hyperplane, implying that all of the non-visualized coordinates have fixed values, or was it a more general hypersurface? A typical example of the latter choice is one where the non-visualized coordinates take on values that minimize the potential energy given the value of the visualized coordinate(s). Thus, in the case of a single visualized dimension, the curve attempts to illustrate the minimum energy path associated with varying the visualized coordinate. [We must say 'attempts' here, because an actual continuous path connecting any two structures on a PES may involve any number of structures all of which have the same value for a single internal coordinate. When that

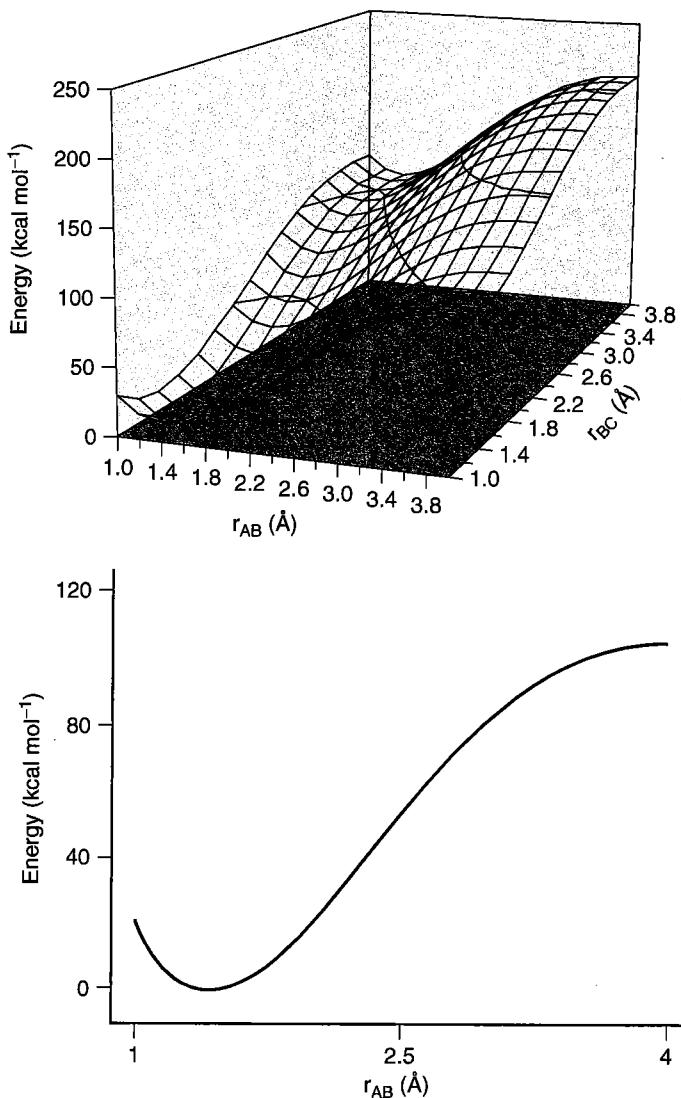
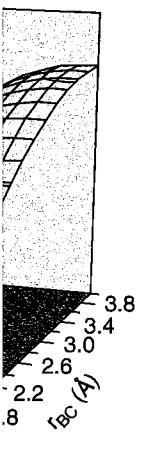


Figure 1.3 The full PES for the hypothetical molecule ABC requires four dimensions to display ($3N - 6 = 3$ coordinate degrees of freedom plus one dimension for energy). The three-dimensional plot (top) represents a hyperslice through the full PES showing the energy as a function of two coordinate dimensions, the AB and BC bond lengths, while taking a fixed value for the angle ABC (a typical choice might be the value characterizing the global minimum on the full PES). A further slice of this surface (bottom) now gives the energy as a function of a single dimension, the AB bond length, where the BC bond length is now also treated as-frozen (again at the equilibrium value for the global minimum)

path is
number
dimensions
varied c
curve m
'partially
to ensur

Figure 1
0, located
correspon
in the u
2 under
coordina
point) is
symmetr
two-dim
we only
solid cu
from the
respective
continuo
driving
for inter
example

path is projected onto the dimension defined by that single coordinate (or any reduced number of dimensions including it) the resulting curve is a non-single-valued function of the dimension. When we arbitrarily choose to use the lowest energy point for each value of the varied coordinate, we may introduce discontinuities in the actual structures, even though the curve may appear to be smooth (Figure 1.4). Thus, the generation and interpretation of such 'partially relaxed' potential energy curves should involve a check of the individual structures to ensure that such a situation has not arisen.]



1
4

requires four dimensions to dimension for energy). The PES showing the energy as a while taking a fixed value for e global minimum on the full function of a single dimension, frozen (again at the equilibrium

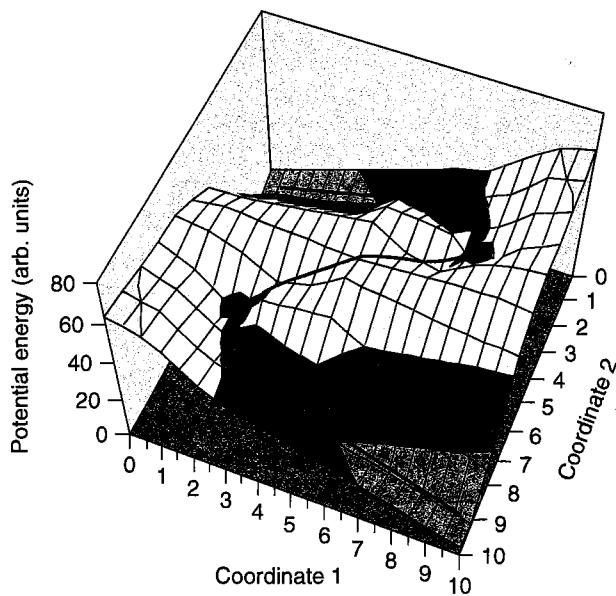


Figure 1.4 The bold line in (a) traces out a lowest-energy path connecting two minima of energy 0, located at coordinates (0,1) and (10,9), on a hypothetical three-dimensional PES – shaded regions correspond to contour levels spanning 20 energy units. Following the path starting from point (0,1) in the upper left, coordinate 1 initially smoothly increases to a value of about 7.5 while coordinate 2 undergoes little change. Then, however, because of the coupling between the two coordinates, coordinate 1 begins *decreasing* while coordinate 2 changes. The 'transition state structure' (saddle point) is reached at coordinates (5,5) and has energy 50. On this PES, the path downward is the symmetric reverse of the path up. If the full path is projected so as to remove coordinate 2, the two-dimensional potential energy diagram (b) is generated. The solid curve is what would result if we only considered lowest energy structures having a given value of coordinate 1. Of course, the solid curve is discontinuous in coordinate 2, since approaches to the 'barrier' in the solid curve from the left and right correspond to structures having values for coordinate 2 of about 1 and 9, respectively. The dashed curve represents the higher energy structures that appear on the smooth, continuous, three-dimensional path. If the lower potential energy diagram were to be generated by driving coordinate 1, and care were not taken to note the discontinuity in coordinate 2, the barrier for interconversion of the two minima would be underestimated by a factor of 2 in this hypothetical example. (For an actual example of this phenomenon, see Cramer *et al.* 1994.)

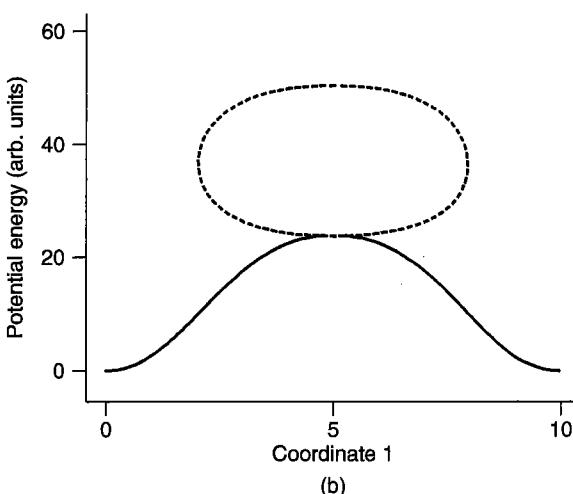


Figure 1.4 (Continued)

Finally, sometimes slices are chosen so that all structures in the slicing surface belong to a particular symmetry point group. The utility of symmetry will be illustrated in various situations throughout the text.

With the complete PES in hand (or, more typically, with the region of the PES that would be expected to be chemically accessible under the conditions of the experimental system being modeled), one can take advantage of standard precepts of statistical mechanics (see Chapter 10) to estimate equilibrium populations for situations involving multiple stable molecular structures and compute ensemble averages for physical observables.

1.3.3 Chemical Properties

One can arbitrarily divide the properties one might wish to estimate by computation into three classes. The first is ‘single-molecule’ properties, that is, properties that could in principle be measured from a single molecule, even though, in practice, use of a statistical ensemble may be required for practical reasons. Typical examples of such properties are spectral quantities. Thus, theory finds considerable modern application to predicting nuclear magnetic resonance (NMR) chemical shifts and coupling constants, electron paramagnetic resonance (EPR) hyperfine coupling constants, absorption maxima for rotational, vibrational, and electronic spectra (typically in the microwave, infrared, and ultraviolet/visible regions of the spectrum, respectively), and electron affinities and ionization potentials (see Chapter 9).

With respect to molecular energetics, one can, in principle, measure the total energy of a molecule (i.e., the energy required to separate it into its constituent nuclei and electrons all infinitely separated from one another and at rest). More typically, however, laboratory measurements focus on thermodynamic quantities such as enthalpy, free energy, etc., and

this is the to estimate minima derived state str formation recognit to name being m as solva such co

Final One ma However istry – s tronic, proven obje

In cas that con quantiti unique good ex concept

1.4

1.4.1

Why ha taking t these tw perspec experim

Ch rials, be ardent t Rather, as to ta

With into th some a photoly

this is the second category into which predicted quantities fall. Theory is extensively used to estimate equilibrium constants, which are derived from free energy differences between minima on a PES, and rate constants, which, with certain assumptions (see Chapter 15), are derived from free energy differences between minima on a PES and connected transition-state structures. Thus, theory may be used to predict reaction thermochemistries, heats of formation and combustion, kinetic isotope effects, complexation energies (key to molecular recognition), acidity and basicity (e.g., pK_a values), ‘stability’, and hydrogen bond strengths, to name a few properties of special interest. With a sufficiently large collection of molecules being modeled, theory can also, in principle, compute bulk thermodynamic phenomena such as solvation effects, phase transitions, etc., although the complexity of the system may render such computations quite challenging.

Finally, there are computable ‘properties’ that do not correspond to physical observables. One may legitimately ask about the utility of such ontologically indefensible constructs! However, one should note that unmeasurable properties long predate computational chemistry – some examples include bond order, aromaticity, reaction concertedness, and isoelectronic, -steric, and -lobal behavior. These properties involve *conceptual* models that have proven sufficiently useful in furthering chemical understanding that they have overcome objections to their not being uniquely defined.

In cases where such models take measurable quantities as input (e.g., aromaticity models that consider heats of hydrogenation or bond-length alternation), clearly those measurable quantities are also computable. There are additional non-observables, however, that are unique to modeling, usually being tied to some aspect of the computational algorithm. A good example is atomic partial charge (see Chapter 9), which can be a very useful chemical concept for understanding molecular reactivity.

1.4 Cost and Efficiency

1.4.1 Intrinsic Value

Why has the practice of computational chemistry skyrocketed in the last few years? Try taking this short quiz: Chemical waste disposal and computational technology – which of these two keeps getting more and more expensive and which less and less? From an economic perspective, at least, theory is enormously attractive as a tool to reduce the costs of doing experiments.

Chemistry’s impact on modern society is most readily perceived in the creation of materials, be they foods, textiles, circuit boards, fuels, drugs, packaging, etc. Thus, even the most ardent theoretician would be unlikely to suggest that theory could ever *supplant* experiment. Rather, most would opine that opportunities exist for *combining* theory with experiment so as to take advantage of synergies between them.

With that in mind, one can categorize efficient combinations of theory and experiment into three classes. In the first category, theory is applied *post facto* to a situation where some ambiguity exists in the interpretation of existing experimental results. For example, photolysis of a compound in an inert matrix may lead to a single product species as

in the slicing surface belong
will be illustrated in various
the region of the PES that
conditions of the experimental
concepts of statistical mechanics
ions involving multiple stable
ical observables.

estimate by computation into
properties that could in prin-
practice, use of a statistical
mples of such properties are
lication to predicting nuclear
stants, electron paramagnetic
maxima for rotational, vibra-
frared, and ultraviolet/visible
and ionization potentials (see

measure the total energy of
nstituent nuclei and electrons
ypically, however, laboratory
thalpy, free energy, etc., and

analyzed by spectroscopy. However, the identity of this unique product may not be obvious given a number of plausible alternatives. A calculation of the energies and spectra for *all* of the postulated products provides an opportunity for comparison and may prove to be definitive.

In the second category, theory may be employed in a simultaneous fashion to optimize the design and progress of an experimental program. Continuing the above analogy, *a priori* calculation of spectra for plausible products may assist in choosing experimental parameters to permit the observation of minor components which might otherwise be missed in a complicated mixture (e.g., theory may allow the experimental instrument to be tuned properly to observe a signal whose location would not otherwise be predictable).

Finally, theory may be used to predict properties which might be especially difficult or dangerous (i.e., costly) to measure experimentally. In the difficult category are such data as rate constants for the reactions of trace, upper-atmospheric constituents that might play an important role in the ozone cycle. For sufficiently small systems, levels of quantum mechanical theory can now be brought to bear that have accuracies comparable to the best modern experimental techniques, and computationally derived rate constants may find use in complex kinetic models until such time as experimental data are available. As for dangerous experiments, theoretical pre-screening of a series of toxic or explosive compounds for desirable (or undesirable) properties may assist in prioritizing the order in which they are prepared, thereby increasing the probability that an acceptable product will be arrived at in a maximally efficient manner.

1.4.2 Hardware and Software

All of these points being made, even computational chemistry is not without cost. In general, the more sophisticated the computational model, the more expensive in terms of computational resources. The talent of the well-trained computational chemist is knowing how to maximize the accuracy of a prediction while minimizing the investment of such resources. A primary goal of this text is to render more clear the relationship between accuracy and cost for various levels of theory so that even relatively inexperienced users can make informed assessments of the likely utility (before the fact) or credibility (after the fact) of a given calculation.

To be more specific about computational resources, we may, without going into a great deal of engineering detail, identify three features of a modern digital computer that impact upon its utility as a platform for molecular modeling. The first feature is the speed with which it carries out mathematical operations. Various metrics are used when comparing the speed of 'chips', which are the fundamental processing units. One particularly useful one is the number of floating-point operations per second (FLOPS) that the chip can accomplish. That is, how many mathematical manipulations of decimal numbers can be carried out (the equivalent measure for integers is IPS). Various benchmark computer codes are available for comparing one chip to another, and one should always bear in mind that measured processor speeds are dependent on which code or set of codes was used. Different

the product may not be obvious
energies and spectra for all
parison and may prove to be

sultaneous fashion to optimize
ng the above analogy, *a priori*
osing experimental parameters
herwise be missed in a compli-
ment to be tuned properly to
itable).

ight be especially difficult or
fficult category are such data
c constituents that might play
1 systems, levels of quantum
accuracies comparable to the
erived rate constants may find
ntal data are available. As for
toxic or explosive compounds
izing the order in which they
able product will be arrived at

is not without cost. In general,
xpensive in terms of computa-
al chemist is knowing how to
investment of such resources. A
hip between accuracy and cost
nced users can make informed
ity (after the fact) of a given

ay, without going into a great
n digital computer that impact
first feature is the speed with
are used when comparing the
One particularly useful one is
that the chip can accomplish.
y represented numbers can be
us benchmark computer codes
ould always bear in mind that
et of codes was used. Different

kinds of mathematical operations or different orderings of operations can have effects as large as an order of magnitude on individual machine speeds because of the way the processors are designed and because of the way they interact with other features of the computational hardware.

The second feature affecting performance is memory. In order to carry out a floating-point operation, there must be floating-point numbers on which to operate. Numbers (or characters) to be processed are stored in a magnetic medium referred to as memory. In a practical sense, the size of the memory associated with a given processor sets the limit on the total amount of information to which it has 'instant' access. In modern multiprocessor machines, this definition has grown more fuzzy, as there tend to be multiple memory locations, and the speed with which a given processor can access a given memory site varies depending upon their physical locations with respect to one another. The somewhat unsurprising bottom line is that more memory and shorter access times tend to lead to improved computational performance.

The last feature is storage, typically referred to as disk since that has been the read/write storage medium of choice for the last several years. Storage is exactly like memory, in the sense that it holds number or character data, but it is accessible to the processing unit at a much slower rate than is memory. It makes up for this by being much cheaper and being, in principle, limitless and permanent. Calculations which need to read and/or write data to a disk necessarily proceed more slowly than do calculations that can take place entirely in memory. The difference is sufficiently large that there are situations where, rather than storing on disk data that will be needed later, it is better to throw them away (because memory limits require you to overwrite the locations in which they are stored), as subsequent recomputation of the needed data is faster than reading it back from disk storage. Such a protocol is usually called a 'direct' method (see Almlöf, Faegri, and Korsell 1982).

Processors, memory, and storage media are components of a computer referred to as 'hardware'. However, the efficiency of a given computational task depends also on the nature of the instructions informing the processor how to go about implementing that task. Those instructions are encoded in what is known as 'software'. In terms of computational chemistry, the most obvious piece of software is the individual program or suite of programs with which the chemist interfaces in order to carry out a computation. However, that is by no means the only software involved. Most computational chemistry software consists of a large set of instructions written in a 'high-level' programming language (e.g., FORTRAN or C++), and choices of the user dictate which sets of instructions are followed in which order. The collection of all such instructions is usually called a 'code' (listings of various computational chemistry codes can be found at websites such as <http://cmm.info.nih.gov/modeling/software.html>). But the language of the code cannot be interpreted directly by the processor. Instead, a series of other pieces of software (compilers, assemblers, etc.) translate the high-level language instructions into the step-by-step operations that are carried out by the processing unit. Understanding how to write code (in whatever language) that takes the best advantage of the total hardware/software environment on a particular computer is a key aspect to the creation of an efficient software package.

1.4.3 Algorithms

In a related sense, the manner in which mathematical equations are turned into computer instructions is also key to efficient software development. Operations like addition and subtraction do not allow for much in the way of innovation, needless to say, but operations like matrix diagonalization, numerical integration, etc., are sufficiently complicated that different algorithms leading to the same (correct) result can vary markedly in computational performance. A great deal of productive effort in the last decade has gone into the development of so-called ‘linear-scaling’ algorithms for various levels of theory. Such an algorithm is one that permits the cost of a computation to scale roughly linearly with the size of the system studied. At first, this may not sound terribly demanding, but a quick glance back at Coulomb’s law [Eq. (1.2)] will help to set this in context. Coulomb’s law states that the potential energy from the interaction of charged particles depends on the pairwise interaction of all such particles. Thus, one might expect any calculation of this quantity to scale as the *square* of the size of the system (there are $n(n - 1)/2$ such interactions where n is the number of particles). However, for sufficiently large systems, sophisticated mathematical ‘tricks’ permit the scaling to be brought down to linear.

In this text, we will not be particularly concerned with algorithms – not because they are not important but because such concerns are more properly addressed in advanced textbooks aimed at future practitioners of the art. Our focus will be primarily on the conceptual aspects of particular computational models, and not necessarily on the most efficient means for implementing them.

We close this section with one more note on careful nomenclature. A ‘code’ renders a ‘model’ into a set of instructions that can be understood by a digital computer. Thus, if one applies a particular model, let us say the molecular mechanics model called MM3 (which will be described in the next chapter) to a particular problem, say the energy of chair cyclohexane, the results should be completely independent of which code one employs to carry out the calculation. If two pieces of software (let’s call them MYPROG and YOURPROG) differ by more than the numerical noise that can arise because of different round-off conventions with different computer chips (or having set different tolerances for what constitutes a converged calculation) then one (or both!) of those pieces of software is *incorrect*. In colloquial terms, there is a ‘bug’ in the incorrect code(s).

Furthermore, it is never correct to refer to the results of a calculation as deriving from the code, e.g., to talk about one’s ‘MYPROG structure’. Rather, the results derive from the model, and the structure is an ‘MM3 structure’. It is not simply incorrect to refer to the results of the calculation by the name of the code, it is confusing: MYPROG may well contain code for several *different* molecular mechanics models, not just MM3, so simply naming the program is insufficiently descriptive.

It is regrettable, but must be acknowledged, that certain models found in the chemical literature are themselves not terribly well defined. This tends to happen when features or parameters of a model are updated without any change in the name of the model as assigned by the original authors. When this happens, codes implementing older versions of the model will disagree with codes implementing newer versions even though each uses the same name for the model. Obviously, developers should scrupulously avoid ever allowing this situation

Physical (unit nan)
Angular m
Mass
Charge
Vacuum p
Length (b
Energy (h
Electric d
Electric p
Planck's c
Speed of l
Bohr mag
Nuclear m

to arise.
state wh
results (c

1.5 N

In descri
render ed
proton, a
defined t
to Gauss
magnitud
equation
can be d
distance
symboliz
also calle
useful qu
precision

Bibliog

Cramer, C
for Sol

Table 1.1 Useful quantities in atomic and other units

Physical quantity (unit name)	Symbol	Value in a.u.	Value in SI units	Value(s) in other units
Angular momentum	\hbar	1	1.055×10^{-34} J s	2.521×10^{-35} cal s
Mass	m_e	1	9.109×10^{-31} kg	
Charge	e	1	1.602×10^{-19} C	1.519×10^{-14} statC
Vacuum permittivity	$4\pi\epsilon_0$	1	1.113×10^{-10} C ² J ⁻¹ m ⁻¹	2.660×10^{-21} C ² cal ⁻¹ Å ⁻¹
Length (bohr)	a_0	1	5.292×10^{-11} m	0.529 Å 52.9 pm
Energy (hartree)	E_h	1	4.360×10^{-18} J	627.51 kcal mol ⁻¹ 2.626×10^3 kJ mol ⁻¹ 27.211 eV 2.195×10^5 cm ⁻¹
Electric dipole moment	ea_0	1	8.478×10^{-30} C m	2.542 D
Electric polarizability	$e^2a_0^2E_h^{-1}$	1	1.649×10^{-41} C ² m ² J ⁻¹	
Planck's constant	h	2π	6.626×10^{-34} J s	
Speed of light	c	1.370×10^2	2.998×10^8 m s ⁻¹	
Bohr magneton	μ_B	0.5	9.274×10^{-24} J T ⁻¹	
Nuclear magneton	μ_N	2.723×10^{-4}	5.051×10^{-27} J T ⁻¹	

to arise. To be safe, scientific publishing that includes computational results should always state what code or codes were used, *to include version numbers*, in obtaining particular model results (clearly version control of computer codes is thus just as critical as it is for models).

1.5 Note on Units

In describing a computational model, a clear equation can be worth 1000 words. One way to render equations more clear is to work in atomic (or theorist's) units. In a.u., the charge on the proton, e , the mass of the electron, m_e , and \hbar (i.e., Planck's constant divided by 2π) are all defined to have magnitude 1. When converting equations expressed in SI units (as opposed to Gaussian units), $4\pi\epsilon_0$, where ϵ_0 is the permittivity of the vacuum, is also defined to have magnitude 1. As the magnitude of these quantities is unity, they are dropped from relevant equations, thereby simplifying the notation. Other atomic units having magnitudes of unity can be derived from these three by dimensional analysis. For instance, $\hbar^2/m_e e^2$ has units of distance and is defined as 1 a.u.; this atomic unit of distance is also called the 'bohr' and symbolized by a_0 . Similarly, e^2/a_0 has units of energy, and defines 1 a.u. for this quantity, also called 1 hartree and symbolized by E_h . Table 1.1 provides notation and values for several useful quantities in a.u. and also equivalent values in other commonly used units. Greater precision and additional data are available at <http://www.physics.nist.gov/PhysRefData/>.

Bibliography and Suggested Additional Reading

- Cramer, C. J., Famini, G. R., and Lowrey, A. 1993. 'Use of Quantum Chemical Properties as Analogs for Solvatochromic Parameters in Structure–Activity Relationships', *Acc. Chem. Res.*, **26**, 599.

- Irikura, K. K., Frurip, D. J., Eds. 1998. *Computational Thermochemistry*, American Chemical Society Symposium Series, Vol. 677, American Chemical Society: Washington, DC.
- Jensen, F. 1999. *Introduction to Computational Chemistry*, Wiley: Chichester.
- Jorgensen, W. L. 2004. 'The Many Roles of Computation in Drug Discovery', *Science*, 303, 1813.
- Leach, A. R. 2001. *Molecular Modelling*, 2nd Edn., Prentice Hall: London.
- Levine, I. N. 2000. *Quantum Chemistry*, 5th Edn., Prentice Hall: New York.
- Truhlar, D. G. 2000. 'Perspective on "Principles for a direct SCF approach to LCAO-MO *ab initio* calculations"' *Theor. Chem. Acc.*, 103, 349.

References

- Almlöf, J., Faegri, K., Jr., and Korsell, K. 1982. *J. Comput. Chem.*, 3, 385.
- Cramer, C. J., Denmark, S. E., Miller, P. C., Dorow, R. L., Swiss, K. A., and Wilson, S. R. 1994. *J. Am. Chem. Soc.*, 116, 2437.
- Ghosh, A. 2003. *Curr. Opin. Chem. Biol.*, 7, 110.

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

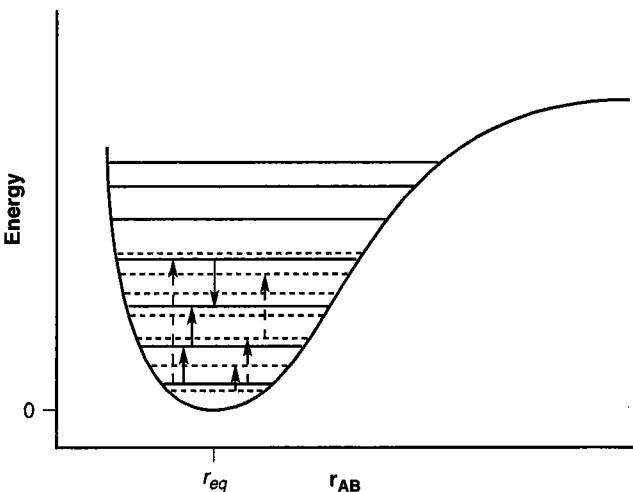


Figure 2.1 The first seven vibrational energy levels for a lighter (solid horizontal lines) and heavier (horizontal dashed lines) isotopomer of diatomic AB. Allowed vibrational transitions are indicated by solid vertical arrows, forbidden transitions are indicated by dashed vertical arrows

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

$$\begin{aligned} U(r) = U(r_{\text{eq}}) + \frac{dU}{dr} \Big|_{r=r_{\text{eq}}} (r - r_{\text{eq}}) + \frac{1}{2!} \frac{d^2U}{dr^2} \Big|_{r=r_{\text{eq}}} (r - r_{\text{eq}})^2 \\ + \frac{1}{3!} \frac{d^3U}{dr^3} \Big|_{r=r_{\text{eq}}} (r - r_{\text{eq}})^3 + \dots \end{aligned} \quad (2.1)$$

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

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

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 char
rium bond le
came to be c

Concomita
to a reasona
enthalpies. T
of identica
differences i
from differen
the positive
enthalpies. S
analysis.

One migh
bond length
molecules, o
der Waals i
lengthen. T
force consta
angle-bendi
suggested b
be used to p
general idea
functions to
and were ab

The rest
the force-fie
general. At
is provided

2.2 Pot

2.2.1 Bo

Before we
total steric
truncated T
Thus, if we
from its op
bond is str
positive, w
is to includ
a potential

and 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, in 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 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 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 shorten. 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 to practice of this general idea 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 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 Potential Energy Functional Forms

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

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

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

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

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

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

constant (also called the ‘anharmonic’ quadratic one. The cubic force constants have very high stretching energy application, however; Eq. (2.3) gives the lowest possible energy for bonds having the form of Eq. (2.3) without havoc with automated minimization.

term in the Taylor expansion,

$$\alpha_{AB}^2(r_{AB} - r_{AB,eq})^2 \quad (2.4)$$

nic force field, MM3 (a large part of this chapter). Many force fields that are used for specific biopolymers), due to their greater computational efficiency.

seen no discussion of the Morse

$$\alpha_{AB}^2 \quad (2.5)$$

fitting constant. The hypothetical function over a much wider range of force fields decline to use the exponential function to evaluate the exponential term. Moreover, most force fields whose degrees of freedom are all in kcal/mol. Over such a range, the exponential is usually negligible.

considering the Morse function. The series expansion truncated at

$$\alpha_{AB}^2(r_{AB} - r_{AB,eq})^2 \quad (2.6)$$

gives

$$\alpha_{AB,eq}^2 \left[(r_{AB} - r_{AB,eq})^2 \right] \quad (2.7)$$

here 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 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 valence 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

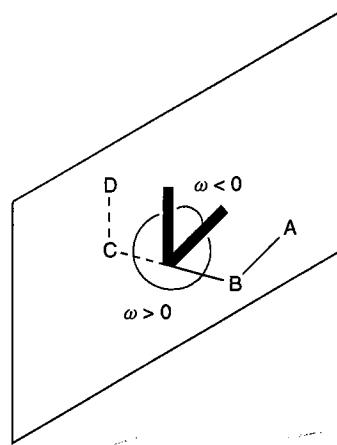


Figure 2.2 Definition and sign convention for dihedral angle ω . The bold lines are the projections of the AB and CD bonds into the bisecting plane. Note that the sign of ω is independent of whether one chooses to view the bisecting plane from the AB side or the CD side

h force fields typically handle

re 1.2 shows that a convenient O bond length, a BCD valence with the ABCD linkage. As angle between bonds AB and CD 1. The convention is to define bisecting plane in a clockwise direction, the torsion angle is positive angle, in which case the however, the minimum energy $\omega = \pi$. Thus, the convention use.

onal potential energy. As such, expansion of periodic functions, se

$$CD + \psi_{j,ABCD})] \quad (2.10)$$

st of periodicities $\{j\}$ included that deleting a particular value amplitude for that value of j

(1 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 j can contribute to U . The factor of $(-1)^{j+1}$ is included so that the function in brackets in 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 electrostatic 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 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 Tom, Hefner 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

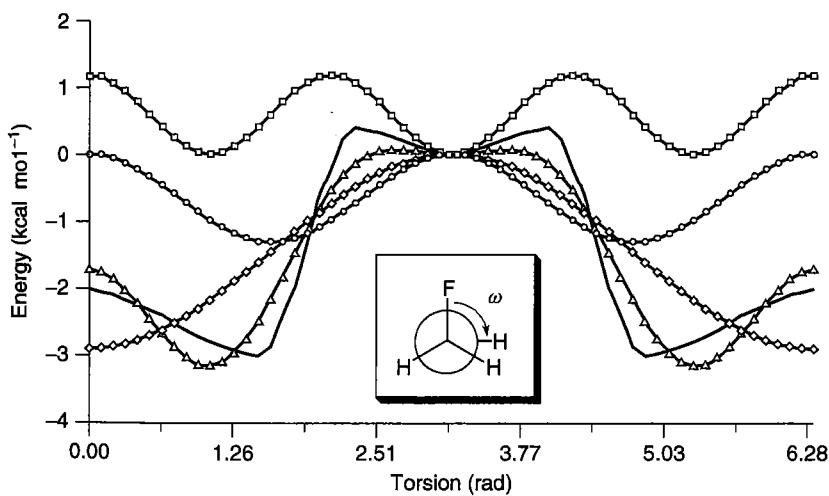


Figure 2.3 Fourier decomposition of the torsional energy for rotation about the C–O bond of fluoromethanol (bold black curve, energetics approximate). The Fourier sum (Δ) is composed of the onefold (\diamond), twofold (\triangle), and threefold (\square) periodic terms, respectively. In the Newman projection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

The bold lines are the projections of ω is independent of whether side

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 three-fold 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

tively. Thus, at $\omega = 0$, the $\psi = \pi$ they are parallel (least to be a minimum at $\omega = 0$, This term makes the largest roughly double either of the

cts. Hyperconjugation is the only a σ orbital, with a nearby Appendix D within the context thanol, the filled orbital that pty orbital lowest in energy (gen lone pair) is the C–F σ^* is sometimes called negative led σ orbitals as donors, is angles of roughly $\pm\pi/2$. The f fluoromethanol is roughly

bond eclipsing interactions, d be expected to show three- only be expected were each st that fluorine and hydrogen e moment. As expected, the o the hyperconjugative term. ve refer to the unfavorable molecular mechanics in essence , as discussed in more detail tainly acceptable. It should not billiard balls bumping tric interaction derives from come closer to one another, ll energetic issues in chemi effects is perhaps overly nore nuclear chemistry, are

e pointed out that a number can be seen in Figure 2.3, the fit by restricting the Fourier ing, since the ‘perfect’ fitting rier terms, but the poorness . This may be most readily tionary points – two minima ut we also want their nature o fit their first derivatives as

(making the first derivative equal to zero defines them as stationary points). Thus, we trying to fit eight constraints using only three variables (namely, the term amplitudes). construction, we are actually guaranteed that 0 and π will have correct first derivatives, that the energy value for π will be correct (since it is required to be the relative zero), that still leaves five constraints on three variables. If we add non-zero phase angles ψ , 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 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 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 H₃/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

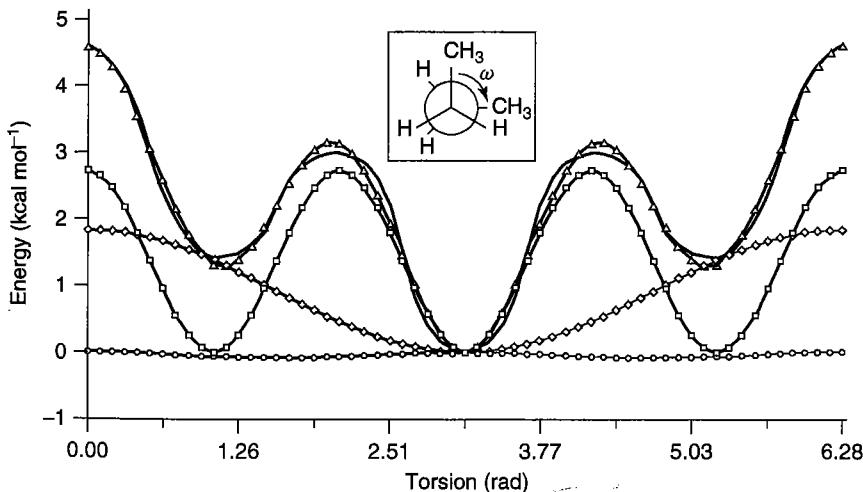


Figure 2.4 Fourier decomposition of the torsional energy for rotation about the C–C bond of *n*-butane (bold black curve, energetics approximate). The Fourier sum (Δ) has a close overlap, and is composed of the onefold (\diamond), twofold (\circ), and threefold (\square) periodic terms, respectively

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

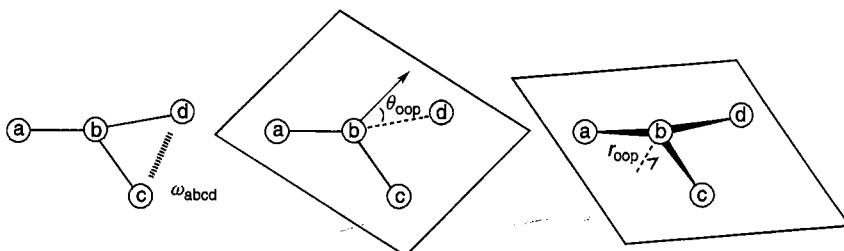


Figure 2.5 Alternative molecular coordinates that can be used to compute the energetics of distortions from planarity about a triply substituted central atom

y different term amplitudes is
parameters are not statistically
with other parameters. With all
here valuable physical insights
te.

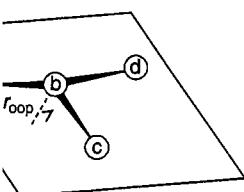
ow to handle the valence angle
s are present. Such a case is
ts multiple minima. Thus, the
compute angle bending energy

$$; + \psi)] \quad (2.11)$$

$$(2.12)$$

also be used to ensure approximations where $\theta = \pi$. [As a digression, I designed to handle multiple minima altogether. It is replaced by a 'Wy-Bradley' term) which tends to central atom will tend to organize two. This 'points-on-a-sphere' ination chemistry.]

iscussion, arises in the case of otherwise unconnected atoms, e.g., case of step IV of Figure 1.2, by a bond length to the central er, as Figure 2.5 makes clear, of step IV of Figure 1.2, i.e., om, and then a dihedral angle defined as connected. Such an



compute the energetics of distortions

ment 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 'proper 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 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 can choose. One alternative is to quantify deviations from planarity by the angle $\theta_{o.o.p.}$ that the substituent makes with the plane defined by the other three (o.o.p. = 'out of plane'). Another is to quantify the elevation $r_{o.o.p.}$ 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 terms in this potential are primarily associated with steric interactions between eclipsing 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: from how great a height can the model be dropped and remain intact?) Thus, in cases where dipole–dipole and hyperconjugative interactions are all 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.

2.4 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

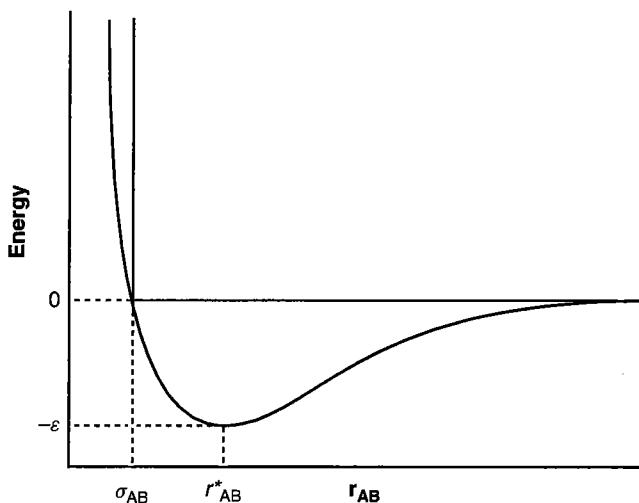


Figure 2.6 Non-attractive hard-sphere potential (straight lines) and Lennard-Jones potential (curve). Key points on the energy and bond length axes are labeled

closely, which is to say the potential energy discontinuously becomes infinite for $r < 2r_{\text{vdw}}$. 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;

the con
potentia
at $r =$
to the
in certa
chemist
The
nation
where
‘Lenna
The
no theo
algorith
ingly a
depend
(and th
five ti
of the
evaluat
which
involve
sian co
defined

If only
quibbl
of a se
times
analys
 N is t
energy
need t
multip
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 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 100 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 nibbling 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

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

d by the constants ϵ and σ ,
d is the interatomic separation
that $U = 0$. If we differentiate

$$\left[\frac{\sigma_{AB}}{r_{AB}} \right]^6 \quad (2.17)$$

imum in the Lennard-Jones

$$(2.18)$$

value for the bond length in
 ϵ is the Lennard-Jones well

force fields, particularly those
fields. In more general force
more complicated functional
used (computational times for
d-Jones potential is of little
5) and the 'Hill' potential

$$\frac{\beta_{AB}}{r_{AB} - 6} \left(\frac{r_{AB}^*}{r_{AB}} \right)^6 \quad (2.19)$$

me meanings as in previous
interaction, some force fields
nally related) by a constant

ample of two noble gas atoms
consideration of non-bonded
by non-zero local electrical

asonably large distance, each
moments. Classical electro-

$$(2.20)$$

ite $\mathbf{M}^{(A)}$ 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

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

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),

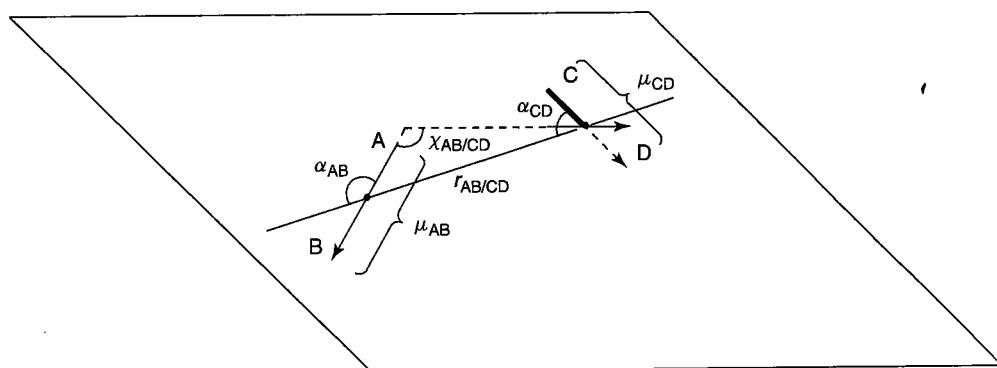


Figure 2.7 Prescription for evaluating the interaction energy between two dipoles. Each angle α is defined as the angle between the positive end of its respective dipole and the line passing through the two dipole centroids. The length of the line segment connecting the two centroids is r . To determine 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

; the conversion to energy units involves multiplication of the r.h.s. reaction energy between two unit h is of the same order of energy g, or torsional coordinate.

study a particular molecule (i.e., chosen to accurately reproduce the molecule. Various schemes

for the chemical bonds, the most the interaction energy is defined

$$\cos \alpha_{AB} \cos \alpha_{CD}) \quad (2.23)$$

intered midway along the bonds x are defined in Figure 2.7.

ϵ is subscripted. Although one permittivity of free space, such an interactions introduced by the use of e viewed as a parameter of the le values. For use in Eq. (2.22),

possible choice might be

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

This indicates 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, and are evaluated with a dielectric constant of 1.5. Dielectric constants can also be defined 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 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 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 -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

between two dipoles. Each angle α is the angle and the line passing through the two centroids is r . To determine if a plane, and the CD dipole is parallel, χ is defined to be the angle between the extension is from the intersection (as illustrated), otherwise

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 and Additional Non-bonded 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 BeH₂. 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 sp² 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

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

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

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

where $k_{AB,ABC}$ 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.

derived from polarization appear in molecules in condensed-phase including polarization.

Terms

ordinates: they couple with one consider BeH_2 . In its preferred i.e., each Be hybrid orbital used character. If we now decrease the say, a bond angle of $\pi/3$, which the p character in the Be bonding it relies on rather basic molecular field expect that as a bond angle is then to decrease the non-bonded

ing by expanding the full molecule, which is a generalization of

$$q_{k,\text{eq}}) \frac{\partial^3 U}{\partial q_i \partial q_j \partial q_k} \Big|_{q=q_{\text{eq}}} + \dots \quad (2.26)$$

1 coordinates and the expansion two terms on the r.h.s. are zero first derivatives being zero for and discussed the ‘diagonal’ terms of the summation indices are equal double summation corresponds to a coordinate, it is clear that by terms like

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

Eq. (2.26). Typically, the mixed that do not share common atoms,

force fields, stretch–stretch terms can be useful in modeling systems characterized by rotation. In amides, for instance, the coupling force constant between CO and CN has been found to be roughly 15% as large as the respective diagonal bond-stretch constants (Fogarasi and Balázs, 1985). Stretch–bend coupling terms tend to be most highly strained systems, and for the computation of vibrational frequencies (see Chapter 3). Stretch–torsion coupling can be useful in systems where eclipsing interactions occur at high degrees of strain. The coupling has the form

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

is the periodicity of the torsional term and ψ is a phase angle. Thus, if the term is 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 is the *central* bond in the torsional linkage.

useful coupling terms include stretch–stretch coupling (typically between two adjacent bonds) and bend–bend coupling (typically between two angles sharing a common central bond). 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.

In the case of non-bonded interactions, the discussion in prior sections focused on atom type interactions. However, for larger molecules, and particularly for biomolecules, it is often possible to adopt a more coarse-grained description of the overall system by focusing on elements of secondary structure, i.e., structural motifs that are frequently, like α -helices in proteins or base-pairing or -stacking arrangements in nucleotides. When such structural motifs are highly transferable, it is sometimes possible to model an entire fragment (e.g., an entire amino acid in a protein) using a number of interaction sites and potential energy functions that is very much reduced compared to what would be required in an atomistic description. Such reduced models sacrifice atomic detail and structural analysis, but, owing to their simplicity, significantly expand the speed with which energy evaluations may be accomplished. Such efficiency can prove decisive in the simulation of biomolecules over long time scales, as discussed in Chapter 3. Many research groups are now using such coarse-grained models to study, *inter alia*, the process whereby proteins fold from denatured states into their native forms (see, for example, Hassinen and Karjalainen 2001).

In a separate example, Harvey *et al.* (2003) have derived expressions for pseudobonds and pseudoaangles in DNA and RNA modeling that are designed to predict base-pairing and stacking interactions when rigid bases are employed. While this model is coarse-grained, it is worth noting that even when a fully atomistic force field is being used, it may sometimes be necessary to add such additional interaction sites so as better to enforce elements of secondary structure like those found in biopolymers.

Finally, for particular biomolecules, experiment sometimes provides insight into elements of secondary structure that can be used in conjunction with a standard force field to more accurately determine a complete molecular structure. The most typical example of this approach is the imposition of atom–atom distance restraints based on nuclear Overhauser

effect (nOe) data determined from NMR experiments. For each nOe, a pseudobond between the two atoms involved is defined, and a potential energy ‘penalty’ function depending on their interatomic distance is added to the overall force field energy. The most typical form for these penalty functions is a flat-bottomed linearized parabola. That is, there is no penalty over a certain range of bond distances, but outside that range the energy increases quadratically up to a certain point and then linearly thereafter. When the structure of a particular biomolecule is referred to as an ‘NMR structure’, what is meant is that the structure was determined from a force-field minimization incorporating experimental NMR restraints. Typically, a set of NMR structures is generated and deposited in the relevant database(s), each member of which satisfied the experimental restraints to within a certain level of tolerance. The quality of any NMR structure depends on the number of restraints that were available experimentally—the more (and the more widely distributed throughout the molecule) the better.

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 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

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

with n_{OE} , a pseudobond between atoms i and j . The ‘penalty’ function depending on the energy is the sum of the terms in the formula. That is, there is no penalty if the energy increases quadratically with the structure of a particular molecule. The relevant point is that the structure was determined by experimental NMR restraints. Typically, the relevant database(s), each contains a certain level of tolerance of restraints that were available throughout the molecule.

It is important to note that a force field is nothing more than a collection of associated constants. Within a given element, atomic connectivity must be taken into account, and the energy associated with every bond type. In addition, there are typically a rather large number of parameters, and the use of a digital computer makes the task straightforward.

As a sum of energies from individual coordinates and on atomic partial charges, one might have paid much attention to the choice of force constants, equilibrium coordinate values, and the relationship of many of them. Let us now look more closely at the ‘Art of Force Field Design’.

The goal is to define a process. The goal is to fit the parameters to as high a degree as possible to the available experimental data. For molecules containing organic data, and, possibly, data on inorganic compounds, associated with each kind of datum, one needs to define a ‘penalty function’. How much deviation there is between calculated and observed will then be to select force-field parameters. Note that the penalty function is necessarily non-negative.

$$\left[\frac{1}{j} \right]^{1/2} \quad (2.29)$$

Observables might include bond lengths, bond angles, torsion angles, heats of formation, enthalpies, entropies, 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 and different observables, but also the degree of tolerance the penalty function will have for deviation of calculation from experiment for those observables. Thus, for instance, one can 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 mathematical techniques can be used (see, for example, Schlick 1992). The minimization of Z , 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 consider 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, and quadruple 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 values of σ and ϵ if we use Coulomb’s law for electrostatics and a Lennard-Jones potential 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 higher-order 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 continues until all parameters have been chosen. The process of choosing which parameters to optimize in which order is as arbitrary as the choice of a penalty function, but may be guided by 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 alleviate 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 that 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

re in hand, it becomes quite clear alone. Thus, for instance, bond one characterized by its own (e.g., single, aromatic, double) atoms when multiple bonding different angle bending equilibrium to include metals, usually different energetic properties (indeed, the properties is what inorganic chemis

may have a very large number of atoms and a small number of nuclei. The primary atom types, respectively. The two carbohydrates) OPLS (optimized), have 41 atoms types each. The usual force field (UFF) has 126 atoms determined optimization of parameters.

of the problem? One approach is to let the atoms themselves functions (Eq. (2.16)), one usually defines

(2.30)

(2.31)

diatomic parameters to only DREIDING, UFF, and VALBOND from a fairly small set of atoms, but as their limitations continue, broad, general utility.]

make certain constants depend on the VALBOND force field, angular properties of the metal-ligand force constants, equilibrium bond and π bond orders between atoms

units of a 'classical' model, since they introduce quantum mechanics along with moving the model in the atoms – but such QM enhancement is costly.

What is required is to adopt a so-called 'atom as the fundamental unit

field, one also defines certain functional groups, usually hydrocarbon groups, methylene, aryl CH, etc. The group has its own single set of non-bonded and others – effectively, this reduces the total number of atoms by one less than the incorporated into the united atom group.

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

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

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

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

Force-field Energies and Thermodynamics

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, 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 C₂H₆O. However, while ethanol is defined by the force field to be composed of two sp³ carbon atoms, one sp³ 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 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

In both instances, the minimum instants and sensible behavior for bond length or angle adopts it in which every coordinate adopts a single term in our fluoromethane by proper choice of phase angles zero as a minimum (although no non-bonded terms for the moment strain energy', since it represents m.

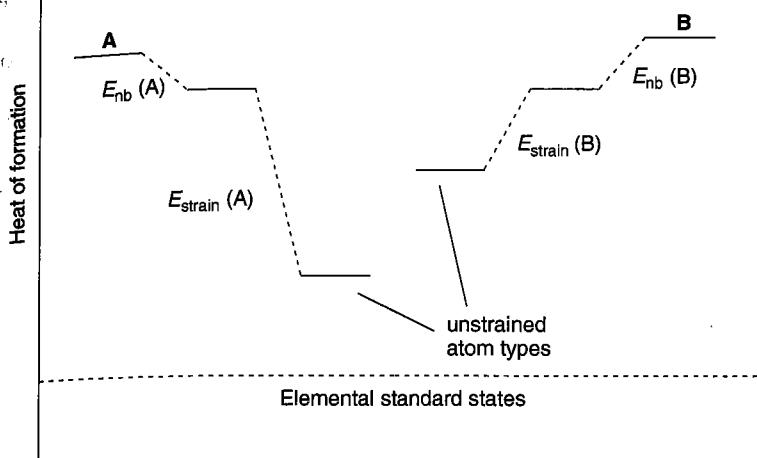
Energies for two different molecules *is identical*. This is probably comparison of the molecules ethane have the chemical formula C_2H_6O composed of two sp^3 carbon atoms and one alcohol hydrogen atom of the carbon-bound type. Each hypothetical reference system, and ms should be thermodynamically

is to define the heat of formation of a heat of formation can then be atom types plus the strain energy calculated using additivity methods originally (Benson 1993). The process is

is really just an aspect of parameterizing force-field energy, which could be on energies to small non-negative force-field energy calculation will report consequence of the deviation of the (i) a force-field energy, which function energies, and (iii) a heat of the reference heats of formation

ing to assign a reference heat of atom types, the force field cannot comparisons are necessarily limited to any change in atom types.

as the development of an energy regular geometries. While the energy



Molecules **A** and **B** are chemical isomers but are composed of different atomic types (isomers?). Thus, the sums of the heats of formation of their respective unstrained atom types 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. For example, note that **A** is predicted to have a lower heat of formation than **B** even though it has substantially larger strain energy (and force-field energy); this difference is more than offset by the difference in the reference zeroes.

An arbitrary structure can be interesting, real molecules vibrate thermally about their equilibrium structures, so finding minimum energy structures is key to describing equilibrium states, comparing to experiment, etc. Thus, as emphasized above, one priority in force-field energy 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 enter into the problem.

Optimization Algorithms

that, in principle, geometry optimization could be a separate chapter of this text. In its most general form, 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 that problem once, in the context of parameter optimization. In the case of parameter optimization, however, it is not necessarily obvious how the penalty function being minimized depends on a given variable, and moreover the problem is highly underdetermined. In the case of geometry optimization, we are working with far fewer variables (the geometric degrees of freedom) and have, at least with a force field, analytic expressions for how the energy depends on the variables. The mathematical approach can thus be quite different.] As the problem is general, so, too, many of the details presented below will be general to any energy

functional. However, certain special considerations associated with force-field calculations merit discussion, and so we will proceed first with an overview of geometry optimization, and then examine force-field specific aspects.

Because this text is designed primarily to illuminate the conceptual aspects of computational chemistry, and not to provide detailed descriptions of algorithms, we will examine only the most basic procedures. Much more detailed treatises of more sophisticated algorithms are available (see, for instance, Jensen 1999).

For pedagogical purposes, let us begin by considering a case where we do not know how our energy depends on the geometric coordinates of our molecule. To optimize the geometry, all we can do is keep trying different geometries until we are reasonably sure that we have found the one with the lowest possible energy (while this situation is atypical with force fields, there are still many sophisticated electronic structure methods for which it is indeed the only way to optimize the structure). How can one most efficiently survey different geometries?

It is easiest to proceed by considering a one-dimensional case, i.e., a diatomic with only the bond length as a geometric degree of freedom. One selects a bond length, and computes the energy. One then changes the bond length, let us say by shortening it 0.2 Å, and again computes the energy. If the energy goes down, we want to continue moving the bond length in that direction, and we should take another step (which need not necessarily be of the same length). If the energy goes up, on the other hand, we are moving in the wrong direction, and we should take a step in the opposite direction. Ultimately, the process will provide three adjacent points where the one in the center is lower in energy than the other two. Three non-collinear points uniquely define a parabola, and in this case the parabola must have a minimum (since the central point was lower in energy than the other two). We next calculate the energy for the bond length corresponding to the parabolic minimum (the degree to which the computed energy agrees with that from the parabolic equation will be an indication of how nearly harmonic the local bond stretching coordinate is). We again step left and right on the bond stretching coordinate, this time with smaller steps (perhaps an order of magnitude smaller) and repeat the parabolic fitting process. This procedure can be repeated until we are satisfied that our step size falls below some arbitrary threshold we have established as defining convergence of the geometry. Note that one can certainly envision variations on this theme. One could use more than three points in order to fit to higher order polynomial equations, step sizes could be adjusted based on knowledge of previous points, etc.

In the multi-dimensional case, the simplest generalization of this procedure is to carry out the process iteratively. Thus, for LiOH, for example, we might first find a parabolic minimum for the OH bond, then for the LiO bond, then for the LiOH bond angle (in each case holding the other two degrees of freedom fixed), and then repeat the process to convergence. Of course, if there is strong coupling between the various degrees of freedom, this process will converge rather slowly.

What we really want to do at any given point in the multi-dimensional case is move not in the direction of a *single* coordinate, but rather in the direction of the greatest downward slope in the energy with respect to *all* coordinates. This direction is the opposite of the

ated with force-field calculations. In this section we will give an overview of geometry optimization.

In this section we will discuss the conceptual aspects of computational geometry optimization. After a brief overview of the basic algorithms, we will examine one of the most common ways of performing geometry optimization, namely the steepest descent method.

Let us consider a simple case where we do not know the energy function of our molecule. To optimize the structure, we would start by moving all atoms until we are reasonably sure that the energy has been minimized (while this situation is atypical, it is representative of the kind of numeric structure methods for which we will focus). We can then move one atom at a time and see how the energy changes. We can one most efficiently survey the energy landscape.

For example, consider the case of a diatomic molecule, i.e., a diatomic with only two atoms. If we move one atom and compute the energy, we can then move the bond length by shortening it 0.2 Å, and again compute the energy. If we continue moving the bond length in this direction, we will find that the energy does not necessarily decrease. In fact, if we move the bond length in the wrong direction, the energy will increase. For example, if we move the bond length by 0.2 Å in the wrong direction, the energy will increase. In this case, the process will not converge to a minimum energy state.

We can then move the bond length by smaller steps (perhaps as small as 0.05 Å) and repeat the process. This procedure can be continued until we reach a point where the energy is no longer decreasing. At this point, we have reached a local minimum. It is important to note that one can certainly envision situations where the energy landscape has many local minima. In such cases, it is necessary to use more sophisticated optimization techniques based on knowledge of previous energy minimization results.

The goal of geometry optimization is to find the global minimum energy structure. One way to do this is to start with a random initial structure and then iteratively move atoms until the energy converges to a minimum. The number of degrees of freedom in the system determines the number of iterations required for convergence. For a system with many degrees of freedom, this process will take a long time.

In general, the optimization process is more efficient if the initial structure is close to the global minimum. In addition, the optimization process is more efficient if the initial structure is not too far from the global minimum. This is because the optimization process is more likely to converge to the global minimum if the initial structure is close to the global minimum.

vector, \mathbf{g} , which is defined as

$$\mathbf{g}(\mathbf{q}) = \begin{bmatrix} \frac{\partial U}{\partial q_1} \\ \frac{\partial U}{\partial q_2} \\ \frac{\partial U}{\partial q_3} \\ \vdots \\ \frac{\partial U}{\partial q_n} \end{bmatrix} \quad (2.32)$$

$\mathbf{g}(\mathbf{q})$ is an n -dimensional coordinate vector ($n = 3N - 6$ where N is the number of atoms in the system). If we are working in internal coordinates, $n = 3N$ if we are working in Cartesian coordinates, and so on. In general, we cannot compute the partial derivatives that make up \mathbf{g} analytically, we can do so numerically. However, that numerical evaluation requires at least one additional energy calculation for each degree of freedom. Thus, we would increase (or decrease) every degree of freedom by some step size, compute the slope of the resulting line derived from the energy difference between our initial structure and the perturbed structure, and use this slope as an estimate of the partial derivative. Such a ‘forward difference’ estimation is typically not very accurate, so it would be better to take an additional point in the opposite direction for each degree of freedom and then compute the ‘central difference’ slope from the corresponding parabola. It is also obvious that, as the number of degrees of freedom increases, it can be particularly difficult to have an energy function for which the first derivative is known *analytically*.

Let us now examine this point a bit more closely for the force-field case. For this example, let us assume that we are working in Cartesian coordinates, in which case $\mathbf{q} = \mathbf{X}$ of Eq. (1.4). To compute, say, the partial derivative of the energy with respect to the x coordinate of atom A, we will need to compute the changes in energy for the various terms contributing to the full force-field energy as a function of moving atom A in the x direction. For simplicity, let us consider only the bond stretching terms. Clearly, only the energy of those bonds that have A at one end will be affected by A’s movement. We may then use the chain rule to write

$$\frac{\partial U}{\partial x_A} = \sum_{i \text{ bonded to } A} \frac{\partial U}{\partial r_{Ai}} \frac{\partial r_{Ai}}{\partial x_A} \quad (2.33)$$

Differentiation of E with respect to r_{Ai} for Eq. (2.4) gives

$$\frac{\partial U}{\partial r_{Ai}} = \frac{1}{2}[2k_{Ai} + 3k_{Ai}^{(3)}(r_{Ai} - r_{Ai,\text{eq}}) + 4k_{Ai}^{(4)}(r_{Ai} - r_{Ai,\text{eq}})^2](r_{Ai} - r_{Ai,\text{eq}}) \quad (2.34)$$

The bond length r_{Ai} was defined in Eq. 2.15, and its partial derivative with respect to x_A is

$$\frac{\partial r_{Ai}}{\partial x_A} = \frac{(x_A - x_i)}{\sqrt{(x_A - x_i)^2 + (y_A - y_i)^2 + (z_A - z_i)^2}} \quad (2.35)$$

Thus, we may quickly assemble the bond stretching contributions to this particular component of the gradient. Contributions from the other terms in the force field can be somewhat more tedious to derive, but are nevertheless available analytically. This makes force fields highly efficient for the optimization of geometries of very large systems.

With \mathbf{g} in hand, we can proceed in a fashion analogous to the one-dimensional case outlined above. We step along the direction defined by $-\mathbf{g}$ until we locate a minimum in the energy for this process; since we are taking points in a linear fashion, this movement is called a 'line search' (even though we may identify our minimum by fitting our points to a polynomial curve). Then, we recompute \mathbf{g} at the located minimum and repeat the process. Our new search direction is necessarily orthogonal to our last one, since we minimized E in the last direction. This particular feature of a steepest descent curve can lead to *very* slow convergence in unfavorable cases.

A more robust method is the Newton-Raphson procedure. In Eq. (2.26), we expressed the full force-field energy as a multidimensional Taylor expansion in arbitrary coordinates. If we rewrite this expression in matrix notation, and truncate at second order, we have

$$U(\mathbf{q}^{(k+1)}) = U(\mathbf{q}^{(k)}) + (\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)})\mathbf{g}^{(k)} + \frac{1}{2}(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)})^\dagger \mathbf{H}^{(k)}(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)}) \quad (2.36)$$

where the reference point is $\mathbf{q}^{(k)}$, $\mathbf{g}^{(k)}$ is the gradient vector for the reference point as defined by Eq. (2.32), and $\mathbf{H}^{(k)}$ is the 'Hessian' matrix for the reference point, whose elements are defined by

$$H_{ij}^{(k)} = \left. \frac{\partial^2 U}{\partial q_i \partial q_j} \right|_{\mathbf{q}=\mathbf{q}^{(k)}} \quad (2.37)$$

If we differentiate Eq. (2.36) term by term with respect to the i th coordinate of $\mathbf{q}^{(k+1)}$, noting that no term associated with point k has any dependence on a coordinate of point $k+1$ (and hence the relevant partial derivative will be 0), we obtain

$$\begin{aligned} \frac{\partial U(\mathbf{q}^{(k+1)})}{\partial q_i^{k+1}} &= \frac{\partial \mathbf{q}^{(k+1)}}{\partial q_i^{k+1}} \mathbf{g}^{(k)} + \frac{1}{2} \frac{\partial \mathbf{q}^{(k+1)^\dagger}}{\partial q_i^{k+1}} \mathbf{H}^{(k)}(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)}) \\ &\quad + \frac{1}{2} (\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)})^\dagger \mathbf{H}^{(k)} \frac{\partial \mathbf{q}^{(k+1)}}{\partial q_i^{k+1}} \end{aligned} \quad (2.38)$$

The l.h.s. of Eq. (2.38) is the i th element of the vector $\mathbf{g}^{(k+1)}$. On the r.h.s. of Eq. (2.38), since the partial derivative of \mathbf{q} with respect to its i th coordinate is simply the unit vector in the i th coordinate direction, the various matrix multiplications simply produce the i th element of the multiplied vectors. Because mixed partial derivative values are independent of the order of differentiation, the Hessian matrix is Hermitian, and we may simplify

derivative with respect to x_A is

$$\frac{\partial E}{\partial (z_A - z_i)} = \frac{\partial E}{\partial z_A} - \frac{\partial E}{\partial z_i} \quad (2.35)$$

ions to this particular component of the force field can be somewhat more difficult. This makes force fields highly non-local.

us to the one-dimensional case. We move until we locate a minimum in a linear fashion, this movement is to find a minimum by fitting our points to a local minimum and repeat the process. The first step, since we minimized E in one dimension, can lead to very slow convergence.

In Eq. (2.26), we expressed the gradient expansion in arbitrary coordinates. At second order, we have

$$(\mathbf{q}^{(k)})^\dagger \mathbf{H}^{(k)} (\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)}) \quad (2.36)$$

for the reference point as defined by the reference point, whose elements are

$$(2.37)$$

the i th coordinate of $\mathbf{q}^{(k+1)}$, noting that it is the coordinate of point $k + 1$ (and

$$(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)})^\dagger$$

$$+ \frac{\partial^2 E}{\partial z_i^2} \quad (2.38)$$

$+ 1$). On the r.h.s. of Eq. (2.38), the coordinate is simply the unit vector along the i th direction. Substitutions simply produce the i th derivative values are independent of the other coordinates, and we may simplify

as

$$g_i^{(k+1)} = g_i^{(k)} + [\mathbf{H}^{(k)}(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)})]_i \quad (2.39)$$

The notation $[\cdot]_i$ indicates the i th element of the product column matrix. The condition for a stationary point is that the l.h.s. of Eq. (2.39) be 0 for all coordinates, or

$$\mathbf{0} = \mathbf{g}^{(k)} + \mathbf{H}^{(k)}(\mathbf{q}^{(k+1)} - \mathbf{q}^{(k)}) \quad (2.40)$$

This equation may be rearranged to

$$\mathbf{q}^{(k+1)} = \mathbf{q}^{(k)} - (\mathbf{H}^{(k)})^{-1} \mathbf{g}^{(k)} \quad (2.41)$$

This equation provides a prescription for the location of stationary points. In principle, given an arbitrary structure having coordinates $\mathbf{q}^{(k)}$, one would compute its gradient $\mathbf{g}^{(k)}$ and its Hessian matrix \mathbf{H} , and then select a new geometry $\mathbf{q}^{(k+1)}$ according to Eq. (2.41). Equation (2.40) shows that the gradient vector for this new structure will be the zero vector, so we will have a stationary point.

It is important to note, however, that our derivation involved a truncation of the full Taylor expansion at second order. Thus, Eq. (2.40) is only approximate, and $\mathbf{g}^{(k+1)}$ will not necessarily be $\mathbf{0}$. However, it will probably be smaller than $\mathbf{g}^{(k)}$, so we can repeat the whole process to pick $\mathbf{q}^{(k+2)}$. After a sufficient number of iterations, the gradient will hopefully become so small that structures $k + n$ and $k + n + 1$ differ by a chemically insignificant amount, and we can declare our geometry to be converged.

There are a few points with respect to this procedure that merit discussion. First, there is the cost of computing the Hessian matrix. With n^2 elements, where n is the number of coordinates in the geometry vector, it can grow somewhat expensive to construct this matrix at each step even for functions, like those used in most force fields, that have fairly simple analytical expressions for their second derivatives. Moreover, the matrix must be inverted at every step, and matrix inversion formally scales as n^3 , where n is the dimensionality of the matrix. Thus, for purposes of efficiency (or in cases where analytic second derivatives are simply not available) approximate Hessian matrices are often used in the optimization process – after all, the truncation of the Taylor expansion renders the Newton–Raphson method intrinsically approximate. As an optimization progresses, second derivatives can be estimated reasonably well from finite differences in the analytic first derivatives over the previous few steps. For the first step, however, this is not an option, and one typically either pays the cost of computing an initial Hessian analytically for the level of theory in use, or one employs a Hessian obtained at a less expensive level of theory, when such levels are available (which is typically not the case for force fields). To speed up slowly convergent optimizations, it is often helpful to compute an analytic Hessian every few steps and replace the approximate one in use up to that point. For really tricky cases (e.g., where the PES is nearly flat in many directions) one is occasionally forced to compute an analytic Hessian for every step.

Another key issue to note is that Eq. (2.41) provides a prescription to get to what is called the nearest stationary point, but there is no guarantee that that point will be a

minimum. The condition for a minimum is that all coordinate second derivatives (i.e., all diagonal elements of the Hessian matrix) be positive, but Eq. (2.41) places no constraints on the second derivatives. Thus, if one starts with a geometry that is very near a transition state (TS) structure, the Newton–Raphson procedure is likely to converge to that structure. This can be a pleasant feature, if one is looking for the TS in question, or an annoying one, if one is not. To verify the nature of a located stationary point, it is necessary to compute an accurate Hessian matrix and inspect its eigenvalues, as discussed in more detail in Chapter 9. With force fields, it is often cheaper and equally effective simply to ‘kick’ the structure, which is to say, by hand one moves one or a few atoms to reasonably distorted locations and then reoptimizes to verify that the original structure is again found as the lowest energy structure nearby.

Because of the importance of TS structures, a large number of more sophisticated methods exist to locate them. Many of these methods require that two minima be specified that the TS structure should ‘connect’, i.e., the TS structure intervenes in some reaction path that connects them. Within a given choice of coordinates, intermediate structures are evaluated and, hopefully, the relevant stationary point is located. Other methods allow the specification of a particular coordinate with respect to which the energy is to be maximized while minimizing it with respect to all other coordinates. When this coordinate is one of the normal modes of the molecule, this defines a TS structure. The bottom line for all TS structure location methods is that they work best when the chemist can provide a reasonably good initial guess for the structure, and they tend to be considerably more sensitive to the availability of a good Hessian matrix, since finding the TS essentially amounts to distinguishing between different local curvatures on the PES.

Most modern computational chemistry software packages provide some discussion of the relative merits of the various optimizers that they make available, at least on the level of providing practical advice (particularly where the user can set certain variables in the optimization algorithm with respect to step size between structures, tolerances, use of redundant internal coordinates, etc.), so we will not try to cover all possible tricks and tweaks here. We will simply note that it is usually a good idea to visualize the structures in an optimization as it progresses, as every algorithm can sometimes take a pathologically bad step, and it is usually better to restart the calculation with an improved guess than it is to wait and hope that the optimization ultimately returns to normalcy.

A final point to be made is that most optimizers are rather good at getting you to the *nearest* minimum, but an individual researcher may be interested in finding the *global* minimum (i.e., the minimum having the lowest energy of all minima). Again, this is a problem in applied mathematics for which no one solution is optimal (see, for instance, Leach 1991). Most methods involve a systematic or random sampling of alternative conformations, and this subject will be discussed further in the next chapter.

2.4.2 Optimization Aspects Specific to Force Fields

Because of their utility for very large systems, where their relative speed proves advantageous, force fields present several specific issues with respect to practical geometry optimization that merit discussion. Most of these issues revolve around the scaling behavior

ordinate second derivatives (i.e., all but Eq. (2.41) places no constraints on geometry that is very near a transition state likely to converge to that structure). In the TS in question, or an annoying stationary point, it is necessary to values, as discussed in more detail, usually effective simply to 'kick' the few atoms to reasonably distorted al structure is again found as the

number of more sophisticated methods let two minima be specified that the serves in some reaction path that intermediate structures are evaluated. Other methods allow the specification energy is to be maximized while mini coordinate is one of the normal bottom line for all TS structure loca can provide a reasonably good initial more sensitive to the availability of amounts to distinguishing between

ges provide some discussion of the available, at least on the level of an set certain variables in the opti tures, tolerances, use of redundant possible tricks and tweaks here. We the structures in an optimization a pathologically bad step, and it is I guess than it is to wait and hope

er good at getting you to the *nearest* in finding the *global* minimum (ima). Again, this is a problem in al (see, for instance, Leach 1991): of alternative conformations, and

elds

their relative speed proves advanta respect to practical geometry optimiolve around the scaling behavior

speed of a force-field calculation exhibits with respect to increasing system size. When we raise the issues here in the context of geometry optimization, they are equally important in force-field simulations, which are discussed in more detail in the next chapter. If we look at the scaling behavior of the various terms in a typical force field, we see that internal coordinates have very favorable scaling – the number of internal coordinates scales as N^6 , which is linear in N . The non-bonded terms, on the other hand, are computed pairwise interactions, and therefore scale as N^2 . However, this scaling assumes the sum of *all* pairwise terms. If we consider the Lennard-Jones potential, its long-range part decays proportional to r^{-6} . The total number of interactions should grow at most like N^4 (i.e., proportional to the surface area of a surrounding sphere), so the net energetic contribution should decay with an r^{-4} dependence. This quickly becomes negligible (particularly from a gradient standpoint) so force fields usually employ a 'cut-off' range for the calculation of van der Waals energies – a typical choice is 10 Å. Thus, part of the calculation involves the periodic updating of a 'pair list', which is a list of all atoms for which the L-J interaction needs to be calculated (Petrella *et al.* 2003). The update usually occurs only once every several steps, since, of course, evaluation of interatomic distances finally scales as N^2 .

In practice, even though the use of a cut-off introduces only small disparities in the energy, the discontinuity of these disparities can cause problems for optimizers. A more stable approach is to use a 'switching function' which multiplies the van der Waals interaction (and uses it (and possibly its first and second derivatives) to go smoothly to zero at some distance. This function must, of course, be equal to 1 at short distances.

The electrostatic interaction is more problematic. For point charges, the interaction energy was r^{-1} . As already noted, the number of interactions increases by up to r^2 , so the energy in an infinite system might be expected to diverge! Such formal divergence is avoided in most real cases, however, because in systems that are electrically neutral there are many positive interactions as negative, and thus there are large cancellation effects. If we imagine a system composed entirely of neutral groups (e.g., functional groups of a single molecule or individual molecules of a condensed phase), the long-range interaction between them is a dipole–dipole interaction, which decays as r^{-3} , and the total energy contribution to decay as r^{-1} . Again, the actual situation is more favorable because of positive and negative cancellation effects, but the much slower decay of the electrostatic interaction makes it significantly harder to deal with. Cut-off distances (again, ideally implemented with smooth switching functions) must be quite large to avoid structural artifacts (e.g., atoms having large net charges of like sign anomalously segregating at interatomic distances just in excess of the cut-off).

In infinite periodic systems, an attractive alternative to the use of a cut-off distance is the Ewald sum technique, first described for chemical systems by York, Darden and Pedersen (1993). By using a reciprocal-space technique to evaluate long-range contributions, the total electrostatic interaction can be calculated to a pre-selected level of accuracy (i.e., the Ewald sum is exact) with a scaling that, in the most favorable case (called 'Particle-mesh Ewald', or PME), is $N \log N$. Prior to the introduction of Ewald sums, the modeling of electrolytes (e.g., DNA) was rarely successful because of the instabilities introduced

by cut-offs in systems having such a high degree of localized charges (see, for instance, Beveridge and McConnell 2000).

In aperiodic systems, another important contribution has been the development of the so-called ‘Fast Multipole Moment’ (FMM) method (Greengard and Rokhlin 1987). In essence, this approach takes advantage of the significant cancellations in charge–charge interactions between widely separated regions in space, and the increasing degree to which those interactions can be approximated by highly truncated multipole–multipole interactions. In the most favorable case, FMM methods scale linearly with system size.

It should be remembered, of course, that scaling behavior is informative of the relative time one system takes compared to another of different size, and says *nothing* about the *absolute* time required for the calculation. Thus, FMM methods scale linearly, but the initial overhead can be quite large, so that it requires a very large system before it outperforms PME for the same level of accuracy. Nevertheless, the availability of the FMM method renders conceivable the molecular modeling of extraordinarily large systems, and refinements of the method, for example the use of multiple grids (Skeel, Tezcan, and Hardy 2002), are likely to continue to be forthcoming.

An interesting question that arises with respect to force fields is the degree to which they can be used to study reactive processes, i.e., processes whereby one minimum-energy compound is converted into another with the intermediacy of some transition state. As noted at the beginning of this chapter, one of the first applications of force-field methodology was to study the racemization of substituted biphenyls. And, for such ‘conformational reactions’, there seems to be no reason to believe force fields would not be perfectly appropriate modeling tools. Unless the conformational change in question were to involve an enormous amount of strain in the TS structure, there is little reason to believe that any of the internal coordinates would be so significantly displaced from their equilibrium values that the force-field functional forms would no longer be accurate.

However, when it comes to reactions where bonds are being made and/or broken, it is clear that, at least for the vast majority of force fields that use polynomial expressions for the bond stretching energy, the ‘normal’ model is inapplicable. Nevertheless, substantial application of molecular mechanics to such TS structures has been reported, with essentially three different approaches having been adopted.

One approach, when sufficient data are available, is to define new atom types and associated parameters for those atoms involved in the bond-making/bond-breaking coordinate(s). This is rather tricky since, while there may be solid experimental data for activation energies, there are unlikely to be any TS structural data. Instead, one might choose to use structures computed from some QM level of theory for one or more members of the molecular data set. Then, if one assumes the reaction coordinate is highly transferable from one molecule to the next (i.e., this methodology is necessarily restricted to the study of a single reaction amongst a reasonably closely related set of compounds), one can define a force field where TS structures are treated as ‘minima’ – minima in quotes because the equilibrium distances and force constants for the reactive coordinate(s) have values characteristic of the transition state.

This methodology has two chief drawbacks. A philosophical drawback is that movement along the reaction coordinate raises the force-field energy instead of lowering it, which

Figure 2.9 Schematic diagram illustrating the location of a transition state (TS) in a reaction coordinate. The diagram shows a reaction coordinate with a local maximum (transition state) and two local minima (reactants and products). The energy profile is labeled 'Heat of formation' on the right. The reaction coordinate is labeled 'Reaction coordinate'.

lized charges (see, for instance, Engard and Rokhlin 1987).

cancellations in charge–charge and the increasing degree to which multipole–multipole interaction with system size.

is informative of the relative size, and says *nothing* about the methods scale linearly, but the initial system before it outperforms PM.ity of the FMM method render systems, and refinements of the can, and Hardy 2002), are like

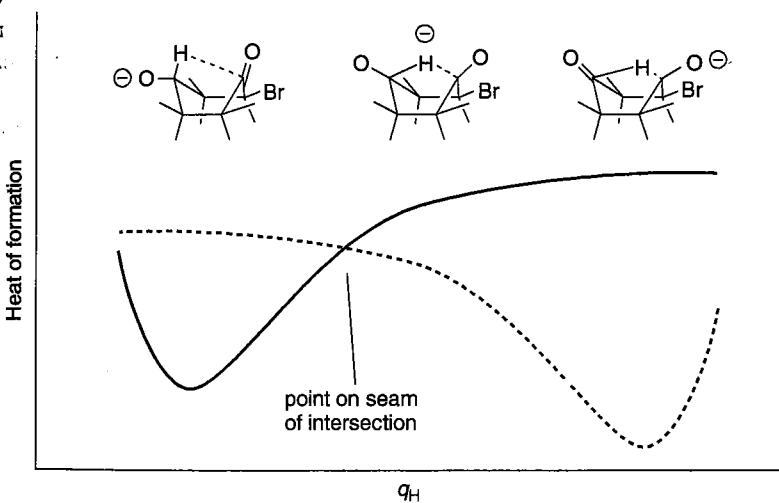
fields is the degree to which is whereby one minimum-energy of some transition state. As notions of force-field methodology, for such ‘conformational reaction’ could not be perfectly appropriate question were to involve an enough reason to believe that any of them from their equilibrium values the.

being made and/or broken, it use polynomial expressions feasible. Nevertheless, substantially has been reported, with essentially

define new atom types and associating/bond-breaking coordinate(s) potential data for activation energies. We might choose to use structure members of the molecular data set separable from one molecule to the study of a single reaction among fine a force field where TS structures equilibrium distances and forces characteristic of the transition state. A practical drawback is that movement instead of lowering it, which

in the real chemical system. A practical drawback is that it tends to be data may need to define a fairly large number of parameters using only a rather number of activation energies and perhaps some QM data. As noted in Section 2.2.7, tension between chemical intuition and statistical rigor. Two papers applying TS to model the acid-catalyzed lactonization of organic hydroxy-acids illustrate the extremes to which such optimizations may be taken (Dorigo and Houk 1987; 1990).

ative approach is one that is valence-bond like in its formulation. A possible TS whose molecular geometry is computed to have the same energy *irrespective of the atomic connectivity is that of the reactant or that of the product* (Olsen and 1990). Consider the example in Figure 2.9 for a hypothetical hydride transfer from an carbon to a carbonyl. When the C–H bond is stretched from the reactant structure, of the reactant-bonded structure goes up, while the energy of the product-bonded goes down because that structure’s C–H bond is coming closer to its equilibrium in which it is initially very highly displaced). The simplest way to view this process two PESs, one defined for the reactant and one for the product. These two will intersect along a ‘seam’, and this seam is where the energy is independent of connectivity is employed. The TS structure is then defined as the *minimum* on the this approach is only valid when the reactant and product energies are computed



2.9 Slice through two intersecting enthalpy ‘surfaces’ along an arbitrary coordinate describing motion of a transferring H atom. The solid curve corresponds to bond stretching of the solid bond from carbon to the H atom being transferred. The dashed curve corresponds analogously to the dashed bond. At the point of intersection, the structure has the same energy irrespective of which bonding is chosen. [For chemical clarity, the negative charge is shown shifting from one oxygen to the other for the method to be valid the two oxygen atom types could not change along either reaction coordinate. Note also that the bromine atom lifts the symmetry that would otherwise be present in this reaction.]

relative to a common zero (e.g., heats of formation are used; see Section 2.3), but one of its chief advantages is that it should properly reflect movement of the TS structure as a function of reaction thermicity. Because the seam of intersection involves structures having highly stretched bonds, care must be taken to use bond stretching functional forms that are accurate over larger ranges than are otherwise typical. When the VB formalism goes beyond the seam approach, and is adopted in full, a new ground-state potential energy surface can be generated about a true TS structure; such an approach is sometimes referred to as multiconfiguration molecular mechanics (MCMM) and is described in detail in Section 13.4.

The third approach to finding TS structures involves either adopting bond making/breaking functional forms that are accurate at all distances (making evaluation of bond energies a rather unpleasant N^2 process), or mixing the force-field representation of the bulk of the molecule with a QM representation of the reacting region. Mixed QM/MM models are described in detail in Chapter 13.

2.5 Menagerie of Modern Force Fields

2.5.1 Available Force Fields

Table 2.1 contains an alphabetic listing of force fields which for the most part continue to be in use today. Nomenclature of force fields can be rather puzzling because developers rarely change the name of the force field as development progresses. This is not necessarily a major issue when new development extends a force field to functionality that had not previously been addressed, but can be singularly confusing if pre-existing parameters or functional forms are changed from one version to the next without an accompanying name change. Many developers have tried to solve this problem by adding to the force field name the last two digits of the year of the most recent change to the force field. Thus, one can have MM3(92) and MM3(96), which are characterized by, *inter alia*, different hydrogen bonding parameters. Similarly, one has consistent force field (CFF) and Merck molecular force field (MMFF) versions identified by trailing year numbers. Regrettably, the year appearing in a version number does not necessarily correspond to the year in which the modifications were published in the open literature. Moreover, even when the developers themselves exercise adequate care, there is a tendency for the user community to be rather sloppy in referring to the force field, so that the literature is replete with calculations inadequately described to ensure reproducibility.

Further confusing the situation, certain existing force fields have been used as starting points for development by new teams of researchers, and the name of the resulting product has not necessarily been well distinguished from the original (which may itself be in ongoing development by its original designers!). Thus, for instance, one has the MM2* and MM3* force fields that appear in the commercial program MACROMODEL and that are based on early versions of the unstarred force fields of the same name (the * indicates the use of point charges to evaluate the electrostatics instead of bond dipoles, the use of a non-directional 10–12 potential for hydrogen bonding in place of an MM3 Buckingham potential, and a different formalism for handling conjugated systems). The commercial program Chem3D

sed; see Section 2.3), but one of the most important of the TS structure as a function of the TS involves structures having highly functional forms that are accurate. B formalism goes beyond the search for a potential energy surface can be generated. This is referred to as multiconfigurational in Section 13.4.

After adopting bond making/breaking, evaluation of bond energies a rather representation of the bulk of the molecule. QM/MM models are described

which for the most part continue to be rather puzzling because development progresses. This is not necessarily a field to functionality that had no meaning if pre-existing parameters exist without an accompanying name, by adding to the force field name of the force field. Thus, one can have, *e.g.*, different hydrogen bonding (e.g.) and Merck molecular force field (e.g.), the year appearing in the year in which the modifications were made. The developers themselves exercise care to be rather sloppy in referring to calculations inadequately described to

force fields have been used as starting point for the name of the resulting product. One (which may itself be in ongoing development, one has the MM2* and MM3* and CROMODEL and that are based on the same (the * indicates the use of point charges, the use of a non-directional MM3 Buckingham potential, and the commercial program Chem3D Pro).

Table 2.1 Force fields

Name (if any)	Range	Comments	Refs	$\Sigma(\text{error})^a$
-	Biomolecules (2nd generation includes organics)	Sometimes referred to as AMBER force fields; new versions are first coded in software of that name. All-atom (AA) and united-atom (UA) versions exist.	Original: Weiner, S. J., Kollman, P. A., Nguyen, D. T., and Case, D. A. 1986. <i>J. Comput. Chem.</i> , 7 , 230. Latest generation: Duan, Y., Wu, C., Chowdhury, S., Lee, M. C., Xiong, G. M., Zhang, W., Yang, R., Cieplak, P., Luo, R., Lee, T., Caldwell, J., Wang, J. M., and Kollman, P. A. 2003. <i>J. Comput. Chem.</i> , 24 , 1999.; Ryjacek, F., Kubar, T., and Hobza, P. 2003. <i>J. Comput. Chem.</i> , 24 , 1891. See also amber.scripps.edu	7 (AMBER*)
-	Organics and biomolecules	The program MACROMODEL contains many modified versions of other force fields, e.g., AMBER*, MM2*, MM3*, OPLSA*.	Mohamadi, F., Richards, N. J. G., Guida, W. C., Liskamp, R., Lipton, M., Caufield, C., Chang, G., Hendrickson, T., and Still, W. C. 1990. <i>J. Comput. Chem.</i> , 11 , 440. Recent extension: Senderowitz, H. and Still, W. C. 1997. <i>J. Org. Chem.</i> , 62 , 1427. See also www.schrodinger.com	4 (MM2*) 5 (MM3*)
BMS	Nucleic Acids		Langley, D. R. 1998. <i>J. Biomol. Struct. Dyn.</i> , 16 , 487.	

(continued overleaf)

Table 2.1 (continued)

Name (if any)	Range	Comments	Refs	$\Sigma(\text{error})^a$
CHARMM	Biomolecules	Many versions of force field parameters exist, distinguished by ordinal number. All-atom and united-atom versions exist.	Original: Brooks, B. R., Bruckner, R. E., Olafson, B. D., States, D. J., Swaminathan, S., and Karplus, M. 1983. <i>J. Comput. Chem.</i> , 4 , 187; Nilsson, L., and Karplus, M. 1986. <i>J. Comput. Chem.</i> , 7 , 591. Latest generation: MacKerell, A. D., Bashford, D., Bellott, M., Dunbrack, R. L., Evansseck, J. D., Field, M. J., Gao, J., Guo, H., Ha, S., Joseph-McCarthy, D., Kuchnir, L., Kuczera, K., Lau, T. F. K., Mattos, C., Michnick, S., Nago, T., Nguyen, D. T., Prodhom, B., Reiher, W. E., Roux, B., Schlenkrich, M., Smith, J. C., Stote, R., Straub, J., Waranabe, M., Wiorkevicz-Kuczera, J., Yin, D., and Karplus, M. 1998. <i>J. Phys. Chem. B</i> , 102 , 3586; MacKerell, A. D. and Banavali, N. 2000. <i>J. Comput. Chem.</i> , 21 , 105; Patel, S. and Brooks, C. L. 2004. <i>J. Comput. Chem.</i> , 25 , 1. See also yuri.harvard.edu	Momany, F. A. and Rone, R. 1992. <i>J. Comput. Chem.</i> , 13 , 888. See also www.accelrys.com
CHARMM	Biomolecules and organics	Version of CHARMM somewhat extended and made available in Accelrys software products.		

Karplus, M. 1998. *J. Phys. Chem. B*, **102**, 3586; MacKerell, A. D. and Banavali, N. 2000. *J. Comput. Chem.*, **21**, 105; Patel, S. and Brooks, C. L. 2004. *J. Comput. Chem.*, **25**, 1.

See also yuri.harvard.edu

Momany, F. A. and Rone, R. 1992. *J. Comput. Chem.*, **13**, 888.

See also www.accelrys.com

CHARMM
Biomolecules and
organics
somewhat extended
and made available in
Accelrys software
products.

Chem-X	Organics	Available in Chemical Design Ltd. software.	Davies, E. K. and MORTON, J. J. <i>J. Comput. Chem.</i> , 13 , 149.
CFF/CVFF	Organics and biomolecules	CVFF is the original; CFF versions are identified by trailing year digits. Bond stretching can be modeled with a Morse potential. Primarily available in Accelrys software.	CVFF: Lifson, S., Hagler, A. T., and Stockfisch, J. P. 1979. <i>J. Am. Chem. Soc.</i> , 101 , 5111, 5122, 5131. CFF: Hwang, M.-J., Stockfisch, T. P., and Hagler, A. T. 1994. <i>J. Am. Chem. Soc.</i> , 116 , 2515; Maple, J. R., Hwang, M.-J., Stockfisch, T. P., Dinur, U., Waldman, M., Ewig, C. S., and Hagler, A. T. 1994. <i>J. Comput. Chem.</i> , 15 , 162; Maple, J. R., Hwang, M.-J., Jalkanen, K. J., Stockfisch, T. P., and Hagler, A. T. 1998. <i>J. Comput. Chem.</i> , 19 , 430; Ewig, C. S., Berry, R., Dinur, U., Hill, J.-R., Hwang, M.-J., Li, C., Maple, J., Peng, Z., Stockfisch, T. P., Thacher, T. S., Yan, L., Ni, X., and Hagler, A. T. 2001. <i>J. Comput. Chem.</i> , 22 , 1782. See also www.accelrys.com
DREIDING	Main-group organics and inorganics	Bond stretching can be modeled with a Morse potential.	Mayo, S. L., Olafson, B. D., and Goddard, W. A., III. 1990. <i>J. Phys. Chem.</i> , 94 , 8897.

(continued overleaf)

Table 2.1 (continued)

Name (if any)	Range	Comments	Refs	$\Sigma(\text{error})^a$
ECEPP	Proteins	Computes only non-bonded interactions for fixed structures. Versions identified by / (ordinal number) after name.	Original: Némethy, G., Pottle, M. S., and Scheraga, H. A. 1983. <i>J. Phys. Chem.</i> , 87 , 1883. Latest generation: Kang, Y. K., No, K. T., and Scheraga, H. A. 1996. <i>J. Phys. Chem.</i> , 100 , 15588.	
ESFF	General	Bond stretching is modeled with a Morse potential. Partial atomic charges from electronegativity equalization.	Original: Barlow, S., Rohl, A. L., Shi, S., Freeman, C. M., and O'Hare, D. 1996. <i>J. Am. Chem. Soc.</i> , 118 , 7578. Latest generation: Shi, S., Yan, L., Yang, Y., Fisher-Shaulsky, J., and Thachet, T. 2003. <i>J. Comput. Chem.</i> , 24 , 1059.	
GROMOS	Biomolecules	Coded primarily in the software having the same name.	Daura, X., Mark, A. E., and van Gunsteren, W. F. 1998. <i>J. Comput. Chem.</i> , 19 , 535.; Schulz, L. D., Daura, X., and van Gunsteren, W. F. 2001. <i>J. Comput. Chem.</i> , 22 , 1205. See also igc.ethz.ch/gromos	

Daura, X., Mark, A. E., and van Gunsteren, W. F. 1998. *J. Comput. Chem.*, **19**, 535.; Schuler, L. D., Daura, X., and van Gunsteren, W. F. 2001. *J. Comput. Chem.*, **22**, 1205.
See also igc.ethz.ch/gromos

GRIMOS	Biomolecules	Coded primarily in the software having the same name.	
MM2	Organics	Superseded by MM3 but still widely available in many modified forms.	Comprehensive: Burkert, U. and Allinger, N. L. 1982. <i>Molecular Mechanics</i> , ACS Monograph 177, American Chemical Society: Washington, DC. ⁵
MM3	Organics and biomolecules	Widely available in many modified forms.	Original: Allinger, N. L., Yuh, Y. H., and Li, J.-H. 1989. <i>J. Am. Chem. Soc.</i> , 111 , 8551. MM3(94): Allinger, N. L., Zhou, X., and Bergsma, J. 1994. <i>J. Mol. Struct. (Theochem)</i> , 312 , 69. ⁵ Recent extension: Stewart, E. L., Nevins, N., Allinger, N. L., and Bowen, J. P. 1999. <i>J. Org. Chem.</i> 64 , 5350.
MM4		Hydrocarbons, alcohols, ethers, and carbohydrates	Allinger, N. L., Chen, K. S., and Lii, J. H. 1996. <i>J. Comput. Chem.</i> , 17 , 642; Nevins, N., Chen, K. S., and Allinger, N. L. 1996. <i>J. Comput. Chem.</i> , 17 , 669; Nevins, N., Lii, J. H., and Allinger, N. L. 1996. <i>J. Comput. Chem.</i> , 17 , 695; Nevins, N. and Allinger, N. L. 1996. <i>J. Comput. Chem.</i> , 17 , 730. Recent extension: Lii, J. H., Chen, K. H., and Allinger, N. L. 2004. <i>J. Phys. Chem. A</i> , 108 , 3006.

(continued overleaf)

Table 2.1 (continued)

Name (if any)	Range	Comments	Refs	$\Sigma(\text{error})^a$
MMFF	Organics and biomolecules	Widely available in relatively stable form.	Halgren, T. A. 1996. <i>J. Comput. Chem.</i> , 17 , 490, 520, 553, 616; Halgren, T. A., and Nachbar, R. B. 1996. <i>J. Comput. Chem.</i> , 17 , 587. See also www.schrodinger.com	4 (MMFF93)
MMX	Organics, biomolecules, and inorganics	Based on MM2.	Original: Bernhardt, P. V. and Comba, P. 1992. <i>Inorg. Chem.</i> , 31 , 2638. Latest generation: Comba, P. and Gyr, T. 1999. <i>Eur. J. Inorg. Chem.</i> , 1787 See also www.uni-heidelberg.de/institute/fak12/AC/comba/molmod_momec.html	5
MOMEc	Transition metal compounds		Proteins: Jorgensen, W. L., and Tirado-Rives, J. 1988. <i>J. Am. Chem. Soc.</i> , 110 , 1657; Kaminski, G. A., Friesner, R. A., Tirado-Rives, J., and Jorgensen, W. L. 2001. <i>J. Phys. Chem. B</i> , 105 , 6474.	
OPLS	Biomolecules, some organics	Organic parameters are primarily for solvents. All-atom and united-atom versions exist.		

www.uni-heidelberg.de/institute/fak12/AC/comba/molmod_momec.html

OPLS Biomolecules, some organics Organic parameters are primarily for solvents. All-atom and united-atom versions exist.

PEF95SAC Carbohydrates Based on CFF form.

PFF Proteins Polarizable electrostatics

- Nucleic acids: Pranata, J., Wierschke, S. G., and Jorgensen, W. L. 1991. *J. Phys. Chem. B*, **113**, 2810. Sugars: Damm, W., Frontera, A., Tirado-Rives, J., and Jorgensen, W. L. 1997. *J. Comput. Chem.*, **18**, 1955. Recent extensions: Rizzo, R. C., Jorgensen, W. L. 1999. *J. Am. Chem. Soc.*, **121**, 4827.
- Carbohydrates: Kony, D., Damm, W., Stoll, S., and van Gunsteren, W. F. 2002. *J. Comput. Chem.*, **2**, 1416.
- Fabricius, J., Engelsen, S. B., and Rasmussen, K. 1997. *J. Carbohydr. Chem.*, **16**, 751.
- Kaminski, G. A., Stern, H. A., Berne, B. J., Friesner, R. A., Cao, Y. X., Murphy, R. B., Zhou, R., and Halgren, T. A. 2002. *J. Comput. Chem.*, **23**, 1515.

(continued overleaf)

Table 2.1 (continued)

Name (if any)	Range	Comments	Refs	$\Sigma(\text{error})^a$
SHAPES	Transition metal compounds		Allured, V. S., Kelly, C., and Landis, C. R. 1991. <i>J. Am. Chem. Soc.</i> , 113 , 1.	
SYBYL/Tripos	Organics and proteins	Available in Tripos and some other software.	Clark, M., Cramer, R. D., III, and van Opdenbosch, N. 1989. <i>J. Comput. Chem.</i> , 10 , 982. See also www.tripos.com and www.scivision.com	8–12
TRAPPE	Organic	Primarily for computing liquid/vapor/supercritical fluid phase equilibria	Original: Martin, M. G. and Siepmann, J. I. 1998. <i>J. Phys. Chem. B</i> , 102 , 2569. Latest Generation: Chen, B., Potoff, J. J., and Siepmann, J. I. 2001. <i>J. Phys. Chem. B</i> , 105 , 3093.	
UFF	General	Bond stretching can be modeled with a Morse potential.	Rappé, A. K., Casewit, C. J., Colwell, K. S., Goddard, W. A., III, and Skiff, W. M. 1992. <i>J. Am. Chem. Soc.</i> , 114 , 10024, 10035, 10046.	21
VALBOND	Transition metal compounds	Atomic-orbital-dependent energy expressions.	Root, D. M., Landis, C. R., and Cleveland, T. 1993. <i>J. Am. Chem. Soc.</i> , 115 , 4201.	

^aKcal mol⁻¹. From Gundertofte *et al.* (1991, 1996); see text.

Rappé, A. K., Casevit, C. J., Colwell, K. S.,
Goddard, W. A., III, and Skiff, W. M. 1992.
J. Am. Chem. Soc., **114**, 10024, 10035,
10046.

Bond stretching can be
modeled with a Morse
potential.

Root, D. M., Landis, C. R., and Cleveland, T.
1993. *J. Am. Chem. Soc.*, **115**, 4201.

Atomic-orbital-
dependent energy
expressions.

^aKcal mol⁻¹. From Gundertoffe *et al.* (1991, 1996); see text.

force fields based on MM2 and MM3, and makes no modification to the names of

point of ambiguity, some force fields have not been given names, *per se*, but to be called by the names of the software packages in which they first became available. Thus, the force fields developed by the Kollman group (see Table 2.1) have been referred to generically as AMBER force fields, because this software package is where originally coded. Kollman preferred that they be referred to by the names authors on the relevant paper describing their development, e.g., 'the force field of *et al.*' This is certainly more informative, since at this point the AMBER program contains many different force fields, so reference to the 'AMBER force field' is information.

of the above ambiguities, and because it is scientifically unacceptable to publish an adequate description of how independent researchers might reproduce those respected journals in the chemistry field now have requirements that papers force-field calculations include as supplementary material a complete listing of field parameters (and functional forms, if they too cannot be adequately described required to carry out the calculations described. This also facilitates the dissemination of information to those researchers wishing to develop their own codes for specific

1 also includes a general description of the chemical space over which the force been designed to be effective; in cases where multiple subspaces are addressed, roughly reflects the priority given to these spaces during development. Force fields we undergone many years worth of refinements tend to have generated a rather large publications, and the table does not try to be exhaustive, but effort is made to key references. The table also includes comments deemed to be particularly pertinent to software implementing the force fields. For an exhaustive listing, by force individual papers in which parameters for specific functional groups, metals, etc., developed, readers are referred to Jalaie and Lipkowitz (2000).

Validation

The majority of potential users of molecular mechanics have two primary, related questions: 'How do I pick the best force field for my problem?' and, 'How will I know if the results I get are reliable?' The process of testing the utility of a force field for molecules in those over which it was parameterized is known as 'validation'.

The answer to the first question is obvious, if not necessarily trivial: one should pick a force field that has previously been shown to be most effective for the most closely related problem one can find. That demonstration of effectiveness may have taken place during the process of parameterization (i.e., if one is interested in conformational properties of proteins, one is more likely to be successful with a force field specifically parameterized for proteins than with one which has not been) or by post-development validation. Typically in the literature, papers appear comparing a wide variety of force fields for some defined problem, and the results can be quite useful in guiding the choices of subsequent

researchers (see also, Bays 1992). Gundertofte *et al.* (1991, 1996) studied the accuracy of 17 different force fields with respect to predicting 38 experimental conformational energy differences or rotational barriers in organic molecules. These data were grouped into eight separate categories (conjugated compounds, halocyclohexanes, haloalkanes, cyclohexanes, nitrogen-containing compounds, oxygen-containing compounds, hydrocarbons, and rotational barriers). A summary of these results appears for relevant force fields in Table 2.1, where the number cited represents the sum of the mean errors over all eight categories. In some cases a range is cited because different versions of the same force field and/or different software packages were compared. In general, the best performances are exhibited by the MM2 and MM3 force fields and those other force fields based upon them. In addition, MMFF93 had similar accuracy. Not surprisingly, the most general force fields do rather badly, with UFF faring quite poorly in every category other than hydrocarbons.

Broad comparisons have also appeared for small biomolecules. Barrows *et al.* (1998) compared 10 different force fields against well-converged quantum mechanical calculations for predicting the relative conformational energies of 11 different conformers of D-glucose. GROMOS, MM3(96), and the force field of Weiner *et al.* were found to have average errors of 1.5 to 2.1 kcal/mol in relative energy, CHARMM and MMFF had average errors of from 0.9 to 1.5, and AMBER*, Chem-X, OPLS, and an unpublished force field of Simmerling and Kollman had average errors from 0.6 to 0.8 kcal/mol, which compared quite well with vastly more expensive *ab initio* methods. Shi *et al.* (2003) compared the performance of the very general force fields ESFF, CFF91, and CVFF over five of these glucose conformers and found average errors of 1.2, 0.6, and 1.9 kcal/mol, respectively; a more recent comparison by Heramingsen *et al.* (2004) of 20 carbohydrate force fields over a larger test of sugars and sugar-water complexes did not indicate any single force field to be clearly superior to the others. Beachy *et al.* (1997) carried out a similar comparison for a large number of polypeptide conformations and found OPLS, MMFF, and the force field of Cornell *et al.* to be generally the most robust. Price and Brooks (2002) compared protein dynamical properties, as opposed to polypeptide energetics, and found that the force fields of Cornell *et al.*, CHARMM22, and OPLS-AA all provided similarly good predictions for radii of gyration, backbone order parameters, and other properties for three different proteins.

Of course, in looking for an optimal force field there is no guarantee that *any* system sufficiently similar to the one an individual researcher is interested in has *ever* been studied, in which case it is hard to make a confident assessment of force-field utility. In that instance, assuming some experimental data are available, it is best to do a survey of several force fields to gauge their reliability. When experimental data are *not* available, recourse to well-converged quantum mechanical calculations for a few examples is a possibility, assuming the computational cost is not prohibitive. QM values would then take the place of experimental data. Absent any of these alternatives, any force field calculations will simply carry with them a high degree of uncertainty and the results should be used with caution.

Inorganic chemists may be frustrated to have reached this point having received relatively little guidance on what force fields are best suited to *their* problems. Regrettably, the current state of the art does not provide any single force field that is both robust and accurate over a large range of inorganic molecules (particularly metal coordination

1991, 1996) studied the accuracy of experimental conformational energies. These data were grouped into eight categories: hexanes, haloalkanes, cyclohexanes, alcohols, hydrocarbons, and rotationally constrained force fields in Table 2.1, where the errors for all eight categories. In some cases, different force field and/or different software packages are exhibited by the MM2 and MMFF93 packages. In addition, MMFF93 has force fields do rather badly, with UPFs and carbons.

For biomolecules. Barrows *et al.* (1998) performed quantum mechanical calculations on 11 different conformers of D-glucose. All conformers were found to have average errors of about 0.05 Å. MM2 and MMFF had average errors of from 0.1 to 0.2 Å. A published force field of Simmerling *et al.* (2001) for ethanol, which compared quite well with MM2. More recently, Krieger *et al.* (2003) compared the performance of the MM2 and MMFF with five of these glucose conformers and found them to be equally good; a more recent comparison of MM2 and MMFF over a larger test of sugar molecules found MM2 to be clearly superior. Another comparison for a large number of molecules found the force field of Cornell *et al.* to be the best. When compared protein dynamical properties, it was found that the force fields of Cornell *et al.* gave the best predictions for radii of gyration and root-mean-square fluctuations for different proteins.

It is important to note that there is no guarantee that *any* system that one is interested in has *ever* been studied experimentally. In that case, it is best to do a survey of several different force fields. If experimental data are *not* available, recourse to a few examples is a possibility. The calculated values would then take the place of the experimental ones. Force field calculations will simply give the best results. However, one must be careful at this point having received relatively little information related to *their* problems. Regrettably, there is no single force field that is both robust and accurate for all molecules (particularly metal coordination complexes).

As noted above, parameter transferability tends to be low, i.e., the number of types potentially requiring parameterization for a single metal atom, together with associated very large number of geometric and non-bonded constants, tends to significantly exceed available data. Instead, individual problems tend to be best solved with highly specific force fields, when they are available (see for example, Comba and Remenyi 2002), by combining QM and MM methods (see Chapter 13), or by accepting that the use of a highly generalized force field increases the risk for significant errors and focusing primarily on structural perturbations over a related series of compounds rather than absolute structures or energetics is advised (see also Hay 1993; Norrby and Norrby 2001).

A point that should be raised with regard to validation is that any comparison between theory and experiment must proceed in a consistent fashion. Consider molecular structures. Chemists typically visualize molecules as having 'structure'. Thus, for example, crystal X-ray diffractometry can be used to determine a molecular structure, and at the same time molecular mechanics minimization one has a molecular structure, but is it strictly valid to compare them?

It is best to consider this question in a series of steps. First, recall that the goal of a MM calculation is to find a local minimum on the PES. That local minimum has a unique structure, and each molecular coordinate has a precise value. What about the structure from experiment? Since most experimental techniques for assigning structure sample an ensemble of molecules (or one molecule many, many times), the experimental measurement is properly described as an expectation value, which is denoted by angle brackets about the measured quantity. Real molecules vibrate, even at temperatures arbitrarily close to absolute zero, so calculated structural parameters are actually expectation values over the molecular vibrations. For example, the length of the bond between atoms A and B in its ground vibrational state is a quantum mechanical harmonic oscillator, $\langle r_{AB} \rangle = r_{AB,eq}$, but real bond stretching vibrations are anharmonic, and this inevitably leads to $\langle r_{AB} \rangle > r_{AB,eq}$ (see Section 9.3.2). In the case of He_2 , mentioned above, the effect of vibrational averaging is rather extreme, leading to a difference between $\langle r_{AB} \rangle$ and $r_{AB,eq}$ of more than 50 Å! Obviously, one should judge the quality of the calculated $r_{AB,eq}$ value based on comparison to the experimental value. Note that discrepancies between $\langle r_{AB} \rangle$ and $r_{AB,eq}$ will increase if the experimental technique includes molecules in excited vibrational states. To be rigorous in comparison, either the calculation should be extended to compute $\langle r_{AB} \rangle$ (by computation of the vibrational wave function(s) and appropriate averaging) or the experiment must be analyzed to determine the equilibrium structure, e.g., as described in Figure 2.1.

However, the above discussion assumes that the experimental technique measures exactly what the computational technique does, namely, the separation between the nuclear centroids of a bond. X-ray crystallography, however, measures maxima in scattering amplitudes, which scatters not off nuclei but off electrons. Thus, if electron density maxima do not correspond to nuclear positions, there is no reason to expect agreement between theory and experiment (for heavy atoms this is not much of an issue, but for very light ones it can be). Furthermore, the conditions of the calculation typically correspond to an isolated molecule at low temperature as an ideal gas (i.e., experiencing no intermolecular interactions), while a technique

like X-ray crystallography obviously probes molecular structure in a condensed phase where crystal packing and dielectric effects may have significant impact on the determined structure (see, for example, Jacobson *et al.* 2002).

The above example illustrates some of the caveats in comparing theory to experiment for a structural datum (see also Allinger, Zhou and Bergsma 1994). Care must also be taken in assessing energetic data. Force-field calculations typically compute potential energy, whereas equilibrium distributions of molecules are dictated by free energies (see Chapter 10). Thus, the force-field energies of two conformers should not necessarily be expected to reproduce an experimental equilibrium constant between them. The situation can become still more confused for transition states, since experimental data typically are either activation free energies or Arrhenius activation energies, neither of which corresponds directly with the difference in potential energy between a reactant and a TS structure (see Chapter 15). Even in those cases where the force field makes possible the computation of heats of formation and the experimental data are available as enthalpies, it must be remembered that the effect of zero-point vibrational energy is accounted for in an entirely average way when atom-type reference heats of formation are parameterized, so some caution in comparison is warranted.

Finally, any experimental measurement carries with it some error, and obviously a comparison between theory and experiment should never be expected to do better than the experimental error. *The various points discussed in this last section are all equally applicable to comparisons between experiment and QM theories as well, and the careful practitioner would do well always to bear them in mind.*

2.6 Force Fields and Docking

Of particular interest in the field of drug design is the prediction of the strength and specificity with which a small to medium sized molecule may bind to a biological macromolecule (Lazaridis 2002; Shoichet *et al.* 2002). Many drugs function by binding to the active sites of particular enzymes so strongly that the normal substrates of these enzymes are unable to displace them and as a result some particular biochemical pathway is stalled.

If we consider a case where the structure of a target enzyme is known, but no structure complexed with the drug (or the natural substrate) exists, one can imagine using computational chemistry to evaluate the energy of interaction between the two for various positionings of the two species. This process is known as 'docking'. Given the size of the total system (which includes a biopolymer) and the very large number of possible arrangements of the drug molecule relative to the enzyme that we may wish to survey, it is clear that speedy methods like molecular mechanics are likely to prove more useful than others. This becomes still more true if the goal is to search a database of, say, 100 000 molecules to see if one can find any that bind still *more* strongly than the current drug, so as to prospect for pharmaceuticals of improved efficacy.

One way to make this process somewhat more efficient is to adopt rigid structures for the various molecules. Thus, one does not attempt to perform geometry optimizations, but simply puts the molecules in some sort of contact and evaluates their interaction energies. To that extent, one needs only to evaluate non-bonded terms in the force field, like those

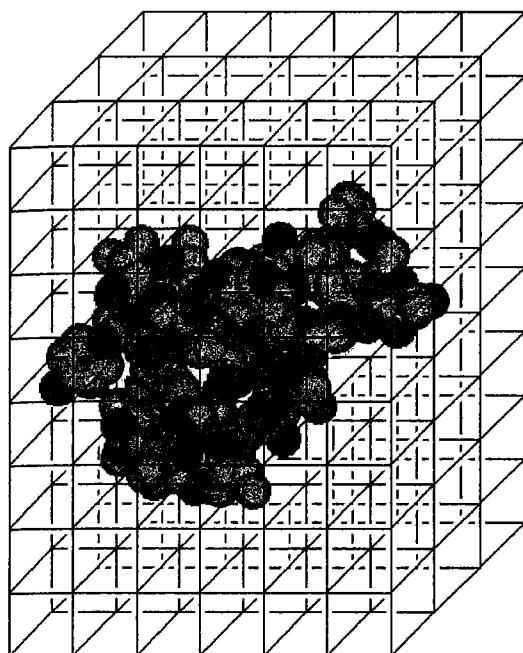
Figure
field in
improve

modeled
the rig
Given
a mole
Then,
positio
one co
each p
interac
suitab
dockin

Of
in co
of th
we d
docki
to a n
winni

structure in a condensed phase where the impact on the determined structure

comparing theory to experiment for 1994). Care must also be taken to compute potential energy, whereas energies (see Chapter 10). Thus, it necessarily be expected to reproduce the situation can become still more typically are either activation frequencies which corresponds directly with the S structure (see Chapter 15). Even computation of heats of formation must be remembered that the effect is entirely average way when atom-type caution in comparison is warranted some error, and obviously a computer is expected to do better than the experimenter are all equally applicable and the careful practitioner would



2.10 Docking grid constructed around a target protein. Each gridpoint can be assigned a force interaction potential for use in evaluating binding affinities. Note that this grid is very coarse to viewing clarity; an actual grid might be considerably finer.

ction of the strength and specificity to a biological macromolecule by binding to the active site. Enzymes of these enzymes are unable to 1 pathway is stalled.

enzyme is known, but no structure, one can imagine using computation the two for various positioning. Given the size of the total system, number of possible arrangements of the to survey, it is clear that speed is useful than others. This becomes, say, 100 000 molecules to see if current drug, so as to prospect for

ent is to adopt rigid structures for form geometry optimizations, but evaluates their interaction energies terms in the force field, like those

ed by Eqs. (2.16) and (2.22). Moreover, to further simplify matters, one may consider the enzyme to be surrounded by a three-dimensional grid, as illustrated in Figure 2.10. At a fixed geometry, one may compute the interaction potential at each grid point for a molecular mechanics atom having unit values of charge and Lennard-Jones parameters. To compute interaction energies, one places a proto-drug molecule at some arbitrary position in space, and assigns each atom to be associated with the grid point nearest it (or could interpolate if one were willing to pay the computational cost). The potential for a point is then multiplied by the appropriate atomic parameters, and the sum of all atomic interactions defines the docking energy for that particular position and orientation. After a large number of random or directed choices of position have been surveyed, the lowest energy is recorded, and one moves on to the next molecule in the test set. Of course, this analysis is rather crude, since it ignores a number of physical phenomena in computing an interaction energy. For instance, we failed to account for the desolvation of the enzyme and the substrate along the surfaces over which they come into contact, and did not consider the entropy loss associated with binding. As such, the goal of most docking studies tends to be to provide a simple filter that can narrow a vast database down to a merely large database, to which more refined techniques may be applied so as to further narrow down possible leads.

Note that after having made so many approximations in the modeling protocol, there is no particular reason to believe that nonbonded interactions evaluated using particular force field parameters will be better than others that might be developed specifically for the purpose of docking. Thus, other grid-based scoring methods are widely used (see, for example, Meng, Shoichet, and Kuntz 1992), including more recent ones that incorporate some analysis of desolvation penalties (Zou, Sun, and Kuntz 1999; Salichs *et al.* 2002; Li, Chen, and Weng 2003; Kang, Shafer, and Kuntz 2004).

2.7 Case Study: (*2R*^{*},*4S*^{*})-1-Hydroxy-2,4-dimethylhex-5-ene

Synopsis of Stahl *et al.* (1991), 'Conformational Analysis with Carbon-Carbon Coupling Constants. A Density Functional and Molecular Mechanics Study'.

Many natural products contain one or more sets of carbon backbones decorated with multiple stereogenic centers. A small such fragment that might be found in propiogenic natural products is illustrated in Figure 2.11. From a practical standpoint, the assignment of absolute configuration to each stereogenic center (*R* or *S*), or even of the relative configurations between centers, can be difficult in the absence of single-crystal X-ray data. When many possibilities exist, it is an unpleasant task to synthesize each one.

An alternative means to assign the stereochemistry is to use nuclear magnetic resonance (NMR). Coupling constant data from the NMR experiment can be particularly useful in assigning stereochemistry. However, if the fragments are highly flexible, the interpretation of the NMR data can be complicated when the interconversion of conformers is rapid on the NMR timescale. In that case, rather than observing separate, overlapping spectra for every conformer, only a population-averaged spectrum is obtained.

Deconvolution of such spectra can be accomplished in a computational fashion by (i) determining the energies of all conformers contributing to the equilibrium population, (ii) predicting the spectral constants associated with each conformer, and (iii) averaging over all spectral data weighted by the fractional contribution of each conformer to the equilibrium (the fractional contribution is determined by a Boltzmann average over the energies, see Eq. (10.49)). The authors adopted this approach for (*2R*^{*},*4S*^{*})-1-hydroxy-2,4-dimethylhex-5-ene, where the conformer energies were determined using the MM3 force field and the NMR coupling constants were predicted at the density functional level of theory. As density functional theory is the subject of Chapter 8 and the prediction of NMR data is not discussed until Section 9.4, we will focus here simply on the performance of MM3 for predicting conformer energies and weighting spectral data.

In order to find the relevant conformers, the authors employed a Monte Carlo/minimization strategy that is described in more detail in the next chapter – in practice, (*2R*^{*},*4S*^{*})-1-hydroxy-2,4-dimethylhex-5-ene is sufficiently small that one could survey every possible torsional isomer by brute force, but it would be very tedious. Table 2.2 shows, for the nine lowest energy conformers, their predicted energies, their contribution to the 300 K equilibrium population, their individual $^3J_{CC}$ coupling constants between atoms C(2)C(5), C(2)C(8), C(1)C(4), and C(4)C(7), and the mean absolute error in these coupling constants compared to experiment (see Figure 2.11 for atom-numbering convention). In addition, the spectral data predicted from a population-weighted equilibrium average over the nine conformers making up 82% of the equilibrium population are shown.

In the modeling protocol, there is evaluated using particular force fields specifically for the purpose. It is often used (see, for example, Meier et al. 2002; Li, Chen, and Wei,

population-averaged data are those in best agreement with experiment. Conformer G shows similar agreement (the increased error is within the rounding limit for the table), but its energy is not sufficiently high in energy that it is unlikely that MM3 could be sufficiently accurate for it to be the only conformer at equilibrium. As a separate assessment of this point, one can carry out *ab initio* calculations at a correlated level of electronic structure theory (e.g., Z2P//HF/TZ2P; this notation and the relevant theories are discussed in Chapters 6 and 7, but exact details are not important here), and observe what they characterize as very good agreement between the force-field energies and the *ab initio* energies (the data are not included).

In principle, then, when the relative configurations are not known for a flexible chain molecule with an achiral backbone, the technique outlined above could be used to predict predicted NMR spectra for all possibilities, and presuming one prediction matched to experiment significantly more closely than any other, the assignment would be regarded as reasonably secure. At the least, it would suggest how to prioritize synthetic efforts that will be necessary to provide the ultimate proof.

2,4-dimethylhex-5-ene

with Carbon-Carbon Coupling Constants in the Case Study'.

carbon backbones decorated with methyl groups might be found in propiogenic molecules. In practical standpoint, the assignment of *R* or *S*, or even of the relative stereochemistry of single-crystal X-ray data, will be necessary to provide the ultimate proof.

use nuclear magnetic resonance spectra can be particularly useful in determining the conformation of highly flexible, the interpretation of the conversion of conformers is rapid on the basis of separate, overlapping spectra for each conformer obtained.

in a computational fashion by (i) calculating the equilibrium population, (ii) generating conformer, and (iii) averaging the contribution of each conformer to the total energy. A Boltzmann average over the conformers is then calculated for (2*R*^{*},4*S*^{*})-1-hydroxy-2,4-dimethylhex-5-ene determined using the MM3 method at the density functional level described in Chapter 8 and the prediction of the equilibrium population based here simply on the performance of the spectral data.

The authors employed a Monte Carlo search to generate conformers in the next chapter – in practice, it is so small that one could survey them all, but this would be very tedious. Table 2.2 lists the calculated energies, their contribution to the coupling constants between atoms and the absolute error in these coupling constants (from the numbering convention). In the figure, the equilibrium average over the population are shown.

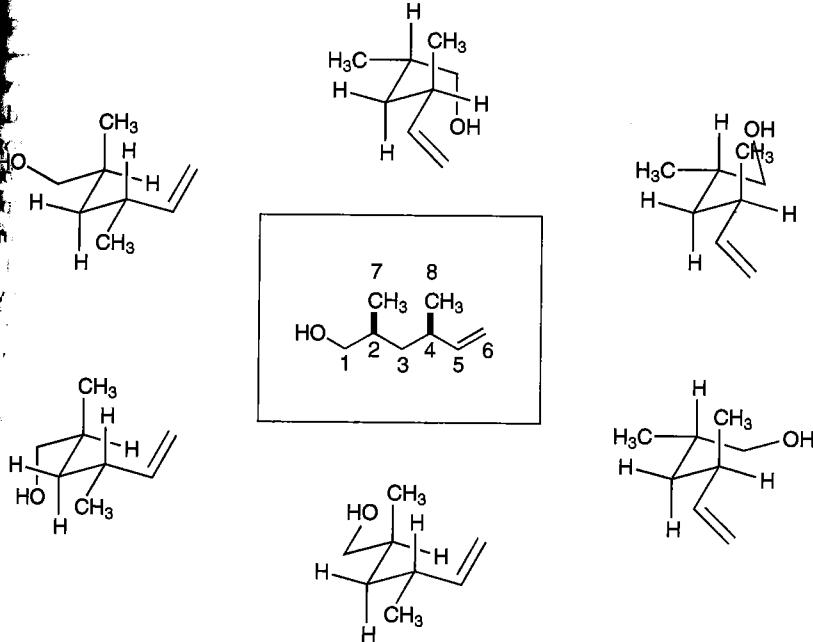


Figure 2.11 Some plausible conformations of ($2R^*,4S^*$)-1-hydroxy-2,4-dimethylhex-5-ene. How many different torsional isomers might one need to examine, and how would you go about generating them? [Note that the notation $2R^*,4S^*$ implies that the relative stereochemical configuration at the 2 and 4 centers is *R,S* – by convention, when the absolute configuration is unknown the first center is always assigned to be R^* . However, the absolute conformations that are drawn here are *S,R* so as to preserve correspondence with the published illustrations of Stahl and coworkers. Since NMR in an achiral solvent does not distinguish between enantiomers, one can work with either absolute configuration in this instance.]

Table 2.2 Relative MM3 energies (kcal mol⁻¹), fractional equilibrium populations *F* (%), predicted NMR coupling constants (Hz), and mean unsigned error in predicted coupling constants for different conformers and the equilibrium average of (*2R*^{*},*4S*^{*})-1-hydroxy-2,4-dimethylhex 5-ene at 300 K.

Conformer	rel <i>E</i>	<i>F</i>	³ <i>J</i>				MUE
			C(2)C(5)	C(2)C(8)	C(1)C(4)	C(4)C(7)	
A	0.0	24	1.1	4.2	3.9	1.3	0.6
B	0.1	21	1.1	4.0	5.8	1.2	1.0
C	0.2	19	1.0	4.2	4.1	1.2	0.7
D	0.9	5	3.8	1.5	1.7	4.5	2.2
E	1.1	4	4.1	0.8	1.1	4.4	2.5
F	1.3	3	4.1	0.9	0.4	5.3	2.9
G	1.4	2	1.2	3.7	3.8	1.5	0.3
H	1.4	2	1.4	4.2	5.7	1.4	0.9
I	1.5	2	0.1	5.1	0.0	5.3	2.5
average		82	1.4	3.7	4.1	1.8	0.3
experiment			1.4	3.3	3.8	2.2	

In that regard, this paper might have been improved by including a prediction (and ideally an experimental measurement) for the NMR coupling data of (*2R*^{*},*4R*^{*})-1-hydroxy-2,4-dimethylhex-5-ene, i.e., the stereoisomer having the *R*^{*},*R*^{*} relative configuration between the stereogenic centers instead of the *R*^{*},*S*^{*} configuration. If each predicted spectrum matched its corresponding experimental spectrum significantly more closely than it matched the non-corresponding experimental spectrum, the utility of the methodology would be still more convincingly demonstrated. Even in the absence of this demonstration, however, the work of Stahl and his coworkers nicely illustrates how accurate force fields can be for 'typical' C,H,O-compounds, and also how different levels of theory can be combined to address different parts of a computational problem in the most efficient manner. In this case, inexpensive molecular mechanics is used to provide an accurate map of the wells on the conformational potential energy surface and the vastly more expensive DFT method is employed only thereafter to predict the NMR spectral data.

Bibliography and Suggested Additional Reading

- Bakken, V. and Helgaker, T. 2002. 'The Efficient Optimization of Molecular Geometries Using Redundant Internal Coordinates', *J. Chem. Phys.*, **117**, 9160.
- Bowen, J. P. and Allinger, N. L. 1991. 'Molecular Mechanics: The Art and Science of Parameterization', in *Reviews in Computational Chemistry*, Vol. 2, Lipkowitz, K. B. and Boyd, D. B. Eds., VCH: New York, 81.
- Brooijmans, N. and Kuntz, I. D. 2003. 'Molecular Recognition and Docking Algorithms', *Annu. Rev. Biophys. Biomol. Struct.* **32**, 335.
- Comba, P. and Hambley, T. W. 2001. *Molecular Modeling of Inorganic Compounds*, 2nd Edn., Wiley-VCH: Weinheim.
- Comba, P. and Remenyi, R. 2003. 'Inorganic and Bioinorganic Molecular Mechanics Modeling—the Problem of Force Field Parameterization', *Coord. Chem. Rev.*, **238–239**, 9.

equilibrium populations F (%)
error in predicted coupling constant
 $(2R^*,4S^*)$ -1-hydroxy-2,4-dimethyl-

C(1)C(4)	C(4)C(7)	MU
3.9	1.3	0.6
5.8	1.2	1.0
4.1	1.2	0.7
1.7	4.5	2.2
1.1	4.4	2.5
0.4	5.3	2.9
3.8	1.5	0.3
5.7	1.4	0.9
0.0	5.3	2.5
4.1	1.8	0.3
3.8	2.2	

including a prediction (and ideally data of $(2R^*,4R^*)$ -1-hydroxy-2,4-dimethyl relative configuration between enantiomers. If each predicted spectrum matched the experiment more closely than it matched any of the methodology would be still valid. In this demonstration, however, the accurate force fields can be followed. A combination of theory and computation can be combined to give the most efficient manner. In this way an accurate map of the wells obtained by the more expensive DFT method is obtained.

Conclusion

Molecular Geometries Using Redundant Parameters', *J. Am. Chem. Soc.*, 1993, 115, 10200–10207.
The Art and Science of Parameterization', *J. Am. Chem. Soc.*, 1993, 115, 10208–10215.
and Docking Algorithms', *Annu. Rev. Biomed. Eng.*, 2002, 3, 1–29.
Organic Compounds', 2nd Edn., Wiley, 1994, 1–200.
Molecular Mechanics Modeling—A Practical Guide', *Acc. Chem. Res.*, 1999, 32, 238–239, 9.

1994. 'Problems and Questions in the Molecular Modeling of Biomolecules', *Biochem. Rev.*, 1994, 22, 1–20.
1991. 'New Approaches to Empirical Force Fields', in *Reviews in Computational Chemistry*, Vol. 2, Lipkowitz, K. B. and Boyd, D. B., Eds., VCH; New York, 99.
1993. 'Electrostatic Interaction Potentials in Molecular Force Fields', *Chem. Rev.*, 1993, 93, 2439–2460.
E. and Houk, K. N. 1993. 'Transition-state Modeling with Empirical Force Fields', *J. Am. Chem. Soc.*, 115, 2439.
1999. *Introduction to Computational Chemistry*, Wiley: Chichester.
Norrbey, P.-O. 2003. 'Transition States from Empirical Force Fields', *Theor. Chem. Acc.*, 110, 1–10.
Shafer, R. H., and Kuntz, I. D. 2004. 'Calculation of Ligand-nucleic Acid Binding Free Energy Using the Generalized-Born Model in DOCK', *Biopolymers*, 73, 192.
Root, D. M., and Cleveland, T. 1995. 'Molecular Mechanics Force Fields for Modeling Organometallic Compounds' in *Reviews in Computational Chemistry*, Vol. 6, Cundari, T. B. and Boyd, D. B., Eds., VCH: New York, 73.
2002. 'Binding Affinity and Specificity from Computational Studies', *Curr. Org. Chem.*, 6, 1–10.
2001. *Molecular Modelling*, 2nd Edn., Prentice Hall: London.
2001. 'Recipe for an Organometallic Force Field', in *Computational Organometallic Chemistry*, Cundari, T. Ed., Marcel Dekker: New York 7.
and Liljefors, T. 1996. 'Molecular Mechanics Calculated Conformational Energies of Organometallic Compounds: A Comparison of Force Fields', in *Reviews in Computational Chemistry*, Vol. 9, Cundari, T. B. and Boyd, D. B., Eds., VCH: New York, 167.
B. 2003. 'Exploring Potential Energy Surfaces for Chemical Reactions: An Overview of Computational Methods', *J. Comput. Chem.*, 24, 1514.
- ## References
- L., Zhou, X., and Bergsma, J. 1994. *J. Mol. Struct. (Theochem.)*, 312, 69.
E., Storer, J. W., Cramer, C. J., French, A. D., and Truhlar, D. G. 1998. *J. Comput. Chem.*, 19, 1033–1052.
1992. *J. Chem. Edu.*, 69, 209.
D., Chasman, D., Murphy, R. B., Halgren, T. A., and Friesner, R. A. 1997. *J. Am. Chem. Soc.*, 119, 5908.
D. L. and McConnell, K. J. 2000. *Curr. Opin. Struct. Biol.*, 10, 182.
and Benson, S. W. 1993. *Chem. Rev.*, 93, 2419.
and Remenyi, R. 2002. *J. Comput. Chem.*, 23, 697.
E. and Houk, K. N. 1987. *J. Am. Chem. Soc.*, 109, 3698.
E. and Balázs, A. 1985. *J. Mol. Struct. (Theochem.)*, 133, 105.
L. and Rokhlin, V. 1987. *J. Comput. Phys.*, 73, 325.
K., Liljefors, T., Norrbey, P.-O., and Petterson, I. 1996. *J. Comput. Chem.*, 17, 429.
K., Palm, J., Petterson, I., and Stamvick, A. 1991. *J. Comput. Chem.*, 12, 200.
C., Wang, C., Teletchea, S., and Lavery, R. 2003. *J. Comput. Chem.*, 24, 1.
T. and Peräkylä, M. 2001. *J. Comput. Chem.*, 22, 1229.
1993. *Coord. Chem. Rev.*, 126, 177.
sen, L., Madsen, D. E., Esbensen, S. L., Olsen, L., and Engelsen, S. B. 2004. *Carbohyd. Res.*, 349, 7–17.
1946. *J. Chem. Phys.*, 14, 465.

- Jacobson, M. P., Friesner, R. A., Xiang, Z. X., and Honig, B. 2002. *J. Mol. Biol.*, **320**, 597.
- Jalaie, M. and Lipkowitz, K. B. 2000. *Rev. Comput. Chem.*, **14**, 441.
- Jensen, F. 1999. *Introduction to Computational Chemistry*, Wiley: Chichester, Chapter 14 and references therein.
- Lazaridis, T. 2002. *Curr. Org. Chem.*, **6**, 1319.
- Leach, A. R. 1991. *Rev. Comput. Chem.*, **2**, 1.
- Li, L., Chen, R., and Weng, Z. P. 2003. *Proteins*, **53**, 693.
- Luo, F., McBane, G. C., Kim, G., Giese, C. F., and Gentry, W. R. 1993. *J. Chem. Phys.*, **98**, 3564.
- Meng, E. C., Shoichet, B. K., and Kuntz, I. D. 1992. *J. Comput. Chem.*, **13**, 505.
- Menger, F. 1990. *J. Am. Chem. Soc.*, **112**, 8071.
- Norrby, P.-O. and Brandt, P. 2001. *Coord. Chem. Rev.*, **212**, 79.
- Olsen, P. T. and Jensen, F. 2003. *J. Chem. Phys.*, **118**, 3523.
- Petrella, R. J., Andricioaei, I., Brooks, B., and Karplus, M. 2003. *J. Comput. Chem.*, **24**, 222.
- Price, D. J. and Brooks, C. L. 2002. *J. Comput. Chem.*, **23**, 1045.
- Radom, L., Hehre, W. J., and Pople, J. A. 1971. *J. Am. Chem. Soc.*, **93**, 289.
- Reichardt, C. 1990. *Solvents and Solvent Effects in Organic Chemistry*, VCH: New York, 12.
- Salichs, A., López, M., Orozco, M., and Luque, F. J. 2002. *J. Comput.-Aid. Mol. Des.*, **16**, 569.
- Schlick, T. 1992. *Rev. Comput. Chem.*, **3**, 1.
- Shi, S., Yan, L., Yang, Y., Fisher-Shaulsky, J., and Thacher, T. 2003. *J. Comput. Chem.*, **24**, 1059.
- Shoichet, B. K., McGovern, S. L., Wei, B. Q., and Irwin, J. J. 2002. *Curr. Opin. Chem. Biol.*, **6**, 439.
- Skeel, R. D., Tezcan, I., and Hardy, D. J. 2002. *J. Comput. Chem.*, **23**, 673.
- Stahl, M., Schopfer, U., Frenking, G., and Hoffmann, R. W. 1991. *J. Am. Chem. Soc.*, **113**, 4792.
- Westheimer, F. H. and Mayer, J. E. 1946. *J. Chem. Phys.*, **14**, 733.
- Wolfe, S., Rauk, A., Tel, L. M., and Csizmadia, I. G. 1971. *J. Chem. Soc. B*, **136**.
- Woods, R. J. 1996. *Rev. Comput. Chem.*, **9**, 129.
- York, D. M., Darden, T. A., and Pedersen, L. G. 1993. *J. Chem. Phys.*, **99**, 8345.
- Zou, X. Q., Sun, Y. X., and Kuntz, I. D. 1999. *J. Am. Chem. Soc.*, **121**, 8033.