CHAPTER FOUR

Empirical Force Field Models: Molecular Mechanics

4.1 Introduction

Many of the problems that we would like to tackle in molecular modelling are unfortunately too large to be considered by quantum mechanics. Quantum mechanical methods deal with the electrons in a system, so that even if some of the electrons are ignored (as in the semi-empirical schemes) a large number of particles must still be considered, and the calculations are time-consuming. Force field methods (also known as molecular mechanics) ignore the electronic motions and calculate the energy of a system as a function of the nuclear positions only. Molecular mechanics is thus invariably used to perform calculations on systems containing significant numbers of atoms. In some cases force fields can provide answers that are as accurate as even the highest-level quantum mechanical calculations, in a fraction of the computer time. However, molecular mechanics cannot of course provide properties that depend upon the electronic distribution in a molecule.

That molecular mechanics works at all is due to the validity of several assumptions. The first of these is the Born–Oppenheimer approximation, without which it would be impossible to contemplate writing the energy as a function of the nuclear coordinates at all. Molecular mechanics is based upon a rather simple model of the interactions within a system with contributions from processes such as the stretching of bonds, the opening and closing of angles and the rotations about single bonds. Even when simple functions (e.g. Hooke's law) are used to describe these contributions the force field can perform quite acceptably. Transferability is a key attribute of a force field, for it enables a set of parameters developed and tested on a relatively small number of cases to be applied to a much wider range of problems. Moreover, parameters developed from data on small molecules can be used to study much larger molecules such as polymers.

4.1.1 A Simple Molecular Mechanics Force Field

Many of the molecular modelling force fields in use today for molecular systems can be interpreted in terms of a relatively simple four-component picture of the intra- and inter-molecular forces within the system. Energetic penalties are associated with the deviation of bonds and angles away from their 'reference' or 'equilibrium' values, there is a function that describes how the energy changes as bonds are rotated, and finally the force field contains terms that describe the interaction between non-bonded parts of the system. More sophisticated force fields may have additional terms, but they invariably contain these four components. An attractive feature of this representation is that the various terms can be ascribed to changes in specific internal coordinates such as bond lengths, angles, the rotation of bonds or movements of atoms relative to each other. This makes it easier to understand how changes in the force field parameters affect its performance, and also helps in the parametrisation process. One functional form for such a force field that can be used to model single molecules or assemblies of atoms and/or molecules is:

$$\mathscr{V}(\mathbf{r}^N) = \sum_{\text{bonds}} \frac{k_i}{2}(l_i - l_{i,0})^2 + \sum_{\text{angles}} \frac{k_i}{2}(\theta_i - \theta_{i,0})^2 + \sum_{\text{torsions}} \frac{V_n}{2}(1 + \cos(n\omega - \gamma))$$

$$+ \sum_{i=1}^{N} \sum_{j=i+1}^{N} \left(4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}\right) \tag{4.1}$$

$\mathscr{V}(\mathbf{r}^N)$ denotes the potential energy, which is a function of the positions ($\mathbf{r}$) of N particles (usually atoms). The various contributions are schematically represented in Figure 4.1. The first term in Equation (4.1) models the interaction between pairs of bonded atoms, modelled here by a harmonic potential that gives the increase in energy as the bond length l_i deviates from the reference value $l_{i,0}$. The second term is a summation over all valence angles in the molecule, again modelled using a harmonic potential (a valence angle is the angle formed between three atoms A–B–C in which A and C are both bonded to B). The third term in Equation (4.1) is a torsional potential that models how the energy changes as a bond rotates. The fourth contribution is the non-bonded term. This is calculated between all pairs of atoms (i and j) that are in different molecules or that are in

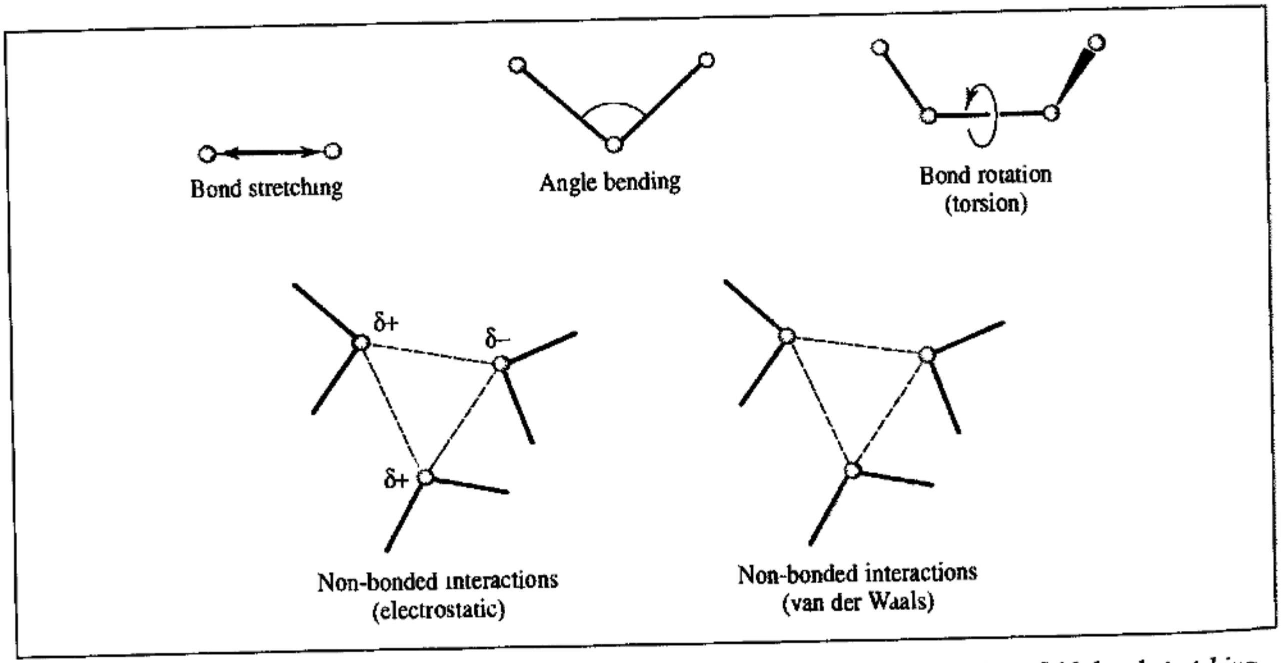


Fig. 4.1 Schematic representation of the four key contributions to a molecular mechanics force field: bond stretching, angle bending and torsional terms and non-bonded interactions

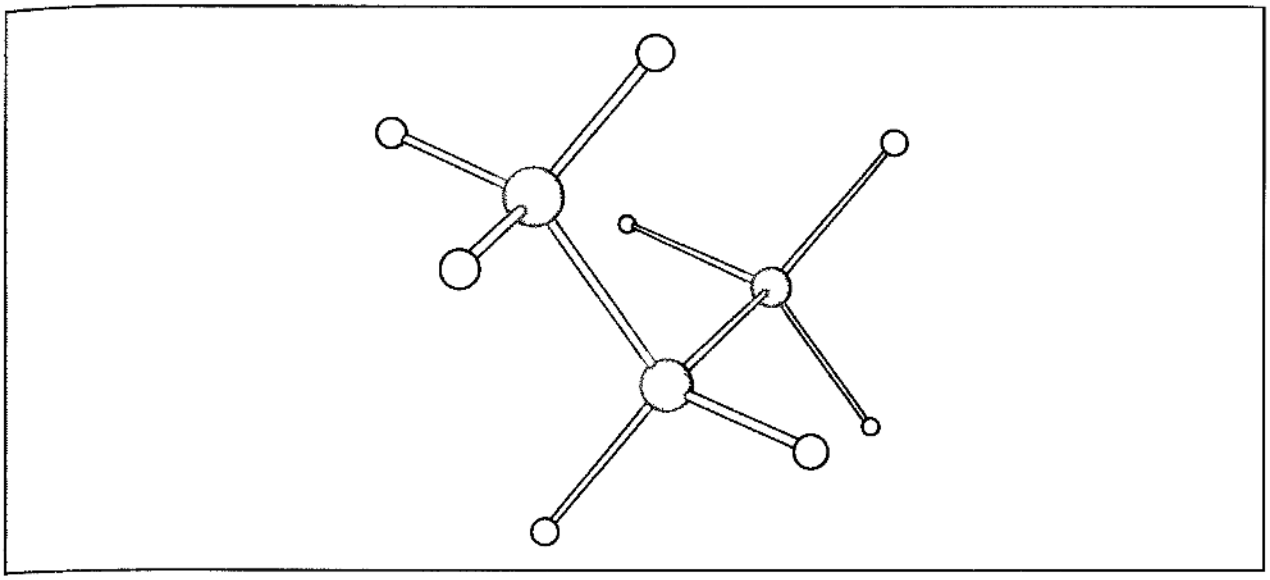


Fig. 4.2. A typical force field model for propane contains ten bond-stretching terms, eighteen angle-bending terms, eighteen torsional terms and 27 non-bonded interactions

the same molecule but separated by at least three bonds (i.e. have a $1, n$ relationship where $n \geq 4$). In a simple force field the non-bonded term is usually modelled using a Coulomb potential term for electrostatic interactions and a Lennard-Jones potential for van der Waals interactions.

We shall discuss the nature of these different contributions in more detail in Sections 4.3–4.10, but here we consider how the simple force field of Equation (4.1) would be used to calculate the energy of a conformation of propane (Figure 4.2). Propane has ten bonds: two C–C bonds and eight C–H bonds. The C–C bonds are symmetrically equivalent but the C–H bonds fall into two classes, one group corresponding to the two hydrogens bonded to the central methylene (CH_2) carbon and one group corresponding to the six hydrogens bonded to the methyl carbons. In some sophisticated force fields different parameters would be used for these two different types of C–H bond, but in most force fields the same bonding parameters (i.e. k_i and $l_{i,0}$) would be used for each of the eight C–H bonds. This is an example of the way in which the same parameters can be used for a wide variety of molecules. There are 18 different valence angles in propane, comprising one C–C–C angle, ten C–C–H angles and seven H–C–H angles. Note that all angles are included in the force field model even though some of them may not be independent of the others. There are 18 torsional terms: twelve H–C–C–H torsions and six H–C–C–C torsions. Each of these is modelled with a cosine series expansion that has minima at the *trans* and *gauche* conformations. Finally, there are 27 non-bonded terms to calculate, comprising 21 H–H interactions and six H–C interactions. The electrostatic contribution would be calculated using Coulomb's law from partial atomic charges associated with each atom and the van der Waals contribution as a Lennard-Jones potential with appropriate ε_{ij} and σ_{ij} parameters. A sizeable number of terms are thus included in the force field model, even for a molecule as simple as propane. Even so, the number of terms (73) is many fewer than the number of integrals that would be involved in an equivalent *ab initio* quantum mechanical calculation.

4.2 Some General Features of Molecular Mechanics Force Fields

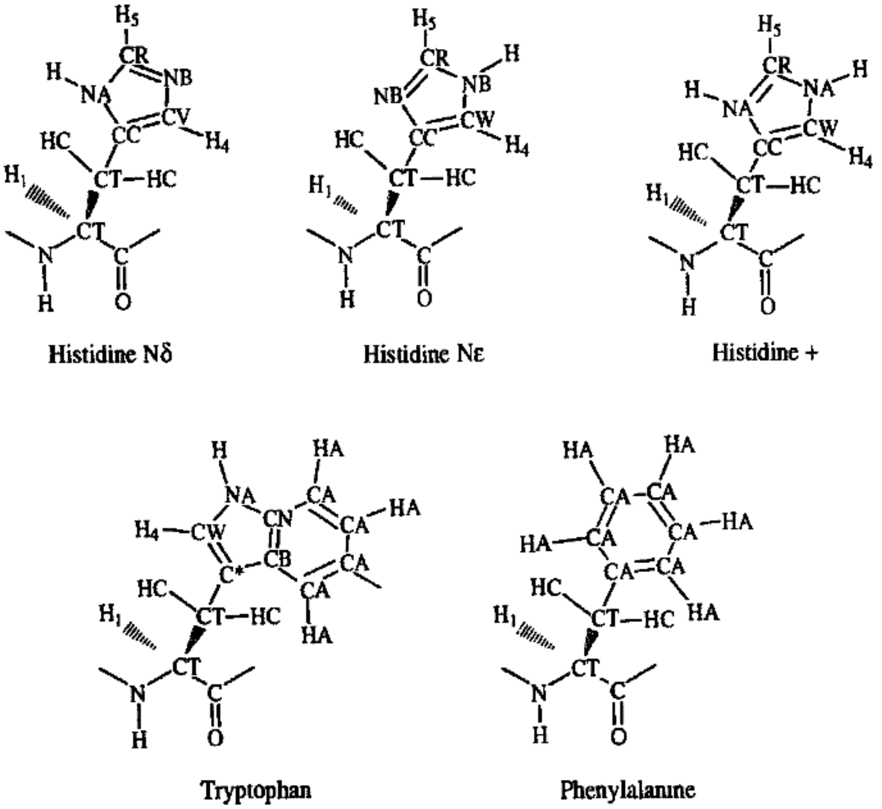
To define a force field one must specify not only the functional form but also the parameters (i.e. the various constants such as k_i, V_n and σ_{ij} in Equation (4.1)); two force fields may use an identical functional form yet have very different parameters. Moreover, force fields with the same functional form but different parameters, and force fields with different functional forms, may give results of comparable accuracy. A force field should be considered as a single entity; it is not strictly correct to divide the energy into its individual components, let alone to take some of the parameters from one force field and mix them with parameters from another force field. Nevertheless, some of the terms in a force field are sufficiently independent of the others (particularly the bond and angle terms) to make this an acceptable approximation in certain cases.

The force fields used in molecular modelling are primarily designed to reproduce structural properties but they can also be used to predict other properties, such as molecular spectra. However, molecular mechanics force fields can rarely predict spectra with great accuracy (although the more recent molecular mechanics force fields are much better in this regard). A force field is generally designed to predict certain properties and will be parametrised accordingly. While it is useful to try to predict other quantities which have not been included in the parametrisation process it is not necessarily a failing if a force field is unable to do so.

Transferability of the functional form and parameters is an important feature of a force field. Transferability means that the same set of parameters can be used to model a series of related molecules, rather than having to define a new set of parameters for each individual molecule. For example, we would expect to be able to use the same set of parameters for all *n*-alkanes. Transferability is clearly important if we want to use the force field to make predictions. Only for some small systems, where particularly accurate work is required, may it be desirable to develop a model specific to that molecule.

One important point that we should bear in mind as we undertake a deeper analysis of molecular mechanics is that force fields are *empirical*; there is no 'correct' form for a force field. Of course, if one functional form is shown to perform better than another it is likely that form will be favoured. Most of the force fields in common use do have a very similar form, and it is tempting to assume that this must therefore be the optimal functional form Certainly such models tend to conform to a useful picture of the interactions present in a system, but it should always be borne in mind that there may be better forms, particularly when developing a force field for new classes of molecule. The functional forms employed in molecular mechanics force fields are often a compromise between accuracy and computational efficiency; the most accurate functional form may often be unsatisfactory for efficient computation. As the performance of computers increases so it becomes possible to incorporate more sophisticated models. An additional consideration is that in order to use techniques such as energy minimisation and molecular dynamics, it is usually desirable to be able to calculate the first and second derivatives of the energy with respect to the atomic coordinates.

A concept that is common to most force fields is that of an *atom type*. When preparing the input for a quantum mechanics calculation it is usually necessary to specify the atomic numbers of the nuclei present, together with the geometry of the system and the overall charge and spin multiplicity. For a force field the overall charge and spin multiplicity are not explicitly required, but it is usually necessary to assign an atom type to each atom in the system. The atom type is more than just the atomic number of an atom; it usually contains information about its hybridisation state and sometimes the local environment. For example, it is necessary in most force fields to distinguish between sp^3-hybridised carbon atoms (which adopt a tetrahedral geometry), sp^2-hybridised carbons (which are trigonal) and sp-hybridised carbons (which are linear). Each force field parameter is expressed in terms of these atom types, so that the reference angle θ_0 for a tetrahedral carbon atom would be near 109.5° and that for a trigonal carbon would be near 120°. The atom types in some force fields reflect the neighbouring environment as well as the hybridisation and can be quite extensive for some atoms. For example, the MM2, MM3 and MM4 force fields of Allinger and co-workers that are widely used for calculations on 'small' molecules [Allinger 1977; Allinger *et al.* 1989, 1990a, b, 1996a, b; Lii and Allinger 1989; Nevins *et al.* 1996a, b, c] distinguish the following types of carbon atom: sp^3, sp^2, sp, carbonyl, cyclopropane, radical, cyclopropene and carbonium ion. In the AMBER force field of Kollman and co-workers [Weiner *et al.* 1984; Cornell *et al.* 1995] the carbon atom at the junction between a six- and a five-membered ring (e.g. in the amino acid tryptophan) is assigned



Histidine Nδ

Histidine Nε

Histidine +

Tryptophan

Phenylalanine

Fig. 4 3 AMBER atom types for the amino acids histidine, tryptophan and phenylalanine. There are three possible protonation states of histidine.

an atom type that is different from the carbon atom in an isolated five-membered ring such as histidine, which in turn is different from the atom type of a carbon atom in a benzene ring. Indeed, the AMBER force field uses different atom types for a histidine amino acid depending upon its protonation state (Figure 4.3). Other, more general, force fields would assign these atoms to the same generic 'sp^2 carbon' atom type. It is often found that force fields which are designed for modelling specific classes of molecule (such as proteins and nucleic acids, in the case of AMBER) use more specific atom types than force fields designed for general-purpose use.

We now discuss in some detail the individual contributions to a molecular mechanics force field, giving a selection of the various functional forms that are in common use. We shall then consider the important task of parametrisation, in which values for the many force constants are derived. Our discussion will be illuminated by examples chosen from contemporary force fields in widespread use and the MM2/MM3/MM4 and AMBER force fields in particular.

4.3 Bond Stretching

The potential energy curve for a typical bond has the form shown in Figure 4.4. Of the many functional forms used to model this curve, that suggested by Morse is particularly useful The Morse potential has the form:

$$\mathscr{v}(l) = D_e\{1 - \exp[-a(l - l_0)]\}^2 \qquad (4.2)$$

D_e is the depth of the potential energy minimum and $a = \omega\sqrt{\mu/2D_e}$, where μ is the reduced mass and ω is the frequency of the bond vibration. ω is related to the stretching constant of the bond, k, by $\omega = \sqrt{k/\mu}$. l_0 is the reference value of the bond. The Morse potential is not usually used in molecular mechanics force fields. In part this is because it is not particularly amenable to efficient computation but also because it requires three parameters to be specified for each bond. Moreover, it is rare in molecular mechanics calculations for

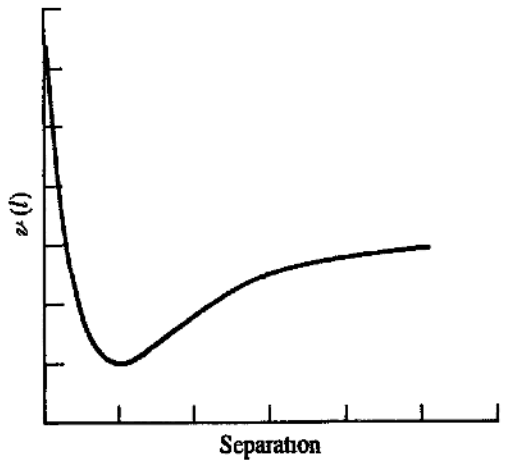


Fig 4.4: Variation in bond energy with interatomic separation.

bonds to deviate significantly from their equilibrium values; the Morse curve describes a wide range of behaviour from the strong equilibrium behaviour to dissociation. Consequently, simpler expressions are often used. The most elementary approach is to use a Hooke's law formula in which the energy varies with the square of the displacement from the reference bond length l_0:

$$v(l) = \frac{k}{2}(l - l_0)^2 \tag{4.3}$$

The astute reader will have noticed our use of the term 'reference bond length' (sometimes called the 'natural bond length') for the parameter l_0. This parameter is commonly called the 'equilibrium' bond length, but to do so can be misleading. The reference bond length is the value that the bond adopts when all other terms in the force field are set to zero. The equilibrium bond length, by contrast, is the value that is adopted in a minimum energy structure, when all other terms in the force field contribute. The complex interplay between the various components in the force field means that the bond may well deviate slightly from its reference value in order to compensate for other contributions to the energy. It is also important to recognise that 'real' molecules undergo vibrational motion (even at absolute zero, there is a zero-point energy due to vibrational motion). A true bond-stretching potential is not harmonic but has a shape similar to that in Figure 4.4, which means that the 'average' length of the bond in a vibrating molecule will deviate from the equilibrium value for the hypothetical motionless state. The effects are usually small, but they are significant if one wishes to predict bond lengths to thousandths of an ångström. When comparing the results of calculations with experimental data, one must also remember that different experimental techniques measure different 'equilibrium' values, especially when the experiments are performed at different temperatures. The errors in experimentally determined bond lengths can be quite large; for example, libration of a molecule in a crystal means that the bond lengths determined by X-ray methods at room temperature may have errors as large as 0.015 Å. MM2 was parametrised to fit the values obtained by electron diffraction, which give the mean distances between atoms averaged over the vibrational motion at room temperature.

The forces between bonded atoms are very strong and considerable energy is required to cause a bond to deviate significantly from its equilibrium value. This is reflected in the magnitude of the force constants for bond stretching; some typical values from the MM2 force field are shown in Table 4.1, where it can be seen that those bonds one would

Bond	**l_0 (Å)**	**k (kcal mol^{-1} Å^{-2})**
Csp^3-Csp^3	1.523	317
Csp^3-Csp^2	1.497	317
$Csp^2{=}Csp^2$	1.337	690
$Csp^2{=}O$	1.208	777
Csp^3-Nsp^3	1.438	367
C–N (amide)	1 345	719

Table 4 1 Force constants and reference bond lengths for selected bonds [Allinger 1977]

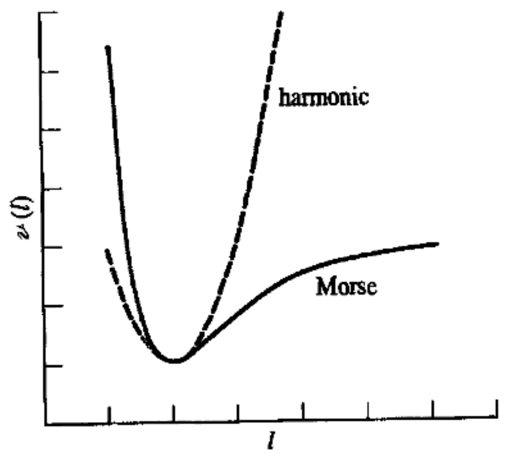


Fig. 4.5: Comparison of the simple harmonic potential (Hooke's law) with the Morse curve

intuitively expect to be stronger have large force constants (contrast C–C with C=C and N≡N). A deviation of just 0.2 Å from the reference value l_0 with a force constant of 300 kcal mol^{-1} Å^{-2} would cause the energy of the system to rise by 12 kcal/mol.

The Hooke's law functional form is a reasonable approximation to the shape of the potential energy curve at the bottom of the potential well, at distances that correspond to bonding in ground-state molecules. It is less accurate away from equilibrium (Figure 4.5). To model the Morse curve more accurately, cubic and higher terms can be included and the bond-stretching potential can be written as follows:

$$v(l) = \frac{k}{2}(l - l_0)^2[1 - k'(l - l_0) - k''(l - l_0)^2 - k'''(l - l_0)^3 \ldots] \tag{4 4}$$

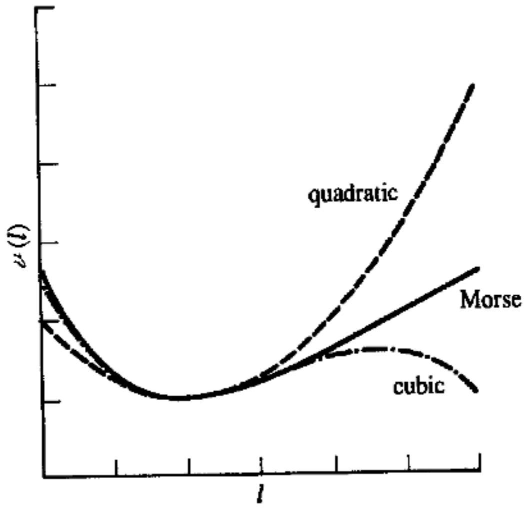


Fig 4 6· A cubic bond-stretching potential passes through a maximum but gives a better approximation to the Morse curve close to the equilibrium structure than the quadratic form

An undesirable side-effect of an expansion that includes just a quadratic and a cubic term (as is employed in MM2) is that, far from the reference value, the cubic function passes through a maximum. This can lead to a catastrophic lengthening of bonds (Figure 4.6). One way to accommodate this problem is to use the cubic contribution only when the structure is sufficiently close to its equilibrium geometry and is well inside the 'true' potential well. MM3 also includes a quartic term; this eliminates the inversion problem and leads to an even better description of the Morse curve.

4.4 Angle Bending

The deviation of angles from their reference values is also frequently described using a Hooke's law or harmonic potential:

$$v(\theta) = \frac{k}{2}(\theta - \theta_0)^2 \tag{4.5}$$

The contribution of each angle is characterised by a force constant and a reference value. Rather less energy is required to distort an angle away from equilibrium than to stretch or compress a bond, and the force constants are proportionately smaller, as can be observed in Table 4.2.

Angle	θ_0	**k (kcal mol^{-1}deg^{-1})**
$Csp^3-Csp^3-Csp^3$	109.47	0.0099
Csp^3-Csp^3-H	109.47	0.0079
$H-Csp^3-H$	109.47	0 0070
$Csp^3-Csp^2-Csp^3$	117.2	0.0099
$Csp^3-Csp^2{=}Csp^2$	121.4	0.0121
$Csp^3-Csp^2{=}O$	122.5	0.0101

Table 4.2 Force constants and reference angles for selected angles [Allinger 1977].

As with the bond-stretching terms, the accuracy of the force field can be improved by the incorporation of higher-order terms. MM2 contains a quartic term in addition to the quadratic term. Higher-order terms have also been included to treat certain pathological cases such as very highly strained molecules. The general form of the angle-bending term then becomes:

$$v(\theta) = \frac{k}{2}(\theta - \theta_0)^2[1 - k'(\theta - \theta_0) - k''(\theta - \theta_0)^2 - k'''(\theta - \theta_0)^3 \ldots] \tag{4.6}$$

4.5 Torsional Terms

The bond-stretching and angle-bending terms are often regarded as 'hard' degrees of freedom, in that quite substantial energies are required to cause significant deformations from their reference values. Most of the variation in structure and relative energies is due to the complex interplay between the torsional and non-bonded contributions.

The existence of barriers to rotation about chemical bonds is fundamental to understanding the structural properties of molecules and conformational analysis. The three minimum-energy staggered conformations and three maximum-energy eclipsed structures of ethane are a classic example of the way in which the energy changes with a bond rotation. Quantum mechanical calculations suggest that this barrier to rotation can be considered to arise from antibonding interactions between the hydrogen atoms on opposite ends of the molecule; the antibonding interactions are minimised when the conformation is staggered and are at a maximum when the conformation is eclipsed. Many force fields are used for modelling flexible molecules where the major changes in conformation are due to rotations about bonds; in order to simulate this it is essential that the force field properly represents the energy profiles of such changes.

Not all molecular mechanics force fields use torsional potentials; it may be possible to rely upon non-bonded interactions between the atoms at the end of each torsion angle (the 1,4 atoms) to achieve the desired energy profile. However, most force fields for 'organic' molecules do use explicit torsional potentials with a contribution from each bonded quartet of atoms A–B–C–D in the system. Thus there would be nine individual torsional terms for ethane and 24 for benzene (6 × C–C–C–C, 12 × C–C–C–H and 6 × H–C–C–H). Torsional potentials are almost always expressed as a cosine series expansion. One functional form is:

$$\upsilon(\omega) = \sum_{n=0}^{N} \frac{V_n}{2} [1 + \cos(n\omega - \gamma)] \tag{4.7}$$

ω is the torsion angle.

An alternative but equivalent expression is:

$$\upsilon(\omega) = \sum_{n=0}^{N} C_n \cos(\omega)^n \tag{4.8}$$

V_n in Equation (4.7) is often referred to as the 'barrier' height, but to do so is misleading, obviously so when more than one term is present in the expansion. Moreover, other terms in the force field equation contribute to the barrier height as a bond is rotated, especially the non-bonded interactions between the 1,4 atoms. The value of V_n does, however, give a qualitative indication of the relative barriers to rotation; for example, V_n for an amide bond will be larger than for a bond between two sp^3 carbon atoms. n in Equation (4.7) is the *multiplicity*; its value gives the number of minimum points in the function as the bond is rotated through 360°. γ (the phase factor) determines where the torsion angle passes through its minimum value. For example, the energy profile for rotation about the single bond between two sp^3 carbon atoms could be represented by a single torsional term with $n = 3$ and $\gamma = 0°$. This would give a threefold rotational profile with minima at torsion angles of +60°, −60° and 180° and maxima at ±120° and 0°. A double bond between two sp^2 carbon atoms would have $n = 2$ and $\gamma = 180°$, giving minima at 0° and 180°. The value of V_n would also be significantly larger for the double bond than for the single

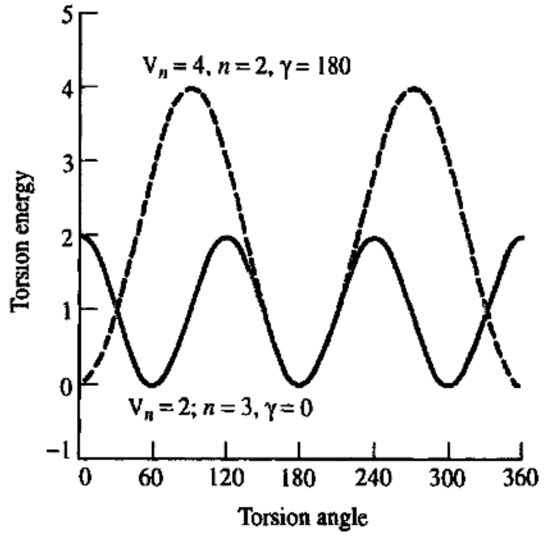


Fig 4 7. Torsional potential varies as shown for different values of V_n, n and γ.

bond. The effects of varying V_n, n and γ are illustrated in Figure 4.7 for commonly occurring torsional potentials.

Many of the torsional terms in the AMBER force field contain just one term from the cosine series expansion, but for some bonds it was found necessary to include more than one term. For example, to correctly model the tendency of O–C–C–O bonds to adopt a *gauche* conformation, a torsional potential with two terms was used for the O–C–C–O contribution:

$$\nu(\omega_{\text{C–O–O–C}}) = 0.25(1 + \cos 3\omega) + 0.25(1 + \cos 2\omega) \tag{4.9}$$

The torsional energy for a $OCH_2{-}CH_2O$ fragment (found in the sugars in DNA) varies with the torsion angle ω as shown in Figure 4.8. Another feature of the AMBER force field is its use of general torsional parameters. The energy profile for rotation about a bond that is described by a general torsional potential depends solely upon the atom types of the two

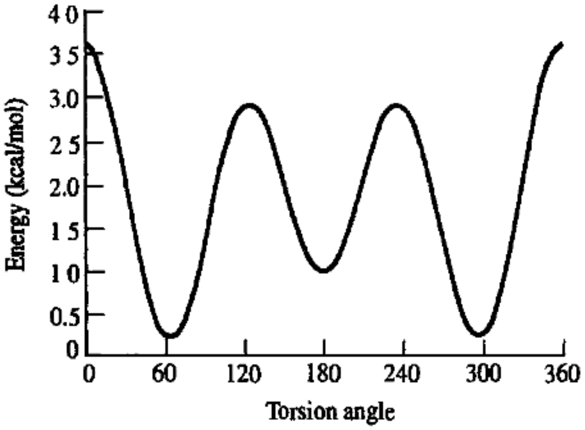


Fig 4 8: Variation in torsional energy (AMBER force field) with O–C–C–O torsion angle (ω) for $OCH_2{-}CH_2O$ fragment The minimum energy conformations arise for $\omega = 60°$ and $300°$

atoms that comprise the central bond and not upon the atom types of the terminal atoms. For example, all torsion angles in which the central bond is between two sp^3-hybridised carbon atoms (e.g. H–C–C–H, C–C–C–C, H–C–C–C) are assigned the same torsional parameters, unless the torsion is a special case such as O–C–C–O. In its treatment of the torsional contribution, AMBER takes a position intermediate between those force fields which only ever use a single term in the torsional expansion and those which consistently use more terms for all torsions. MM2 falls into the latter category; it uses three terms in the expansion:

$$\upsilon(\omega) = \frac{V_1}{2}(1+\cos\omega) + \frac{V_2}{2}(1-\cos 2\omega) + \frac{V_3}{2}(1+\cos 3\omega) \tag{4.10}$$

A physical interpretation has been ascribed to each of the three terms in the MM2 torsional expansion from an analysis of *ab initio* calculations on simple fluorinated hydrocarbons. The first, onefold term corresponds to interactions between bond dipoles, which are due to differences in electronegativity between bonded atoms. The twofold term is due to the effects of hyperconjugation (in alkanes) and conjugation effects (in alkenes), which provide 'double bond' character to the bond. The threefold term corresponds to steric interactions between the 1,4 atoms. It was found that the additional terms in the torsional potential were especially important for systems containing heteroatoms, such as the halogenated hydrocarbons and molecules containing CCOC and CCNC fragments.

With careful parametrisation a force field which uses more than one term in the torsional expansion will be more successful than a force field that uses only a single term (and this is borne out by the MM2 force field). The major drawback is that many parameters are required to model even a modest range of molecules.

4.6 Improper Torsions and Out-of-plane Bending Motions

Let us consider how cyclobutanone would be modelled using a force field containing just standard bond-stretching and angle-bending terms of the type in Equation (4.1). The equilibrium structure obtained with such a force field would have the oxygen atom located out of the plane formed by the adjoining carbon atom and the two carbon atoms bonded to it, as shown in Figure 4.9. In this structure, the angles to the oxygen adopt values close to the reference value of 120°. Experimentally, it is found that the oxygen atom remains in the plane of the cyclobutane ring, even though the C–C=O angles are large (133°). This is because the π-bonding energy, which is maximised in the coplanar arrangement, would be much reduced if the oxygen were bent out of the plane. To achieve the desired geometry it is necessary to incorporate an additional term (or terms) in the force field that keeps the sp^2 carbon and the three atoms bonded to it in the same plane. The simplest way to achieve this is to use an *out-of-plane* bending term.

There are several ways in which out-of-plane bending terms can be incorporated into a force field. One approach is to treat the four atoms as an 'improper' torsion angle (i.e. a torsion angle in which the four atoms are not bonded in the sequence 1-2-3-4). One way to define an improper torsion for cyclobutane would involve the atoms 1-5-3-2 in Figure 4.9.

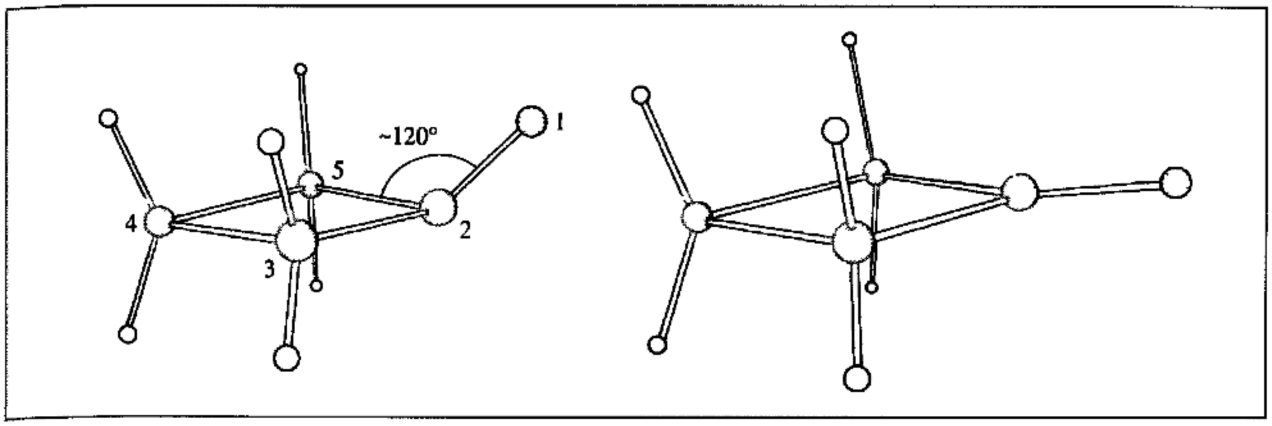


Fig 4 9· Without an out-of-plane term, the oxygen atom in cyclobutane is predicted to lie out of the plane of the ring (left) rather than in the plane.

A torsional potential of the following form is then used to maintain the improper torsion angle at 0° or 180°:

$$\upsilon(\omega) = k(1 - \cos 2\omega) \tag{4.11}$$

Various other ways to incorporate the out-of-plane bending contribution are possible. For example, one definition that is closer to the notion of an 'out-of-plane bend' involves a calculation of the angle between a bond from the central atom and the plane defined by the central atom and the other two atoms (Figure 4.10). A value of 0° corresponds to all four atoms being coplanar. A third approach is to calculate the height of the central atom above a plane defined by the other three atoms (Figure 4.10). With these two definitions the deviation of the out-of-plane coordinate (be it an angle or a distance) can be modelled using a harmonic potential of the form

$$\upsilon(\theta) = \frac{k}{2}\theta^2; \qquad \upsilon(h) = \frac{k}{2}h^2 \tag{4.12}$$

Of these three functional forms, the improper torsion definition is most widely used as it can then be easily included with the 'proper' torsional terms in the force field. However, the

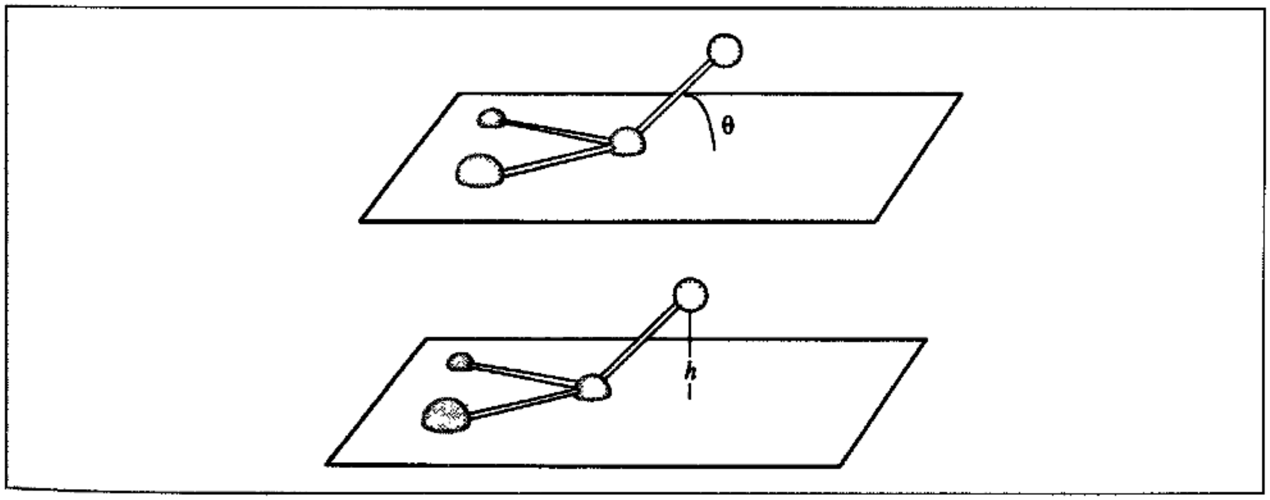


Fig. 4.10: Two ways to model the out-of-plane bending contributions.

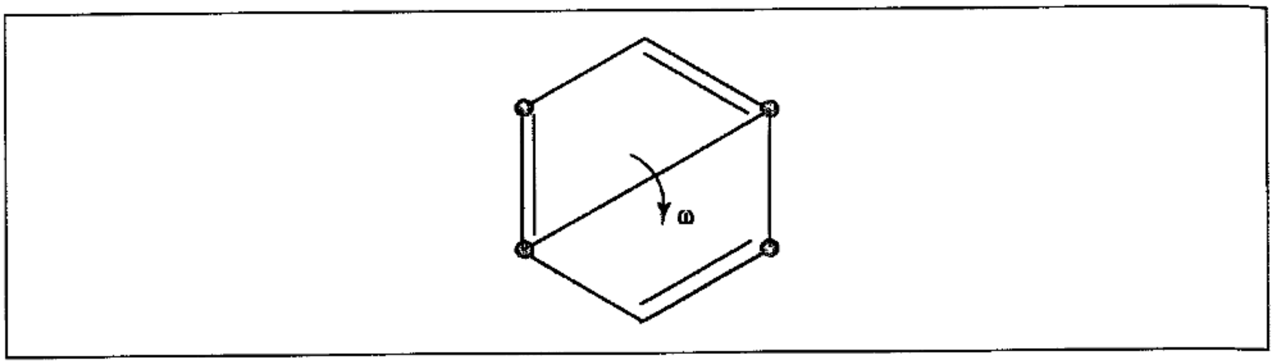


Fig. 4 11. Improper torsional terms can be used to keep a benzene ring planar

other two functional forms may be better ways to implement out-of-plane bending in the force field. Out-of-plane terms may also be used to achieve a particular geometry. For example, if it is desired to ensure that an aromatic ring such as benzene maintains an approximately planar structure then this can be achieved using a suitable set of out-of-plane bending terms involving atoms on opposite sides of the ring (Figure 4.11). Improper torsional terms are commonly used in the so-called united atom force fields to maintain stereochemistry at chiral centres (see Section 4.14). It is important to remember that out-of-plane terms may not always be necessary, and that to include such terms may have a deleterious effect on the performance of the force field. Vibrational frequencies in particular are often rather sensitive to the presence of out-of-plane terms.

4.7 Cross Terms: Class 1, 2 and 3 Force Fields

The presence of *cross terms* in a force field reflects coupling between the internal coordinates. For example, as a bond angle is decreased it is found that the adjacent bonds stretch to reduce the interaction between the 1,3 atoms, as illustrated in Figure 4.12. Cross terms were found to be important in force fields designed to predict vibrational spectra that were the forerunners of molecular mechanics force fields, and so it is not surprising that cross terms must often be included in a molecular mechanics force field to achieve optimal performance. One should in principle include cross terms between all contributions to a force field. However, only a few cross terms are generally found to be necessary in order to reproduce structural properties accurately; more may be needed to reproduce other properties such as vibrational frequencies, which are more sensitive to the presence of such terms. In general, any interactions involving motions that are far apart in a molecule

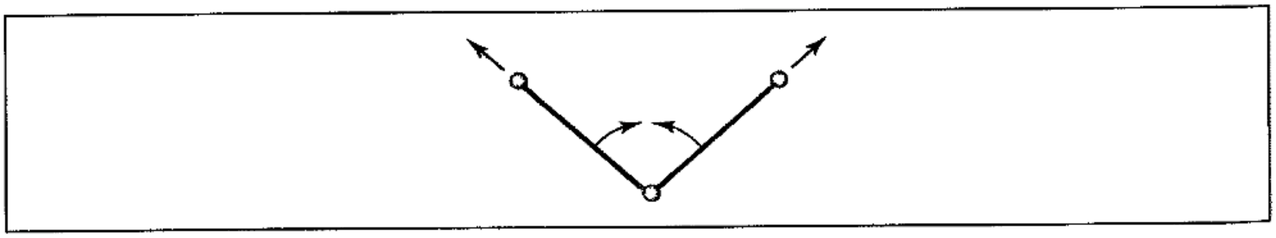


Fig 4.12. Coupling between the stretching of the bonds as an angle closes.

can usually be set to zero. Most cross terms are functions of two internal coordinates, such as stretch–stretch, stretch–bend and stretch–torsion terms, but cross terms involving more than two internal coordinates such as the bend–bend–torsion have also been used. Various functional forms are possible for the cross terms. For example, the stretch–stretch cross term between two bonds 1 and 2 can be modelled as:

$$\upsilon(l_1, l_2) = \frac{k_{l_1,l_2}}{2}[(l_1 - l_{1,0})(l_2 - l_{2,0})] \tag{4.13}$$

The stretching of the two bonds adjoining an angle could be modelled using an equation of the following form (as in MM2, MM3 and MM4):

$$\upsilon(l_1, l_2, \theta) = \frac{k_{l_1,l_2,\theta}}{2}[(l_1 - l_{1,0}) + (l_2 - l_{2,0})](\theta - \theta_0) \tag{4.14}$$

In a *Urey–Bradley* force field, angle bending is achieved using 1,3 non-bonded interactions rather than an explicit angle-bending potential. The stretch-bond term in such a force field would be modelled by a harmonic function of the distance between the 1,3 atoms·

$$\upsilon(r_{1,3}) = \frac{k_{r_{13}}}{2}(r_{1,3} - r^0_{1,3})^2 \tag{4 15}$$

A stretch–torsion cross term can be used to model the stretching of a bond that occurs in an eclipsed conformation. Two possible functional forms are:

$$\upsilon(l, \omega) = k(l - l_0)\cos n\omega \tag{4.16}$$

$$\upsilon(l, \omega) = k(l - l_0)[1 + \cos n\omega] \tag{4.17}$$

n is the periodicity of the rotation about the bond ($n = 3$ for sp^3–sp^3 bonds).

Torsion–bend and torsion–bend–bend terms may also be included; the latter, for example, would couple two angles A–B–C and B–C–D to a torsion angle A–B–C–D. Maple, Dinur and Hagler used quantum mechanics calculations to investigate which of the cross terms are most important and suggested that the stretch–stretch, stretch–bend, bend–bend, stretch–torsion and bend–bend–torsion were most important [Dinur and Hagler 1991] (schematically illustrated in Figure 4.13).

It has been suggested that the presence of cross terms (together with some other features) can provide a general way to classify force fields [Hwang *et al.* 1994]. A class I force field was considered one which is restricted to harmonic terms (e.g. for bond stretching and angle bending) and which does not have any cross terms. A class II force field would have anharmonic terms (e.g. through the use of Morse potentials or quartic terms) and explicit cross terms to account for the coupling between coordinates. The presence of these higher and cross terms would tend to improve the ability of the force field to predict the properties of more unusual systems (such as those which are highly strained) and also to enhance its ability to reproduce vibrational spectra. Another characteristic of a class II force field was that it could be used without modification to model the properties of isolated small molecules, condensed phases and macromolecular systems. It was subsequently suggested by Allinger [Allinger *et al.* 1996b] that a class III force field would also take account of chemical effects and other features such as electronegativity and hyperconjugation. A classic

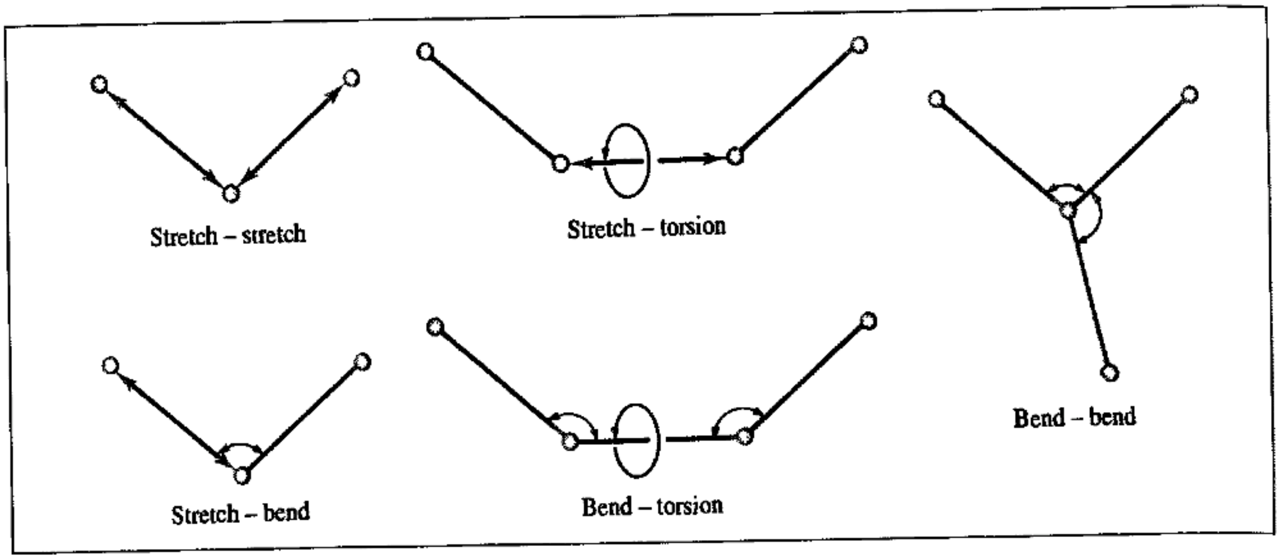


Fig. 4.13. Schematic illustration of the cross terms believed to be most important in force fields. (Adapted from Dinur U and A T Hagler 1991. New Approaches to Empirical Force Fields In Reviews in Computational Chemistry, *Lipkowitz K B and D B Boyd (Editors) New York, VCH Publishers, pp 99–164)*

example of the latter effect (hyperconjugation) is the change in the length of the C–H bond in acetaldehyde with rotation about the C–C bond. When the C–H bond is perpendicular to the plane of the carbonyl group there is maximum overlap between the σ orbital of the C–H bond and the π^* orbital of the carbonyl carbon. Donation of electron density from the C–H bond to this π^* orbital is accompanied by a lengthening of the bond and a greater contribution from the charged resonance structure (Figure 4.14). When the bond to the hydrogen atom is in the plane the overlap is minimal. *Ab initio* calculations suggested that the bond length changed by 0.006 Å between the two forms. This effect was incorporated within MM4 by a term of the following form:

$$\Delta l = k(1 - \cos 2\omega) \tag{4.18}$$

This is a kind of torsion–stretch cross term but different from the one where the central bond changes with torsion angle. There has been some considerable debate about the existence and origin of the hyperconjugative effects, but low-temperature X-ray crystallographic experiments on appropriate compounds together with *ab initio* calculations certainly reveal a detectable effect.

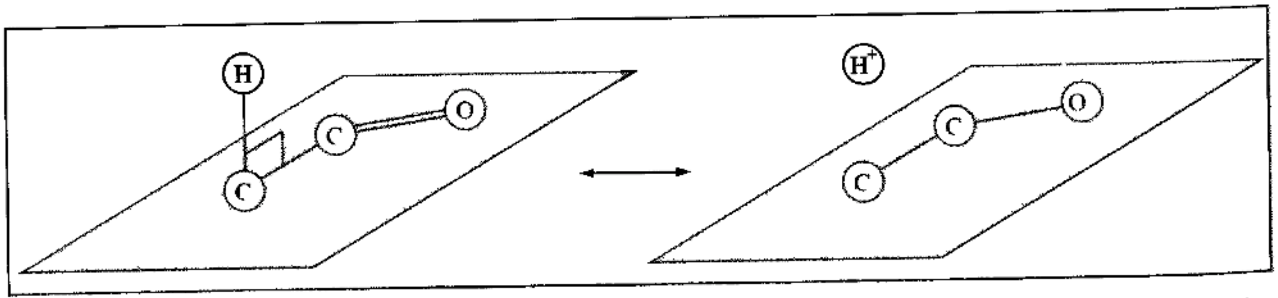


Fig. 4.14. Valence bond representation of the hyperconjugation effect which leads to a lengthening of the C–H bond in acetaldeyde

4.8 Introduction to Non-bonded Interactions

Independent molecules and atoms interact through non-bonded forces, which also play an important role in determining the structure of individual molecular species. The non-bonded interactions do not depend upon a specific bonding relationship between atoms. They are 'through-space' interactions and are usually modelled as a function of some inverse power of the distance. The non-bonded terms in a force field are usually considered in two groups, one comprising electrostatic interactions and the other van der Waals interactions.

4.9 Electrostatic Interactions

4.9.1 The Central Multipole Expansion

Electronegative elements attract electrons more than less electronegative elements, giving rise to an unequal distribution of charge in a molecule. This charge distribution can be represented in a number of ways, one common approach being an arrangement of fractional point charges throughout the molecule. These charges are designed to reproduce the electrostatic properties of the molecule. If the charges are restricted to the nuclear centres they are often referred to as *partial atomic charges* or *net atomic charges*. The electrostatic interaction between two molecules (or between different parts of the same molecule) is then calculated as a sum of interactions between pairs of point charges, using Coulomb's law:

$$\mathscr{V} = \sum_{i=1}^{N_A} \sum_{j=1}^{N_B} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \tag{4.19}$$

N_A and N_B are the numbers of point charges in the two molecules. This approach to the representation and calculation of electrostatic interactions will be considered in more detail in Section 4.9.2. First, we shall consider an alternative approach to the calculation of electrostatic interactions which treats a molecule as a single entity and is (in principle at least) capable of providing a very efficient way to calculate electrostatic intermolecular interactions. This is the *central multipole expansion*, which is based upon the electric moments or multipoles: the charge, dipole, quadrupole, octopole, and so on introduced in Section 2.7.3. These moments are usually represented by the following symbols: q (charge), μ (dipole), Θ (quadrupole) and Φ (octopole). We are often interested in the lowest non-zero electric moment. Thus species such as Na^+, Cl^-, NH_4^+ or $CH_3CO_2^-$ have the charge as their lowest non-zero moment. For many uncharged molecules the dipole is the lowest non-zero moment. Molecules such as N_2 and CO_2 have the quadrupole as their lowest non-zero moment. The lowest non-zero moment for methane and tetrafluoromethane is the octopole. Each of these multipole moments can be represented by an appropriate distribution of charges. Thus a dipole can be represented using two charges placed an appropriate distance apart. A quadrupole can be represented using four charges and an octopole by eight charges. A complete description of the charge distribution around a molecule requires all of the non-zero electric moments to the specified. For some molecules,

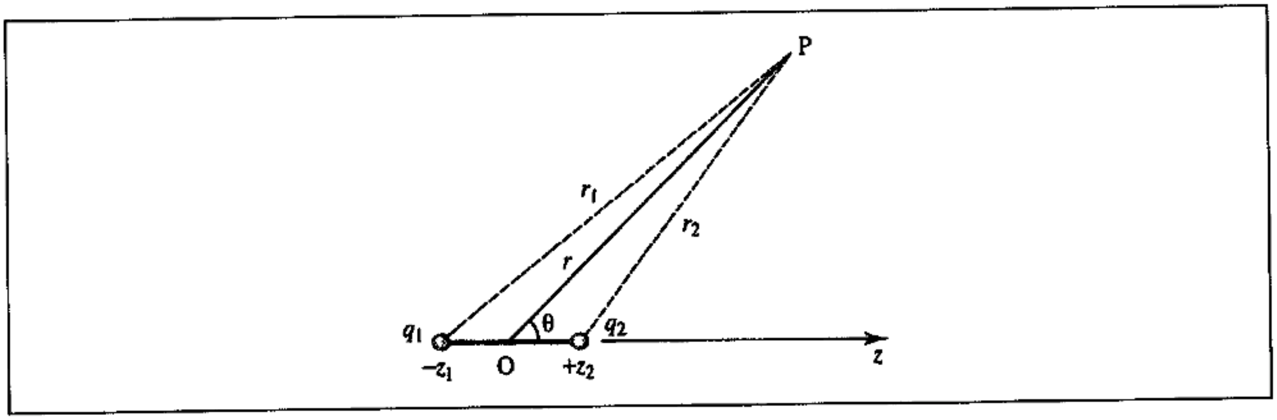


Fig 4.15: The electrostatic potential due to two point charges.

the lowest non-zero moment may not be the most significant and it may therefore be unwise to ignore the higher-order terms in the expansion without first checking their values.

To illustrate how the multipolar expansion is related to a distribution of charges in a system, let us consider the simple case of a molecule with two charges q_1 and q_2, positioned at $-z_1$ and z_2, respectively (Figure 4.15). The electrostatic potential at point P (a distance r from the origin, r_1 from charge q_1 and r_2 from charge q_2) is then given by:

$$\phi(r) = \frac{1}{4\pi\varepsilon_0}\left(\frac{q_1}{r_1} + \frac{q_2}{r_2}\right) \tag{4.20}$$

By applying the cosine rule this can be written as follows (see Figure 4.15):

$$\phi(r) = \frac{1}{4\pi\varepsilon_0}\left(\frac{q_1}{\sqrt{r^2 + z_1^2 + 2rz_1\cos\theta}} + \frac{q_2}{\sqrt{r^2 + z_1^2 - 2rz_1\cos\theta}}\right) \tag{4.21}$$

If $r \gg z_1$ and $r \gg z_2$ then this expression can be expanded as follows:

$$\phi(r) = \frac{1}{4\pi\varepsilon_0}\left(\frac{q_1 + q_2}{r} + \frac{(q_2z_2 - q_1z_1)\cos\theta}{r^2} + \frac{(q_1z_1^2 + q_2z_2^2)(3\cos^2\theta - 1)}{2r^3} + \cdots\right) \tag{4.22}$$

We can now associate the appropriate terms in the expansion with the various electric moments:

$$\phi(r) = \frac{1}{4\pi\varepsilon_0}\left(\frac{q}{r} + \frac{\mu\cos\theta}{r^2} + \frac{\Theta(3\cos^2\theta - 1)}{2r^3} + \cdots\right) \tag{4.23}$$

Thus $(q_1 + q_2)$ is the charge; $(q_2z_2 - q_1z_1)$ is the dipole; $(q_1z_1^2 + q_2z_2^2)$ is the quadrupole, and so on. One interesting feature about a charge distribution is that only the first non-zero moment is independent of the choice of origin. Thus, if a molecule is electrically neutral (i.e. $q_1 + q_2 = 0$) then its dipole moment is independent of the choice of origin. This can be demonstrated for our two-charge system as follows. If the position of the origin is now moved to a point $-z'$, then the dipole moment relative to this new origin is given by:

$$\mu' = q_2(z_2 + z') - q_1(z_1 - z') = \mu + qz' \tag{4.24}$$

Only if the total charge on the system (q) equals zero will the dipole moment be unchanged. Similar arguments can be used to show that if both the charge and the dipole moment are zero then the quadrupole moment is independent of the choice of origin. For convenience, the origin is often taken to be the centre of mass of the charge distribution.

The electric moments are examples of *tensor properties*: the charge is a rank 0 tensor (which is the same as a scalar quantity); the dipole is a rank 1 tensor (which is the same as a vector, with three components along the x, y and z axes); the quadrupole is a rank 2 tensor with nine components, which can be represented as a 3×3 matrix. In general, a tensor of rank n has 3^n components.

For a distribution of charges (one not restricted to lie along one of the Cartesian axes), the dipole moment is given by:

$$\boldsymbol{\mu} = \sum q_i \mathbf{r}_i \tag{4.25}$$

The components of the dipole moment along the x, y and z axes are $\sum q_i x_i$, $\sum q_i y_i$ and $\sum q_i z_i$. The analogous way to define the quadrupole moment is as follows:

$$\Theta = \begin{pmatrix} \sum q_i x_i^2 & \sum q_i x_i y_i & \sum q_i x_i z_i \\ \sum q_i y_i x_i & \sum q_i y_i^2 & \sum q_i y_i z_i \\ \sum q_i z_i x_i & \sum q_i z_i y_i & \sum q_i z_i^2 \end{pmatrix} \tag{4.26}$$

This definition of the quadrupole is obviously dependent upon the orientation of the charge distribution within the coordinate frame. Transformation of the axes can lead to alternative definitions that may be more informative. Thus the quadrupole moment is commonly defined as follows:

$$\Theta = \frac{1}{2} \begin{pmatrix} \sum_i q_i(3x_i^2 - r_i^2) & 3\sum_i q_i x_i y_i & 3\sum_i q_i x_i z_i \\ 3\sum_i q_i x_i z_i & \sum_i q_i(3y_i^2 - r_i^2) & 3\sum_i q_i y_i z_i \\ 3\sum_i q_i x_i z_i & 3\sum_i q_i y_i z_i & \sum_i q_i(3z_i^2 - r_i^2) \end{pmatrix} \tag{4 27}$$

In Equation (4.27) $r_i^2 = x_i^2 + y_i^2 + z_i^2$. This definition enables one to assess the deviation from spherical symmetry as a spherically symmetric charge distribution will have

$$\sum_i q_i x_i^2 = \sum_i q_i y_i^2 = \sum_i q_i z_i^2 = \frac{1}{3} \sum_i q_i r_i^2 \tag{4.28}$$

and so the diagonal elements of the tensor will be zero. Quadrupoles are also reported in terms of the *principal axes;* these are three mutually perpendicular axes α, β and γ, which are linear combinations of x, y and z such that the quadrupole tensor is diagonal (i.e. off-diagonal elements are zero):

$$\Theta = \begin{pmatrix} \Theta_{\alpha\alpha} & 0 & 0 \\ 0 & \Theta_{\beta\beta} & 0 \\ 0 & 0 & \Theta_{\gamma\gamma} \end{pmatrix} \tag{4 29}$$

Let us now consider the effect of placing another molecule with a linear charge distribution (charges q_1' and q_2') with its centre of mass at the point P. The relative orientation of the two

There are other difficulties with the central multipole expansion. The multipole moments are properties of the entire molecule and so cannot be used to determine intramolecular interactions. The central multipole model thus tends to be restricted to calculations involving small molecules that are kept fixed in conformation during the calculation, and where the interactions between molecules act at their centres of mass. It can be a complicated procedure to calculate the forces acting on a molecule with a multipole model. The interaction between multipoles of zero order (i.e. charges) gives rise to a simple translational force. Multipoles of a higher order have directionality, and interactions between these produce a torque, or twisting force. Moreover, whereas the charge–charge forces are equal and opposite, the torque acting on molecule i due to another molecule j is not necessarily equal and opposite to the torque on molecule j due to molecule i.

4.9.2 Point-charge Electrostatic Models

We therefore return to the point-charge model for calculating electrostatic interactions. If sufficient point charges are used then all of the electric moments can be reproduced and the multipole interaction energy, Equation (4.30), is exactly equal to that calculated from the Coulomb summation, Equation (4.19).

An accurate representation of a molecule's electrostatic properties may require charges to be placed at locations other than at the atomic nuclei. A simple example of this is molecular nitrogen, which has a dipole moment of zero. The total charge on nitrogen is zero, and so an atomic partial charge model would put zero charge on each nucleus. However, nitrogen does have a quadrupole moment and this significantly affects its properties. The simplest way to model this is to place three partial charges along the bond: a charge of $-q$ at each nucleus and $+2q$ at the centre of mass. The quadrupole–quadrupole interaction between two nitrogen molecules can then be calculated by summing nine pairs of charge–charge interactions. The value of q can be calculated using the following relationship between the quadrupole moment and the partial charge:

$$\Theta = 2q(l/2)^2 \tag{4.31}$$

l is the bond length. The experimental quadrupole moment is consistent with a charge, q, of approximately 0.5e. In fact, a better representation of the electrostatic potential around the nitrogen molecule is obtained using the five-charge model shown in Figure 4.20.

An alternative to the point charge model is to assign dipoles to the bonds in the molecule. The electrostatic energy is then given as a sum of dipole–dipole interaction energies. This approach (which is adopted in MM2/MM3/MM4) can be unwieldy for molecules that have a formal charge and which require charge–charge and charge–dipole terms to be included in the energy expression. Charged species are dealt with more naturally using the point charge model.

4.9.3 Calculating Partial Atomic Charges

Given the widespread use of the partial atomic charge model, it is important to consider how the charges are obtained. For simple species the atomic charges required to reproduce the dipoles being induced on each atom [Dang *et al.* 1991]. The magnitude of the dipole induced on an atom i is given by:

$$\boldsymbol{\mu}_{\text{ind},i} = \alpha_i \mathbf{E}_i \tag{4.55}$$

α_i is the atomic polarisability, assumed to be isotropic. Appropriate values of α_i have been determined for various systems. The electric field, $\mathbf{E}_i$, at atom i is the vector sum of the field due to the permanent and induced dipoles of the other atoms in the system:

$$\mathbf{E}_i = \sum_{j \neq i} \frac{q_j \mathbf{r}_{ij}}{r_{ij}^3} + \sum_{j \neq i} \frac{\boldsymbol{\mu}_j}{r_{ij}^3} \left(3\mathbf{r}_{ij} \frac{\mathbf{r}_{ij}}{r_{ij}^2} - 1 \right) \tag{4.56}$$

$\mathbf{r}_i$ and $\mathbf{r}_j$ are the position vectors of the atoms i and j. Convergence of these equations in procedures such as molecular dynamics, where successive configurations are generated, can be accelerated if the induced dipoles obtained at each current step are used as the starting points for the next configuration.

An alternative way to model polarisation effects is exemplified by the water model of Sprik and Klein [Sprik and Klein 1988] , where the polarisation centre is represented as a collection of closely spaced charges whose values are permitted to vary but whose total sums to zero. In the water model, shown in Figure 4.29, four tetrahedrally arranged charges are used to model the polarisation centre. These charges endow the molecule with an induced dipole moment of any magnitude and direction. The charges are determined iteratively for each configuration of the system. The isotropic polarisability of a simple ion can similarly be treated using two charges of equal magnitude but opposite sign placed either side of the ion. The direction of the 'bond' linking the two polarisation charges and the ion can reorient to change the direction of the induced dipole. In a subsequent refinement of this model Sprik and Klein replaced the point charges by Gaussian charge distributions at the polarisation sites; these were better at modelling features such as hydrogen bonding.

One appealing approach is the dynamically fluctuating charge model of Berne and colleagues [Rick *et al.* 1994]. This method has much in common with the charge equilibration scheme of Rappé and Goddard (see Section 4.9.6) in its use of the electronegativity equalisation approach, which ensures that the atomic chemical potentials are equal in the molecule. The charges are considered as dynamically fluctuating variables, along with the atomic nuclei in a molecular dynamics simulation. This means that the charges evolve in a natural

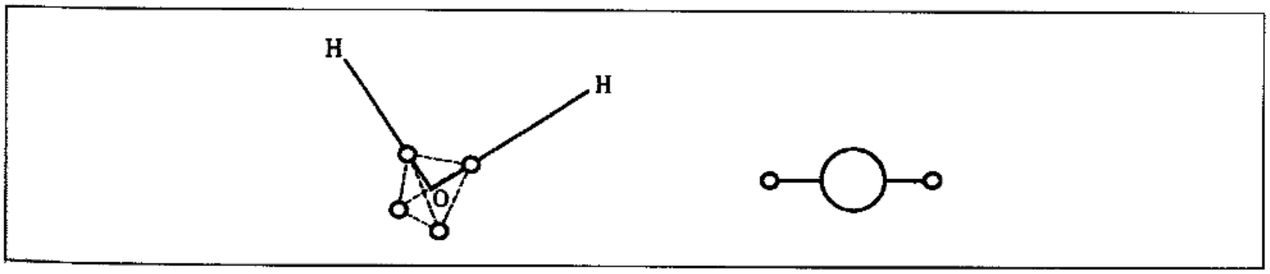


Fig. 4 29. Polarisable models of water and ions developed by Sprik and Klein. (Figure adapted from Sprik M 1993 Effective Pair Potentials and Beyond In Computer Simulation in Chemical Physics, *Allen M P, D J Tildesley (Editors) Dordrecht, Kluwer)*

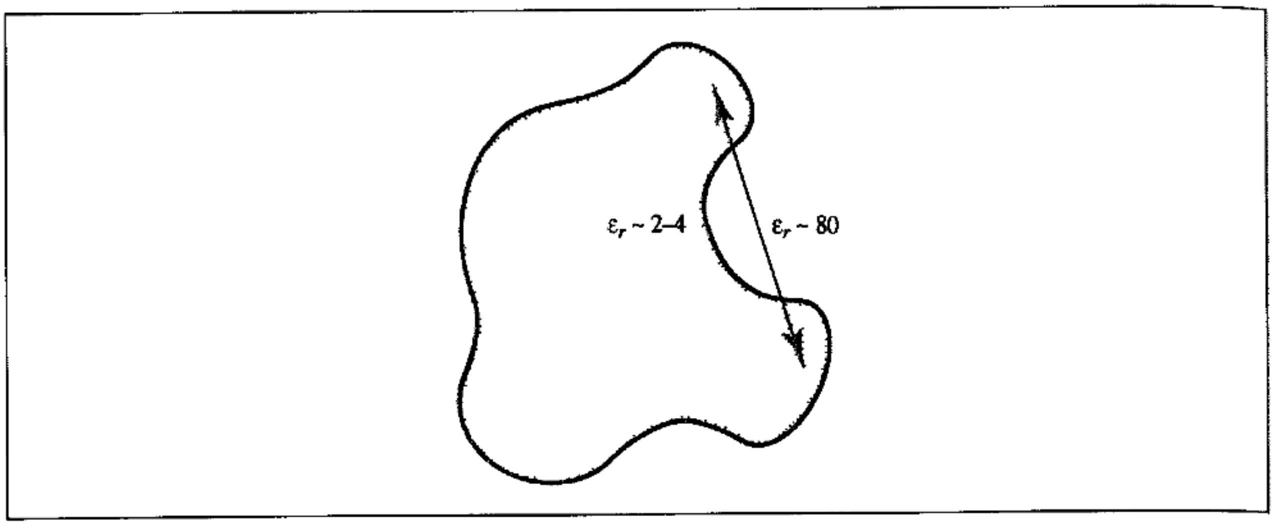


Fig. 4.31 A line joining two points may pass through regions of different permittivity

4.10 Van der Waals Interactions

Electrostatic interactions cannot account for all of the non-bonded interactions in a system. The rare gas atoms are an obvious example; all of the multipole moments of a rare gas atom are zero and so there can be no dipole–dipole or dipole–induced dipole interactions. But there clearly must be interactions between the atoms, how else could rare gases have liquid and solid phases or show deviations from ideal gas behaviour? Deviations from ideal gas behaviour were famously quantitated by van der Waals, thus the forces that give rise to such deviations are often referred to as van der Waals forces.

If we were to study the interaction between two isolated argon atoms using a molecular beam experiment then we would find that the interaction energy varies with the separation in a manner as shown in Figure 4.32. The other rare gases show a similar behaviour. The essential features of this curve are as follows. The interaction energy is zero at infinite distance (and indeed is negligible even at relatively short distances). As the separation is reduced, the energy decreases, passing through a minimum at a distance of approximately 3.8 Å for argon. The energy then rapidly increases as the separation decreases further. The force between the atoms, which equals minus the first derivative of the potential energy with respect to distance, is also shown in Figure 4.32. A variety of experiments have been used to provide evidence for the nature of the van der Waals interactions, including gas imperfections, molecular beams, spectroscopic studies and measurements of transport properties.

4.10.1 Dispersive Interactions

The curve in Figure 4.32 is usually considered to arise from a balance between attractive and repulsive forces. The attractive forces are long-range, whereas the repulsive forces act at short distances. The attractive contribution is due to *dispersive forces*. London first showed how the dispersive force could be explained using quantum mechanics [London 1930] and so this interaction is sometimes referred to as the London force. The dispersive force

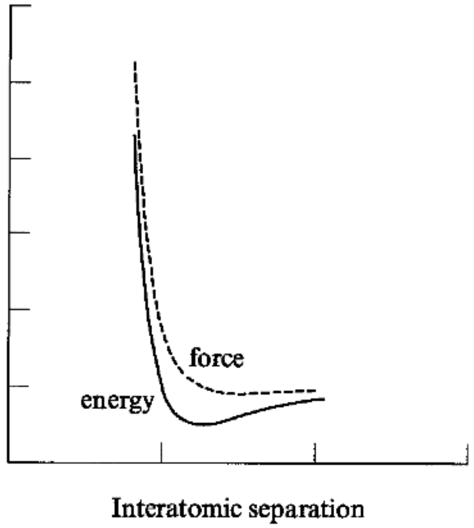


Fig 4 32: The interaction energy and the force between two argon atoms

is due to instantaneous dipoles which arise during the fluctuations in the electron clouds. An instantaneous dipole in a molecule can in turn induce a dipole in neighbouring atoms, giving rise to an attractive inductive effect.

A simple model to explain the dispersive interaction was proposed by Drude. This model consists of 'molecules' with two charges, $+q$ and $-q$, separated by a distance r. The negative charge performs simple harmonic motion with angular frequency ω along the z axis about the stationary positive charge (Figure 4.33). If the force constant for the oscillator is k and if the mass of the oscillating charge is m, then the potential energy of an isolated Drude molecule is $\frac{1}{2}kz^2$, where z is the separation of the two charges. ω is related to the force constant by $\omega = \sqrt{k/m}$. The Schrödinger equation for a Drude molecule is:

$$-\frac{\hbar^2}{2m}\frac{\partial^2\psi}{\partial z^2} + \frac{1}{2}kz^2\psi = E\psi \tag{4.59}$$

This is the Schrödinger equation for a simple harmonic oscillator. The energies of the system are given by $E_\nu = (\nu + \frac{1}{2}) \times \hbar\omega$ and the zero-point energy is $\frac{1}{2}\hbar\omega$.

We now introduce a second Drude molecule, identical to the first, with the positive charge also located on the z axis and an oscillating negative charge (Figure 4.33). When the two molecules are infinitely separated, they do not interact and the total ground-state energy of the system is

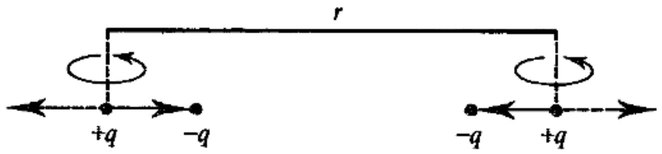


Fig. 4 33 The Drude model for dispersive interactions (Figure adapted from Rigby M, E B Smith, W A Wakeham and G C Maitland 1986 The Forces Between Molecules *Oxford, Clarendon Press)* just twice the zero-point energy of a single molecule, $\hbar\omega/2\pi$. As the molecules approach (along the z axis) there are interactions between the two dipoles, and the interaction energy between the two 'molecules' can be shown to be approximately given by (see Appendix 4.1):

$$\mathscr{v}(r) = -\frac{\alpha^4 \hbar\omega}{2(4\pi\varepsilon_0)^2 r^6} \tag{4.60}$$

The Drude model thus predicts that the dispersion interaction varies as $1/r^6$.

The two-dimensional Drude model can be extended to three dimensions, the result being:

$$\mathscr{v}(r) = -\frac{3\alpha^4 \hbar\omega}{4(4\pi\varepsilon_0)^2 r^6} \tag{4.61}$$

The Drude model only considers the dipole–dipole interaction; if higher-order terms, due to dipole–quadrupole, quadrupole–quadrupole, etc., interactions are included as well as other terms in the binomial expansion, then the energy of the Drude model is more properly written as a series expansion:

$$\mathscr{v}(r) = \frac{C_6}{r^6} + \frac{C_8}{r^8} + \frac{C_{10}}{r^{10}} + \cdots \tag{4.62}$$

All of the coefficients C_n are negative, implying an attractive interaction. Despite its simplicity, the Drude model gives quite reasonable results; if just the C_6 term is included then for argon the resulting dispersion energy is only about 25% too small.

4.10.2 The Repulsive Contribution

Below about 3 Å, even a small decrease in the separation between a pair of argon atoms causes a large increase in the energy. This increase has a quantum mechanical origin and can be understood in terms of the Pauli principle, which formally prohibits any two electrons in a system from having the same set of quantum numbers. The interaction is due to electrons with the same spin, therefore the short-range repulsive forces are often referred to as *exchange forces*. They are also known as overlap forces. The effect of exchange is to reduce the electrostatic repulsion between pairs of electrons by forbidding them to occupy the same region of space (i.e. the internuclear region). The reduced electron density in the internuclear region leads to repulsion between the incompletely shielded nuclei. At very short internuclear separations, the interaction energy varies as $1/r$ due to this nuclear repulsion, but at larger separations the energy decays exponentially, as $\exp(-2r/a_0)$, where a_0 is the Bohr radius.

4.10.3 Modelling Van der Waals Interactions

The dispersive and exchange-repulsive interactions between atoms and molecules can be calculated using quantum mechanics, though such calculations are far from trivial, requiring electron correlation and large basis sets. For a force field we require a means to model the interatomic potential curve accurately (Figure 4.32), using a simple empirical

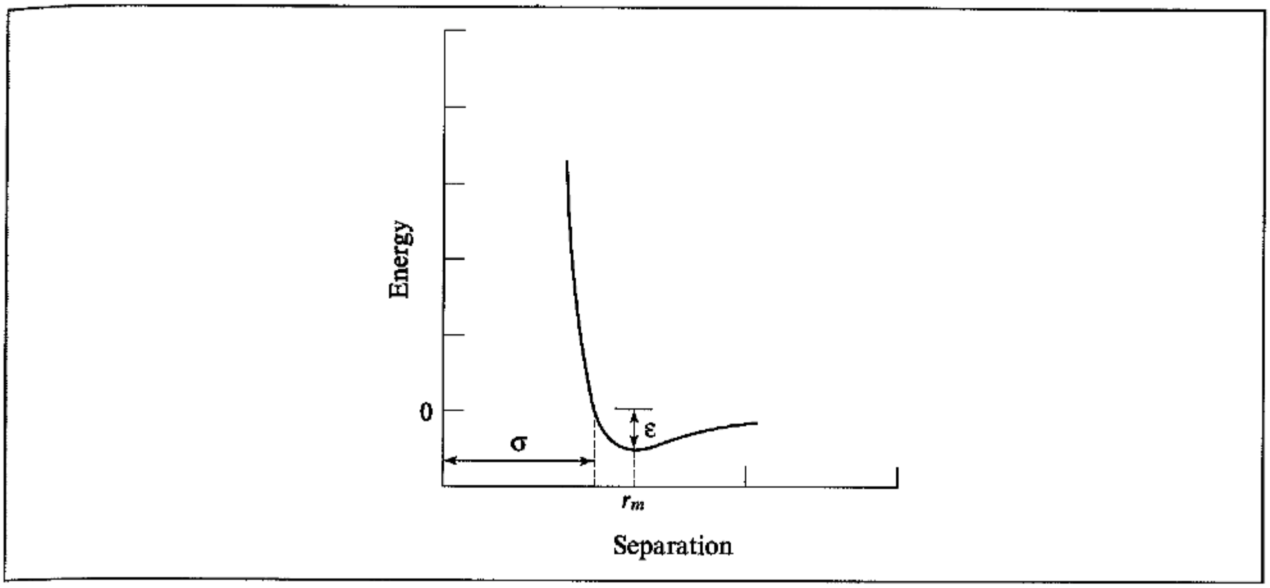


Fig 4 34. The Lennard-Jones potential.

expression that can be rapidly calculated. The need for a function that can be rapidly evaluated is a consequence of the large number of van der Waals interactions that must be determined in many of the systems that we would like to model. The best known of the van der Waals potential functions is the *Lennard-Jones 12–6 function,* which takes the following form for the interaction between two atoms:

$$\upsilon(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \tag{4.63}$$

The Lennard-Jones 12–6 potential contains just two adjustable parameters: the collision diameter σ (the separation for which the energy is zero) and the well depth ε. These parameters are graphically illustrated in Figure 4.34. The Lennard-Jones equation may also be expressed in terms of the separation at which the energy passes through a minimum, r_m (also written r^*). At this separation, the first derivative of the energy with respect to the internuclear distance is zero (i.e. $\partial\upsilon/\partial r = 0$), from which it can easily be shown that $r_\mathrm{m} = 2^{1/6}\sigma$. We can thus also write the Lennard-Jones 12–6 potential function as follows:

$$\upsilon(r) = \varepsilon\{(r_\mathrm{m}/r)^{12} - 2(r_\mathrm{m}/r)^{6}\} \tag{4.64}$$

or

$$\upsilon(r) = A/r^{12} - C/r^{6} \tag{4.65}$$

A is equal to $\varepsilon r_\mathrm{m}^{12}$ (or $4\varepsilon\sigma^{12}$) and C is equal to $2\varepsilon r_\mathrm{m}^{6}$ (or $4\varepsilon\sigma^{6}$).

The Lennard-Jones potential is characterised by an attractive part that varies as r^{-6} and a repulsive part that varies as r^{-12}. These two components are drawn in Figure 4.35. The r^{-6} variation is of course the same power-law relationship found for the leading term in theoretical treatments of the dispersion energy such as the Drude model. There are no strong theoretical arguments in favour of the repulsive r^{-12}, especially as quantum

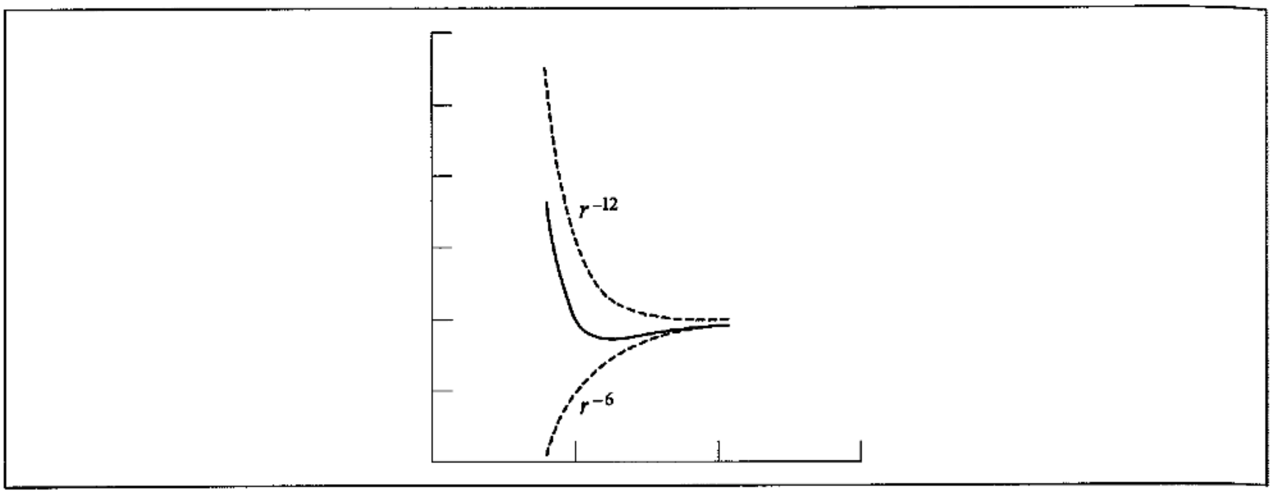


Fig. 4 35 The Lennard-Jones potential is constructed from a repulsive component (αr^{-12}) and an attractive component (αr^{-6})

mechanics calculations suggest an exponential form. The twelfth power term is found to be quite reasonable for rare gases but is rather too steep for other systems such as hydrocarbons. However, the 6–12 potential is widely used, particularly for calculations on large systems, as r^{12} can be rapidly calculated by squaring the r^{-6} term. The r^{-6} term can also be calculated from the square of the distance without having to perform a computationally expensive square root calculation. Different powers have also been used for the repulsive part of the potential; values of 9 or 10 give a less steep curve and are used in some force fields. Lennard-Jones' original potential has been written in the following general form:

$$v(r) = k\varepsilon\left[\left(\frac{\sigma}{r}\right)^{n} - \left(\frac{\sigma}{r}\right)^{m}\right]; \qquad k = \frac{n}{n-m}\left(\frac{n}{m}\right)^{m/(n-m)} \tag{4.66}$$

Equation (4.66) returns the Lennard-Jones potential for $n = 12$ and $m = 6$.

Halgren has proposed an alternative functional form designed to be simple enough to be easily incorporated into molecular mechanics calculations whilst also improving the ability to reproduce experimental data [Halgren 1992, 1996a, b]. In this sense it is an attempt to improve on the Lennard-Jones potential without introducing the complexity of some of the potentials employed by spectroscopists. This potential has the general form:

$$v(r) = \varepsilon_{ij}\left(\frac{1+\delta}{\rho_{ij}+\delta}\right)^{(n-m)}\left(\frac{1+\gamma}{\rho_{ij}^{m}+\gamma} - 2\right) \tag{4.67}$$

In this equation $\rho_{ij} = r_{ij}/r_{ij}^{*}$. The constants δ and γ apply to all interactions between the atoms i and j. This potential reduces to the standard Lennard-Jones 12–6 potential if the following choice of parameters is used: $n = 12$, $m = 6$, $\delta = \gamma = 0$. Halgren proposed a 'buffered 14–7' potential in which $n = 14$, $m = 7$, $\delta = 0.07$ and $\gamma = 0.12$, giving the following equation:

$$v(r) = \varepsilon_{ij}\left(\frac{1.07r_{ij}^{*}}{r_{ij} + 0.07r_{ij}^{*}}\right)^{7}\left(\frac{1.12r_{ij}^{*7}}{r_{ij}^{7} + 0.12r_{ij}^{*7}}\right) \tag{4 68}$$

There were several reasons for developing this functional form. First was the desire to keep the potential finite as the interatomic potential approaches zero (unlike the Lennard-Jones function, which becomes infinite). Second, it gives a more accurate reproduction of the series expansion for the dispersion interaction, Equation (4.62). Third, if a larger value of d is used then the repulsive component is greatly reduced without significantly changing the distance at which the potential crosses zero or the depth of the energy minimum. This feature is useful for optimising structures with crude initial geometries; other functional forms can have significant problems with such situations.

In the buffered 14–7 potential the minimum-energy separation r_{ii}^* for an atom i depends on its atomic polarisability:

$$r_{ii}^* = A_i \alpha_i^{1/4} \tag{4.69}$$

Several formulations in which the r^{-12} term in the standard Lennard-Jones formulation is replaced by a theoretically more realistic exponential expression have been proposed. These include the *Buckingham potential:*

$$v(r) = \varepsilon\left[\frac{6}{\alpha - 6}\exp[-\alpha(r/r_{\mathrm{m}} - 1)] - \frac{\alpha}{\alpha - 6}\left(\frac{r_{\mathrm{m}}}{r}\right)^6\right] \tag{4.70}$$

There are three adjustable parameters in the Buckingham potential (ε, r_{m} and α). A value of α between approximately 14 and 15 gives a potential that closely corresponds to the Lennard-Jones 12–6 potential in the minimum-energy region. When using the Buckingham potential it is important to remember that at very short distances the potential becomes strongly attractive, as shown in Figure 4.36. This could lead to nuclei being fused together during a calculation, and so the program must check that atoms are not becoming too close. The

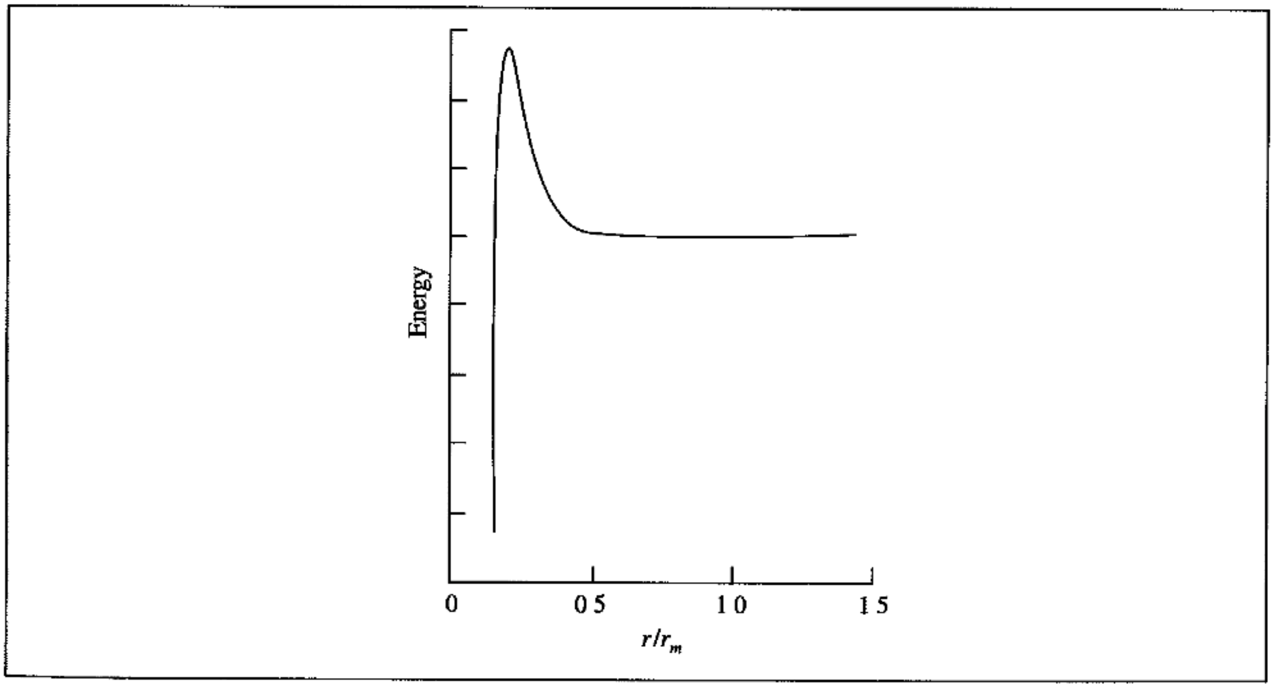


Fig 4 36 A drawback of the Buckingham potential is that it becomes steeply attractive at short distances.

Hill potential is an exponential-6 potential with just two parameters: the minimum energy radius r_m and the well depth ε [Hill 1948]:

$$v(r) = -2.25\varepsilon(r_m/r)^6 + 8.28 \times 10^5 \varepsilon \exp(-r/0.0736 r_m) \tag{4.71}$$

The Hill potential was originally developed to enable the more realistic exponential term to be written in terms of Lennard-Jones parameters. The coefficients 2.25, 8.25 × 10^5 and 0.0736 in Equation (4.71) were determined by fitting to data for the rare gases and were assumed to be applicable to other non-polar gases. A Morse potential may also be used to model the van der Waals interactions in a force field, with appropriate parameters.

4.10.4 Van der Waals Interactions in Polyatomic Systems

The interaction energy between molecules depends not only upon their separation but also on their relative orientations and, where appropriate, their conformations. It is usual to calculate the van der Waals interaction energy between two molecules using a site model in which the interaction is determined as the sum of the interactions between all pairs of sites on the two molecules. The sites are often identified with the nuclear positions, but this need not necessarily be the case.

Polyatomic systems invariably involve the calculation of van der Waals interactions between different types of atoms. For example, to calculate the Lennard-Jones interaction energy between two carbon monoxide molecules using a two-site model would require not only van der Waals parameters for the carbon–carbon interactions and the oxygen–oxygen interactions but also for the carbon–oxygen interactions. A system containing N different types of atom would require $N(N-1)/2$ sets of parameters for the interaction between unlike atoms. The determination of van der Waals parameters can be a difficult and time-consuming process and so it is common to assume that parameters for the cross interactions can be obtained from the parameters of the pure atoms using *mixing rules*. In the commonly used Lorentz-Berthelot mixing rules, the collision diameter σ_{AB} for the A–B interaction equals the arithmetic mean of the values for the two pure species, and the well depth ε_{AB} is given as the geometric mean:

$$\sigma_{AB} = \tfrac{1}{2}(\sigma_{AA} + \sigma_{BB}) \tag{4.72}$$

$$\varepsilon_{AB} = \sqrt{\varepsilon_{AA}\varepsilon_{BB}} \tag{4.73}$$

When written in terms of the separation of minimum energy (r^* or r_m), the following notation may be encountered:

$$r^*_{AB} = R^*_{AA} + R^*_{BB} \tag{4.74}$$

R^*_{AA} and R^*_{BB} are atomic parameters, equal to one half of r^*_{AA} and r^*_{BB}, respectively.

The Lorentz-Berthelot combining rules are most successful when applied to similar species. Their major failing is that the well depth can be overestimated by the geometric mean rule Some force fields calculate the collision diameter for mixed interactions as the geometric mean of the values for the two component atoms. Jorgensen's OPLS force field falls into this category [Jorgensen and Tirado-Reeves 1988].

For the buffered 14–7 functional form more elaborate combination rules are employed:

$$r_{ij}^* = \frac{(r_{ii}^{*3} + r_{jj}^{*3})}{(r_{ii}^{*2} + r_{jj}^{*2})} \tag{4.75}$$

This is similar in spirit to the arithmetic-mean rule but with each individual r_{ii}^* being weighted according to the square of its value. The well depth in this function starts with a formula proposed by Slater and Kirkwood for the C_6 coefficient of the dispersion series expansion:

$$C_{6ij} = \frac{3}{2}\,\frac{\alpha_i\alpha_j}{(\alpha_i/N_i)^{1/2} + (\alpha_j/N_j)^{1/2}} = \frac{2\alpha_i\alpha_j}{\alpha_i^2 C_{ijj} + \alpha_j^2 C_{6ii}} \tag{4.76}$$

In this equation N represents the effective number of electrons and α are atomic polarisabilities; the second formulation in Equation (4.76) is derived using the relationship:

$$N_i = 16C_{6ii}^2/9\alpha_i^3 \tag{4.77}$$

From this the well depths ε are then obtained as follows:

$$\varepsilon_{ij} = \frac{1}{2}\,\frac{kG_iG_jC_{6ij}}{r_{ij}^{*6}} = \frac{181.16G_iG_j\alpha_i\alpha_j}{(\alpha_i/N_i)^{1/2} + (\alpha_i/N_i)^{1/2}}\,\frac{1}{r_{ij}^{*6}} \tag{4.78}$$

Here, k is a factor which converts to units (kcal/mol in this case where the distances are in Å and the polarisabilities in Å^3). G_i and G_j are constants chosen to reproduce the well depths for like-with-like interactions. The atomic polarisability values are obtained from an examination of appropriate molecular experimental data (such as measurements of molar refractivity).

In some force fields the interaction sites are not all situated on the atomic nuclei. For example, in the MM2, MM3 and MM4 programs, the van der Waals centres of hydrogen atoms bonded to carbon are placed not at the nuclei but are approximately 10% along the bond towards the attached atom. The rationale for this is that the electron distribution about small atoms such as oxygen, fluorine and particularly hydrogen is distinctly non-spherical. The single electron from the hydrogen is involved in the bond to the adjacent atom and there are no other electrons that can contribute to the van der Waals interactions. Some force fields also require lone pairs to be defined on particular atoms; these have their own van der Waals and electrostatic parameters.

The van der Waals and electrostatic interactions between atoms separated by three bonds (i.e. the 1,4 atoms) are often treated differently from other non-bonded interactions. The interaction between such atoms contributes to the rotational barrier about the central bond, in conjunction with the torsional potential. These 1,4 non-bonded interactions are often scaled down by an empirical factor; for example, a factor of 2.0 is suggested for both the electrostatic and van der Waals terms in the 1984 AMBER force field (a scale factor of 1/1.2 is used for the electrostatic terms in the 1995 AMBER force field). There are several reasons why one would wish to scale the 1,4 interactions. The error associated with the use of an r^{-12} repulsion term (which is too steep compared with the more correct exponential term) would be most significant for 1,4 atoms. In addition, when two 1,4 atoms come close together some redistribution of the charge along the connecting bonds would be expected that would act to reduce the interaction. Such a charge redistribution would not be possible for two atoms at a similar distance apart if they were in different molecules.

The parameters for the van der Waals interactions can be obtained in a variety of ways. In the early force fields, such parameters were often determined from an analysis of crystal packing. The objective of such studies was to produce a set of van der Waals parameters which enabled the experimental geometries and thermodynamic properties such as the heat of sublimation to be reproduced as accurately as possible. More recent force fields derive their van der Waals parameters using liquid simulations in which the parameters are optimised to reproduce a range of thermodynamic properties such as the densities and enthalpies of vaporisation for appropriate liquids.

4.10.5 Reduced Units

The Lennard-Jones potential is completely specified by the two parameters ε and σ. This means that the results of a calculation performed on (say) liquid argon can be easily converted to give equivalent results for another noble gas. For this reason it is common to simulate the rare gases in terms of reduced units with ε and σ both set to 1. The results can then be converted to any system as appropriate. For example, the reduced density ρ^* is related to the real density by $\rho^* = \rho\sigma^3$; the reduced energy E^* is given by $E^* = E/\varepsilon$, and so on. Electrostatic interactions given by Coulomb's law are also often written in terms of a reduced unit of charge, which corresponds to each charge being divided by $\sqrt{4\pi\varepsilon_0}$. This means that Coulomb's law takes the less cumbersome form:

$$\mathscr{v}(q_1, q_2) = q_1 q_2 / r_{12} \quad \text{or} \quad \mathscr{v}(q_1, q_2) = q_1 q_2 / \varepsilon_r r_{12} \tag{4.79}$$

4.11 Many-body Effects in Empirical Potentials

The electrostatic and van der Waals energies that we have considered so far are calculated between pairs of interaction sites. The total non-bonded interaction energy is thus determined by adding together the interactions between all pairs of sites in the system. However, the interaction between two molecules can be affected by the presence of a third, fourth or more molecules. For example, the interaction energy between three molecules A, B and C is not in general given by the sum of the pairwise interaction energies: $\mathscr{v}(\mathrm{A,B,C}) \neq \mathscr{v}(\mathrm{A,B}) + \mathscr{v}(\mathrm{A,C}) + \mathscr{v}(\mathrm{B,C})$. We have already seen an example of a non-pairwise contribution, namely the polarisation interaction, which is determined using a self-consistent procedure.

Three-body effects can significantly affect the dispersion interaction. For example, it is believed that three-body interactions account for approximately 10% of the lattice energy of crystalline argon. For very precise work, interactions involving more than three atoms may have to be taken into account, but they are usually small enough to be ignored. A potential that includes both two- and three-body interactions would be written in the following potential [Barker *et al.* 1971]. The pair potential is a linear combination of two potentials that each take the following form:

$$v^*(r^*) = e^{\alpha(1-r^*)}[A_0 + A_1(r^* - 1) + A_2(r^* - 1)^2 + A_3(r^* - 1)^3 + A_4(r^* - 1)^4 + A_5(r^* - 1)^5] + \frac{C_6}{\delta + R^{*6}} + \frac{C_8}{\delta + R^{*8}} + \frac{C_{10}}{\delta + R^{*10}} \tag{4.83}$$

This potential function contains eleven constants: α, $A_0 \ldots A_5$, C_6, C_8, C_{10} and δ. The function is expressed in terms of r^*, which is given by $r^* = r/r_\mathrm{m}$, where r_m is the separation at the minimum in the potential. The 'true' interaction energy as a function of the separation, r, is then obtained by multiplying $v^*(r^*)$ by the depth of the potential well, ε:

$$v(r) = \varepsilon v^*(r^*) \tag{4.84}$$

A comparison of the pairwise contribution to the Barker–Fisher–Watts potential with the Lennard-Jones potential for argon is shown in Figure 4.38.

4.13 Hydrogen Bonding in Molecular Mechanics

Some force fields replace the Lennard-Jones 6–12 term between hydrogen-bonding atoms by an explicit hydrogen-bonding term, which is often described using a 10–12 Lennard-Jones potential·

$$v(r) = \frac{A}{r^{12}} - \frac{C}{r^{10}} \tag{4.85}$$

This function is used to model the interaction between the donor hydrogen atom and the heteroatom acceptor atom. Its use is intended to improve the accuracy with which the geometry of hydrogen-bonding systems is predicted. Other force fields incorporate a more complicated hydrogen-bonding function that takes into account deviations from the geometry of the hydrogen bond and is thus dependent upon the coordinates of the donor and acceptor atoms as well as the hydrogen atom. For example, the YETI force field [Vedani 1988] uses the following form for its hydrogen bonding term:

$$v_\mathrm{HB} = \left(\frac{A}{r^{12}_\mathrm{H\ \ Acc}} - \frac{C}{r^{10}_\mathrm{H\ \ Acc}}\right)\cos^2\theta_\mathrm{Don\ \ H\ \ Acc}\cos^4\omega_\mathrm{H\ \ Acc-LP} \tag{4.86}$$

The energy in Equation (4.86) depends upon the distance from the hydrogen to the acceptor, the angle subtended at the hydrogen by the bonds to the donor and the acceptor, and the deviation of the hydrogen bond from the closest lone-pair direction at the acceptor atom ($\omega_\mathrm{H\ \ Acc-LP}$ in Equation (4.86), Figure 4.39).

The GRID program [Goodford 1985] that is used for finding energetically favourable regions in protein binding sites uses a direction-dependent 6–4 function:

$$v_\mathrm{HB} = \left(\frac{C}{d^6} - \frac{D}{d^4}\right)\cos^m\theta \tag{4.87}$$

θ is the angle subtended at the hydrogen and m is usually set to 4.

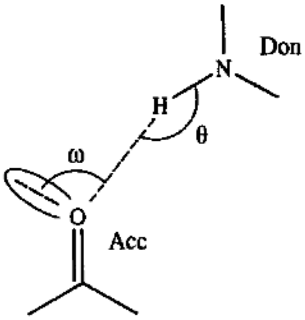


Fig 4 39: Definition of hydrogen-bond geometry used in YETI force field

By no means do all force fields contain explicit hydrogen-bonding terms; most rely upon electrostatic and van der Waals interactions to reproduce hydrogen bonding.

4.14 Force Field Models for the Simulation of Liquid Water

Many of the concepts that we have considered so far can be illustrated by examining some of the empirical models that have been developed to study water. Despite its small size, water acts as a paradigm for the different force field models that we have discussed. Moreover, many of its properties can be easily determined using computer simulation methods and so readily compared with experiment. It is also one of the most challenging systems to model accurately. A wide range of water models have been proposed. The computational efficiency with which the energy can be calculated using a given model is often an important factor as there may be a very large number of water molecules present, together with a solute; most of the force fields used to simulate liquid water thus use effective pairwise potentials with no explicit three-body terms or polarisation effects.

Water models can be conveniently divided into three types. In the simple interaction-site models each water molecule is maintained in a rigid geometry and the interaction between molecules is described using pairwise Coulombic and Lennard-Jones expressions. Flexible models permit internal changes in conformation of the molecule. Finally, models have been developed that explicitly include the effects of polarisation and many-body effects.

4.14.1 Simple Water Models

The 'simple' water models use between three and five interaction sites and a rigid water geometry. The TIP3P [Jorgensen *et al.* 1983] and SPC [Berendsen *et al.* 1981] models use a total of three sites for the electrostatic interactions; the partial positive charges on the hydrogen atoms are exactly balanced by an appropriate negative charge located on the oxygen atom. The van der Waals interaction between two water molecules is computed using a Lennard-Jones function with just a single interaction point per molecule centred on the oxygen atom; no van der Waals interactions involving the hydrogen atoms are calculated. The TIP3P and SPC models differ slightly in the geometry of each water molecule, in the

	SPC	SPC/E	TIP3P	BF	TIP4P	ST2
r(OH), Å	1.0	1.0	0.9572	0.96	0.9572	1.0
HOH, deg	109.47	109.47	104.52	105.7	104.52	109.47
$A \times 10^{-3}$, kcal Å^{12}/mol	629.4	629.4	582.0	560.4	600.0	238.7
C, kcal Å^{6}/mol	625.5	625.5	595.0	837.0	610.0	268.9
q(O)	−0.82	−0.8472	−0.834	0.0	0.0	0.0
q(H)	0.41	0.4238	0.417	0.49	0.52	0.2375
q(M)	0.0	0.0	0.0	−0.98	−1.04	−0 2375
r(OM), Å	0.0	0.0	0.0	0.15	0.15	0.8

Table 4 3 A comparison of various water models [Jorgensen et al *1983]. For the ST2 potential, q(M) is the charge on the 'lone pairs', which are a distance 0 8 Å from the oxygen atom (see Figure 4 40)*

hydrogen charges and in the Lennard-Jones parameters. These differences are indicated in Table 4.3, which also includes data for the SPC/E model [Berendsen *et al.* 1987], which is an updated version of the SPC model. The four-site models such as that of Bernal and Fowler [Bernal and Fowler 1933] (which is now relatively little used but is important for historical reasons as it dates from 1933) and Jorgensen's TIP4P model [Jorgensen *et al.* 1983] shift the negative charge from the oxygen atom to a point along the bisector of the HOH angle towards the hydrogens (Figure 4.40). The parameters for these two models are also given in the table. The most commonly used five-site model is the ST2 potential of Stillinger and Rahman [Stillinger and Rahman 1974]. Here, charges are placed on the hydrogen atoms and on two lone-pair sites on the oxygen. The electrostatic contribution is modulated so that for oxygen–oxygen distances below 2.016 Å it is zero and for distances greater than 3.1287 Å it takes its full value. Between these two distances the electrostatic contribution is modulated using a function that smoothly varies from 0.0 at the shorter distance to 1.0 at the longer distance (see Section 6.7.3).

The experimentally determined dipole moment of a water molecule in the gas phase is 1.85 D The dipole moment of an individual water molecule calculated with any of these simple models is significantly higher; for example, the SPC dipole moment is 2.27 D and that for TIP4P is 2.18 D. These values are much closer to the effective dipole moment of liquid water, which is approximately 2.6 D. These models are thus all effective pairwise models. The simple water models are usually parametrised by calculating various properties using molecular dynamics or Monte Carlo simulations and then modifying the

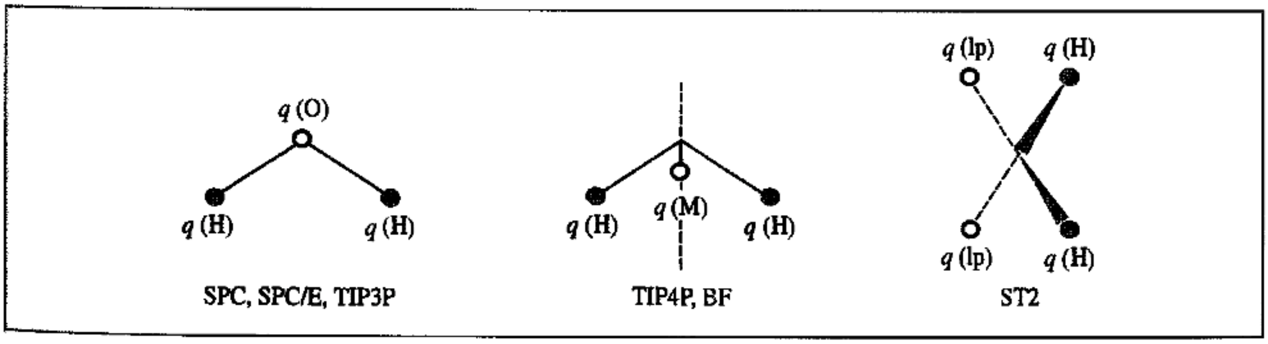


Fig 4.40. Some 'simple' water models (Table 4.3) [Jorgensen et al *1983].*

parameters until the desired level of agreement between experiment and theory is achieved. Thermodynamic and structural properties are usually used in the parametrisation, such as the density, radial distribution function, enthalpy of vaporisation, heat capacity, diffusion coefficient and dielectric constant.* It is found that some properties such as the density and the enthalpy of vaporisation are predicted rather well by all of the models, but there is significant variation in the values for other properties such as the dielectric constant [Jorgensen *et al.* 1983]. When comparing the different models, it is also important to take account of the computational effort each requires. Thus, nine site–site distances must be calculated for each water dimer using a three-site model; ten are required for a four-site model, and seventeen for the ST2 model.

The use of a rigid model for water is obviously an approximation, and it means that some properties cannot be determined at all. For example, only when internal flexibility is included can the vibrational spectrum be calculated and compared with experiment. Flexibility is most easily incorporated by 'grafting' bond-stretching and angle-bending terms onto the potential function for a rigid model. Such an approach needs to be done with care. For example, Ferguson has developed a flexible model for water that is based upon the SPC model [Ferguson 1995]. The partial charges and van der Waals parameters in this model were slightly different from those in the rigid model, and flexibility was achieved using cubic and harmonic bond-stretching terms and a harmonic angle-bending term. The calculated values compared well with experimental results for a wide range of thermodynamic and structural properties, including the dielectric constant and self-diffusion coefficient.

4.14.2 Polarisable Water Models

The simple models give very good results for a wide range of properties of pure liquid water. However, there is some concern that they are not appropriate models to use for the most accurate work. This is especially the case for inhomogeneous systems where there are strong electric field gradients due to the presence of ions, and at the solute–solvent interface. Under such circumstances models that explicitly include polarisation effects and three-body terms are considered to be more appropriate. The inclusion of an explicit polarisation term should also enhance the ability of the model to reproduce the behaviour of water in other phases (e.g. solid and vapour) and at the interface between different phases. The dipole moment of an isolated water molecule in such a model should thus be closer to the gas-phase value rather than to the 'effective' value in liquid water. The simplest way to include polarisation is to use an isotropic molecular polarisability contribution, an alternative is to use atom-centred polarisabilities or the variable charge method. The incorporation of polarisability may significantly increase the computational effort required for a liquid simulation, and even then only the best polarisable models currently compete with the well-established models that use effective pairwise potentials. We have already considered some of the polarisable water models in our discussion of polarisation effects. One early attempt to incorporate such effects into a water model was made by Barnes,

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* A discussion of the calculation of these properties from computer simulation is given in Section 6 2

ε_e is the well depth for an end-to-end arrangement of the ellipsoids when the attractive and repulsive contributions cancel, and ε_s is the corresponding well depth for the side-by-side arrangement (Figure 4.45).

The Gay–Berne potential is rather complex but is governed by a relatively small number of parameters, some of which have readily interpretable meanings. The effect of changing the parameters can be most clearly understood by considering certain orientations, such as the side-by-side, end-to-end, crossed and T-shaped structures (Figure 4.45). In the crossed structure the well depth $\varepsilon(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}})$ and the separation $\sigma(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}})$ are independent of χ and χ'. The ratio of the well depths for the end-to-end and side-by-side arrangements is $\varepsilon_e/\varepsilon_s$. The exponents μ and ν are considered adjustable parameters. One way to obtain values for these is to fit the Gay–Berne function to arrangements of Lennard-Jones particles. For example, Luckhurst, Stevens and Phippen determined a value of 1 for ν and a value of 2 for μ by fitting to a linear array of four Lennard-Jones centres [Luckhurst *et al.* 1990].

Depending upon the parameters chosen, simulations performed using the Gay–Berne potential show behaviour typical of liquid crystalline materials. Moreover, by modifying the potential one can determine what contributions affect the liquid crystalline properties and so help to suggest what types of molecule should be made in order to attain certain properties.

4.16 Derivatives of the Molecular Mechanics Energy Function

Many molecular modelling techniques that use force-field models require the derivatives of the energy (i e the force) to be calculated with respect to the coordinates. It is preferable that analytical expressions for these derivatives are available because they are more accurate and faster than numerical derivatives. A molecular mechanics energy is usually expressed in terms of a combination of internal coordinates of the system (bonds, angles, torsions, etc.) and interatomic distances (for the non-bonded interactions). The atomic positions in molecular mechanics are invariably expressed in terms of Cartesian coordinates (unlike quantum mechanics, where internal coordinates are often used). The calculation of derivatives with respect to the atomic coordinates usually requires the chain rule to be applied. For example, for an energy function that depends upon the separation between two atoms (such as the Lennard-Jones potential, Coulomb electrostatic interaction or bond-stretching term) we can write:

$$r_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2} \tag{4.96}$$

$$\frac{\partial \mathcal{V}}{\partial x_i} = \frac{\partial \mathcal{V}}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial x_i} \tag{4.97}$$

$$\frac{\partial r_{ij}}{\partial x_i} = \frac{(x_i - x_j)}{r_{ij}} \tag{4.98}$$

Thus, for the Lennard-Jones potential:

$$\frac{\partial \mathcal{V}}{\partial r_{ij}} = \frac{24\varepsilon}{r_{ij}} \left[-2\left(\frac{\sigma}{r_{ij}}\right)^{12} + \left(\frac{\sigma}{r_{ij}}\right)^{6} \right] \tag{4 99}$$

The force in the x direction acting on atom i due to its interaction with atom j is given by:

$$\mathbf{f}_{x_i} = (\mathbf{x}_i - \mathbf{x}_j)\frac{24\varepsilon}{r_{ij}^2}\left[2\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] \qquad (4.100)$$

Analytical expressions for the derivatives of the other terms that are commonly found in force fields are also available [Niketic and Rasmussen 1977]. Similar expressions must be derived from scratch when new functional forms are developed.

4.17 Calculating Thermodynamic Properties Using a Force Field

A molecular mechanics program will return an 'energy value' for any configuration or conformation of the system. This value is properly described as a 'steric energy' and is the energy of the system relative to a zero point that corresponds to a hypothetical molecule in which all of the bond lengths, valence angles, torsions and non-bonded separations are set to their strainless values. It is not necessary to know the actual value of the zero point to calculate the *relative* energies of different configurations or different conformations of the system.

Molecular mechanics can be used to calculate heats of formation. To do so requires the energy to form the bonds in the molecule to be added to the steric energy. These bond energies are typically obtained by fitting to experimentally determined heats of formation and are stored as empirical parameters within the force field. The accuracy with which heats of formation can be predicted with molecular mechanics is, in appropriate cases, comparable with experiment. Thus, the steric energy of a given structure may vary considerably from one force field to another, but its heat of formation should be much closer (if the force fields have been properly parametrised).

A third type of 'energy' that can be obtained from a molecular mechanics calculation is the 'strain energy'. Differences in steric energy are only valid for different conformations or configurations of the same system. Strain energies enable different molecules to be compared. To determine the strain energy it is usual to define some 'strainless' reference point. The reference points can be chosen in many ways and so many different definitions of strain energy have been proposed in the literature. For example, Allinger and co-workers defined the reference point using a set of 'strainless' compounds such as the all-*trans* conformations of the straight-chain alkanes from methane to hexane. From this set of compounds it was possible to derive a set of strainless energy parameters for constituent parts of the molecules. The inherent strain energy of a hydrocarbon is then obtained by subtracting the reference 'strainless' energy from the actual steric energy calculated using the force field. One interesting conclusion of this study was that chair cyclohexane has an inherent strain energy due to the presence of 1,4 van der Waals interactions between the carbon atoms within the ring.

The sources of strain are often quantified by examining the different components (bonds, angles, etc.) of the force field. Such analyses can provide useful information, especially for cases such as highly strained rings. However, in many molecules the strain is distributed