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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:

$$\begin{aligned} V(\mathbf{r}^N) = & \sum_{\text{bonds}} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{\text{angles}} \frac{k_j}{2} (\theta_j - \theta_{j,0})^2 + \sum_{\text{torsions}} \frac{V_n}{2} (1 + \cos(n\omega - \gamma)) \\ & + \sum_{i=1}^N \sum_{j=i+1}^N \left(4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right) \end{aligned} \quad (4.1)$$

$V(\mathbf{r}^N)$ 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

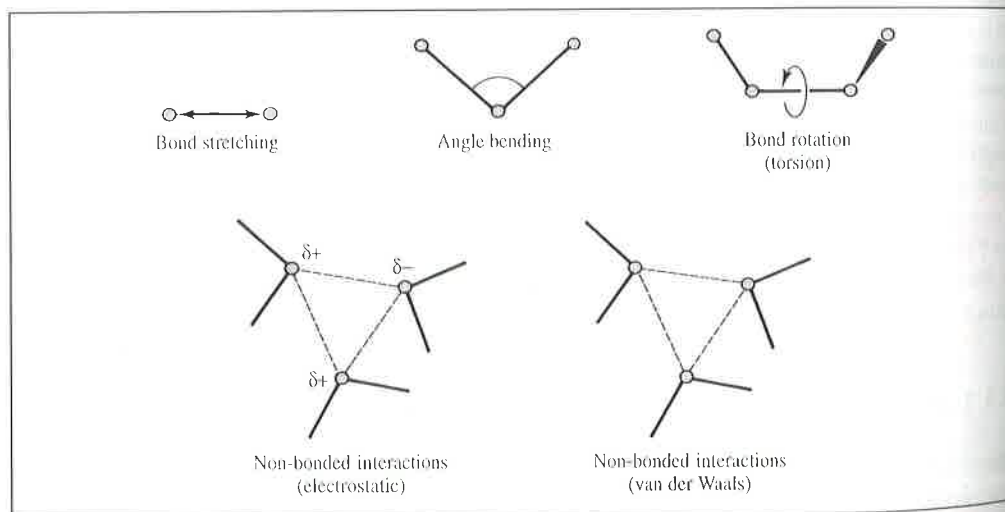


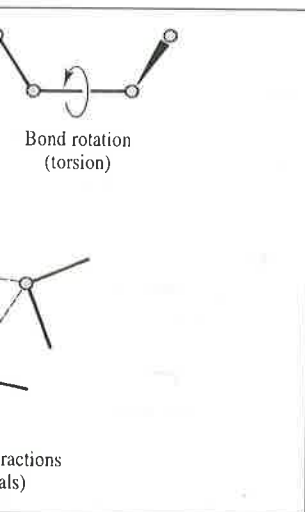
Fig. 4.1: Schematic representation of the four key contributions to a molecular mechanics force field: bond stretching, angle bending and torsional terms and non-bonded interactions.

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$$\frac{V_n}{2} (1 + \cos(n\omega - \gamma))$$

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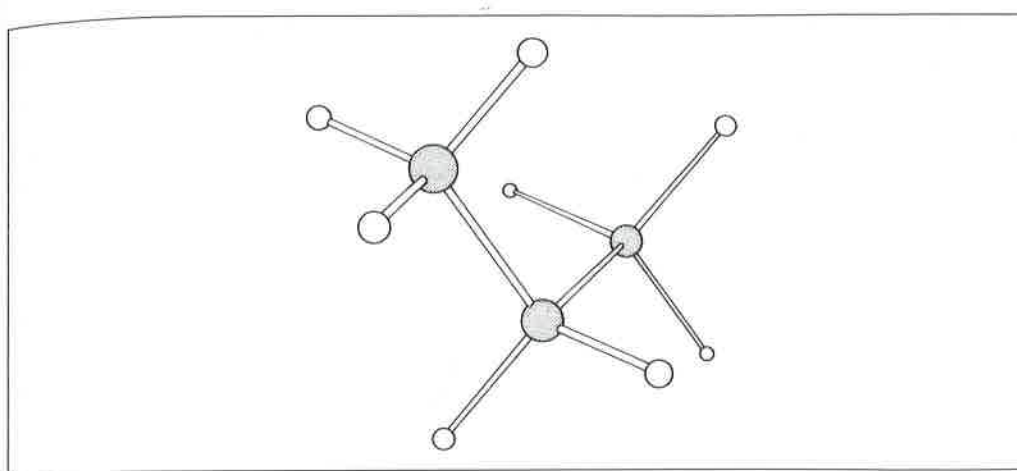


Fig. 4.2: A typical force field model for propane contains ten bond-stretching terms, eighteen angle-bending terms, eighteen torsional terms and 27 non-bonded interactions.

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 (CH₂) 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.

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form but also the parameters of the two force fields may use an overlap. Moreover, force fields with the same units with different functional forms should be considered as a single entity. Its individual components, such as the Lennard-Jones, can be mixed with parameters of other force fields if the force field are sufficiently accurate (or not) to make this an acceptable approximation.

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important feature of a force field. It is difficult to model a series of related force fields with different parameters for each individual force field. Instead, we use the same set of parameters for all force fields. To use the force field to make accurate work is required,

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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

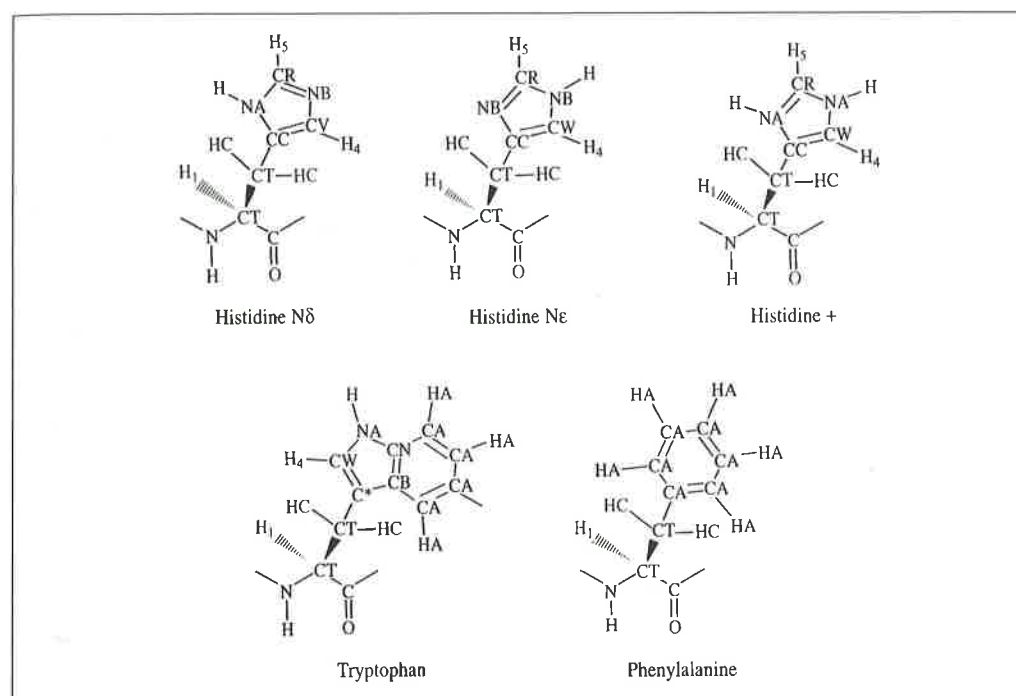


Fig. 4.3: AMBER atom types for the amino acids histidine, tryptophan and phenylalanine. There are three possible protonation states of histidine.

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 'sp² 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:

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

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

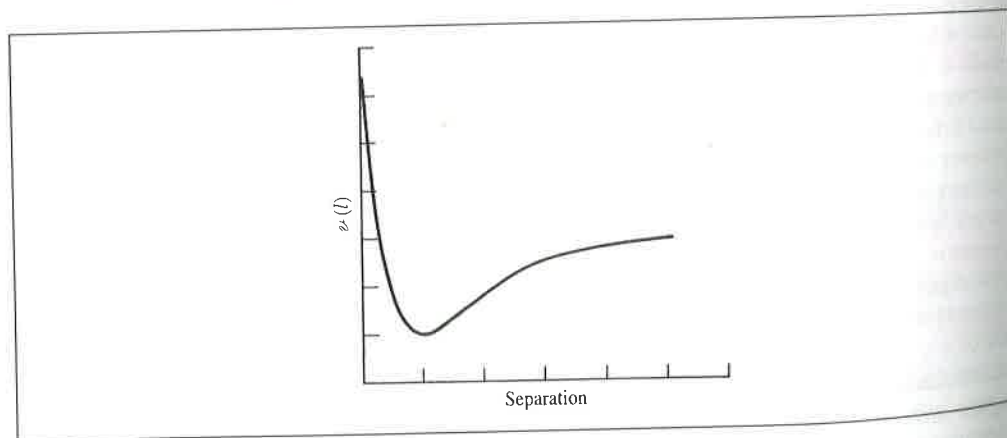


Fig. 4.4: Variation in bond energy with interatomic separation.

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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 :

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

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].

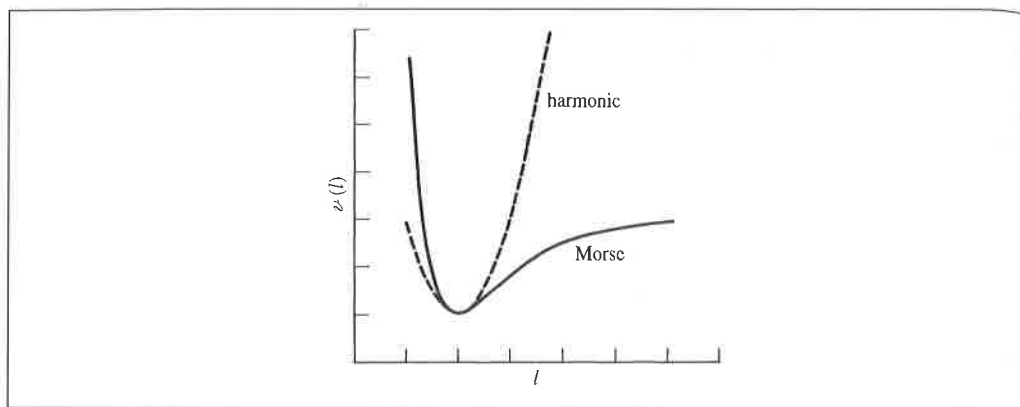


Fig. 4.5: Comparison of the simple harmonic potential (Hooke's law) with the Morse curve.

intuitively expect to be stronger have large force constants (contrast C–C with C=C and N≡N). A deviation of just 0.2 \AA from the reference value l_0 with a force constant of $300 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$ 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:

$$v(l) = \frac{k}{2}(l - l_0)^2 [1 - k'(l - l_0) - k''(l - l_0)^2 - k'''(l - l_0)^3 \dots] \quad (4.4)$$

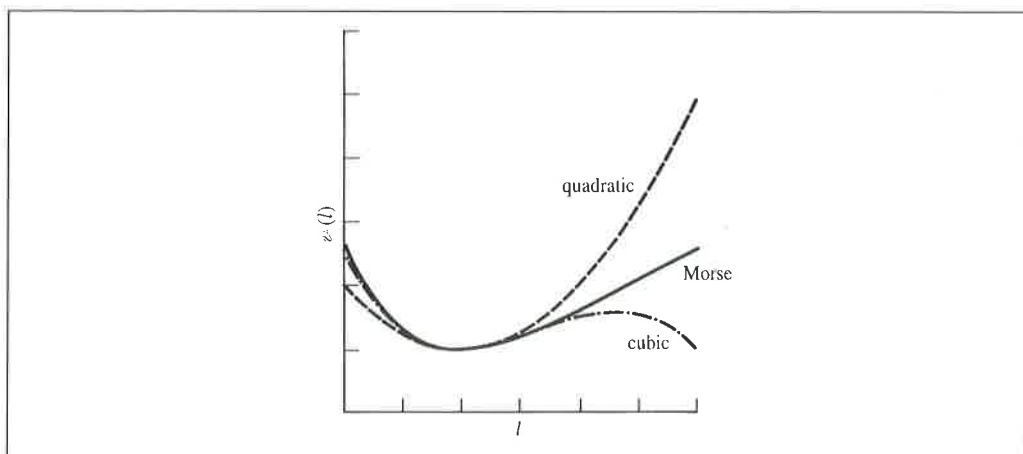


Fig. 4.6: A cubic bond-stretching potential passes through a maximum but gives a better approximation to the Morse curve close to the equilibrium structure than the quadratic form.

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:

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

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:

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

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 ($6 \times \text{C-C-C-C}$, $12 \times \text{C-C-C-H}$ and $6 \times \text{H-C-C-H}$). Torsional potentials are almost always expressed as a cosine series expansion. One functional form is:

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

ω is the torsion angle.

An alternative but equivalent expression is:

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

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 $\gamma = 0^\circ$. This would give a threefold rotational profile with minima at torsion angles of $+60^\circ$, -60° and 180° and maxima at $\pm 120^\circ$ and 0° . A double bond between two sp^2 carbon atoms would have $n = 2$ and $\gamma = 180^\circ$, giving minima at 0° and 180° . The value of V_n would also be significantly larger for the double bond than for the single

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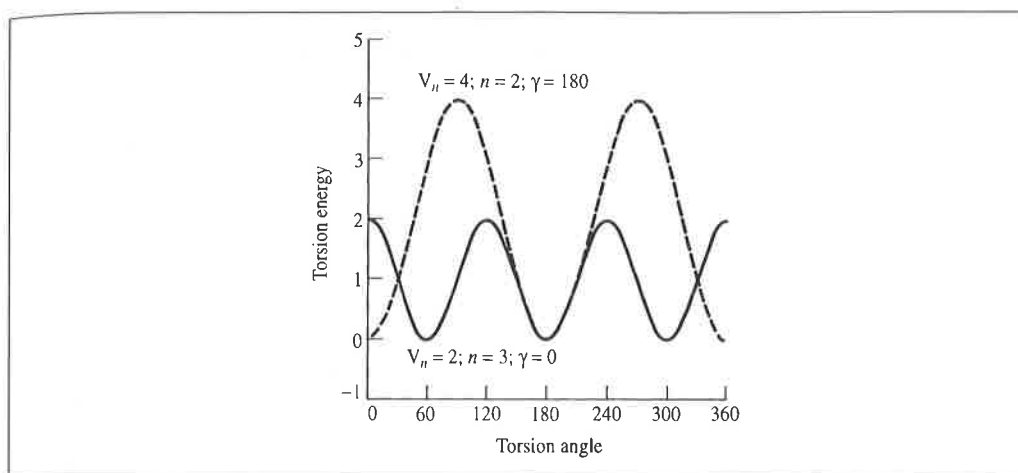


Fig. 4.7: Torsional potential varies as shown for different values of V_n , n and γ .

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:

$$v(\omega_{\text{C-O-O-C}}) = 0.25(1 + \cos 3\omega) + 0.25(1 + \cos 2\omega) \quad (4.9)$$

The torsional energy for a $\text{OCH}_2\text{-CH}_2\text{O}$ 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

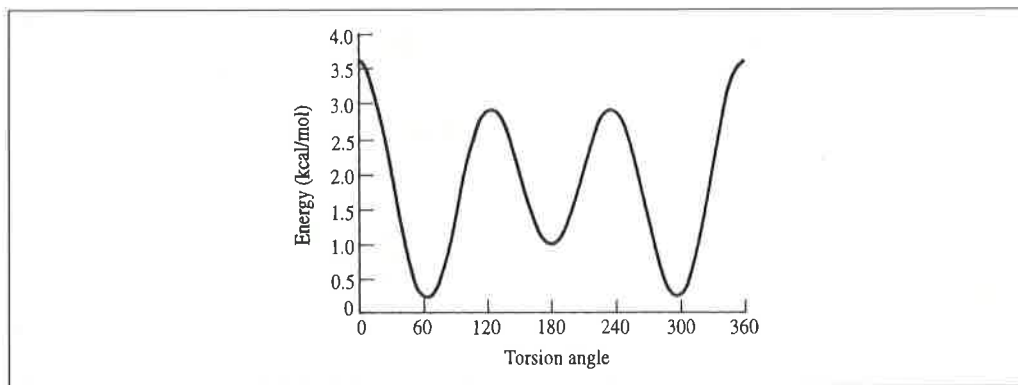


Fig. 4.8: Variation in torsional energy (AMBER force field) with O-C-C-O torsion angle (ω) for $\text{OCH}_2\text{-CH}_2\text{O}$ fragment. The minimum energy conformations arise for $\omega = 60^\circ$ and 300° .

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:

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

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.

of the terminal atoms. For two sp^3 -hybridised carbon atoms assigned the same torsional C–O. In its treatment of the between those force fields and those which consistently category; it uses three terms in

$$1 + \cos 3\omega) \quad (4.10)$$

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Bonding Motions

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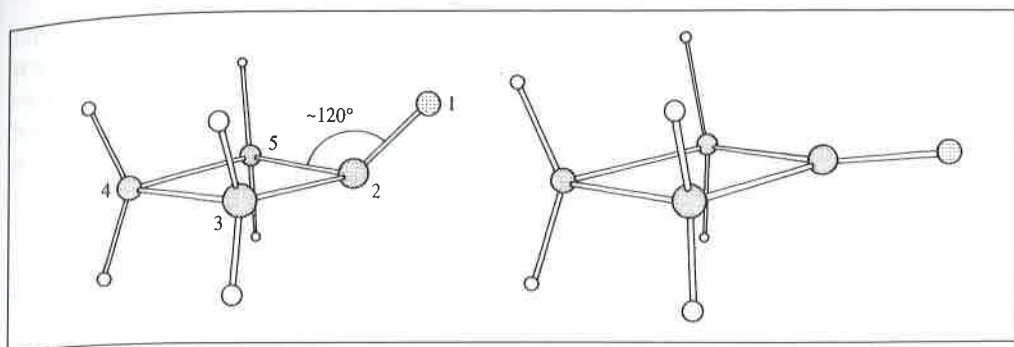


Fig. 4.9: Without an out-of-plane term, the oxygen atom in cyclobutane is predicted to lie out of the plane of the ring (left) rather than in the plane.

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

$$v(\omega) = k(1 - \cos 2\omega) \quad (4.11)$$

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

$$v(\theta) = \frac{k}{2}\theta^2; \quad v(h) = \frac{k}{2}h^2 \quad (4.12)$$

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

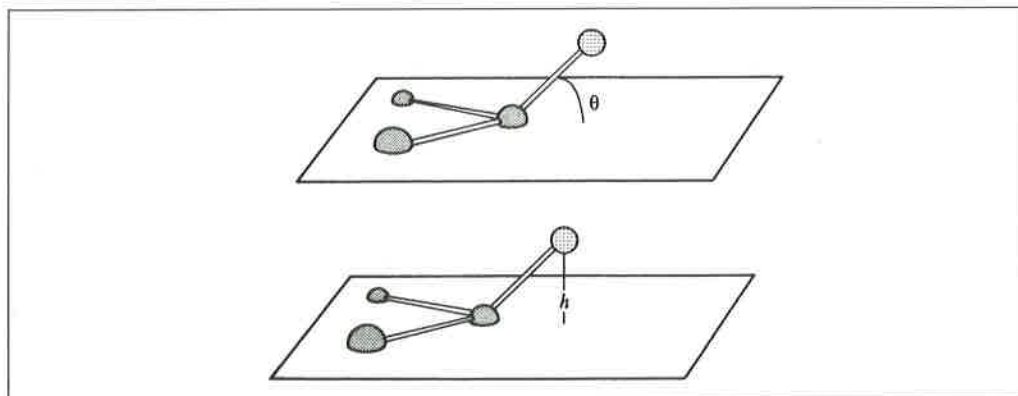


Fig. 4.10: Two ways to model the out-of-plane bending contributions.

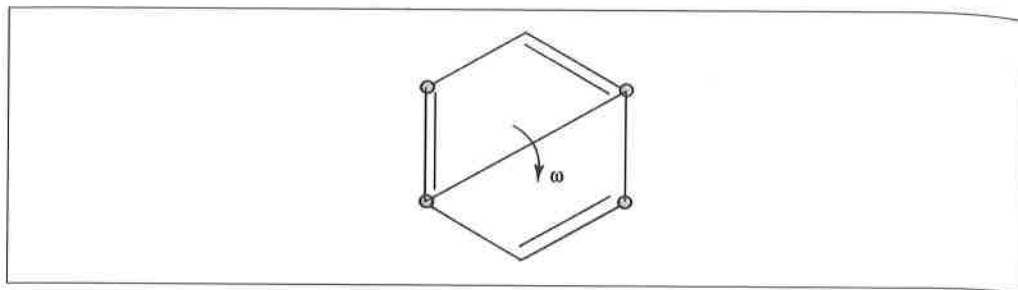


Fig. 4.11: Improper torsional terms can be used to keep a benzene ring planar.

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

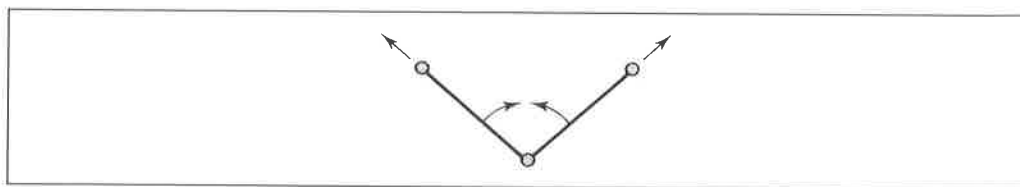


Fig. 4.12: Coupling between the stretching of the bonds as an angle closes.



benzene ring planar.

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Force Fields

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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:

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

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):

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

In the 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:

$$v(r_{1,3}) = \frac{k_{r_{1,3}}}{2} (r_{1,3} - r_{1,3}^0)^2 \quad (4.15)$$

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:

$$v(l, \omega) = k(l - l_0) \cos n\omega \quad (4.16)$$

$$v(l, \omega) = k(l - l_0)[1 + \cos n\omega] \quad (4.17)$$

where 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,
 could 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)
 could provide a general way to classify force fields [Hwang *et al.* 1994]. A class I force field
 is 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 expli-
 cit cross terms to account for the coupling between coordinates. The presence of these higher
 order 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 chemi-
 cal effects and other features such as electronegativity and hyperconjugation. A classic

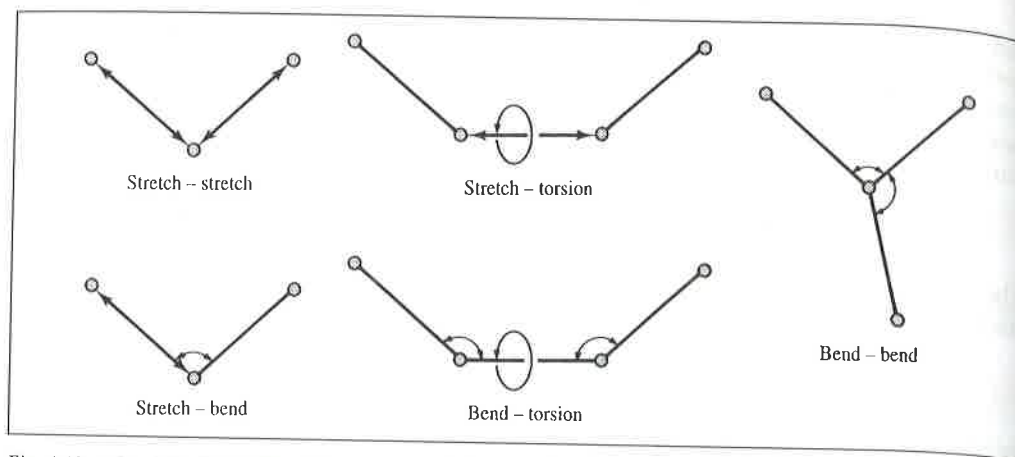


Fig. 4.13: Schematic illustration of the cross terms believed to be most important in force fields. (Adapted from Dinur U and A T Hagler 1991. *New Approaches to Empirical Force Fields*. In *Reviews in Computational Chemistry*, Lipkowitz K B and D B Boyd (Editors). New York, VCH Publishers, pp. 99-164.)

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 \AA between the two forms. This effect was incorporated within MM4 by a term of the following form:

$$\Delta l = k(1 - \cos 2\omega) \quad (4.18)$$

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.

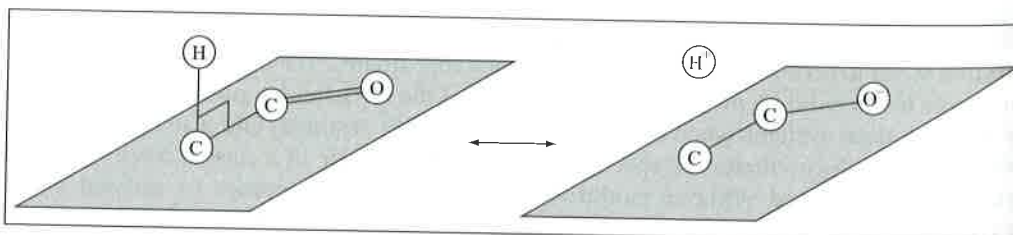


Fig. 4.14: Valence bond representation of the hyperconjugation effect which leads to a lengthening of the C-H bond in acetaldehyde.

4.8 Introduction

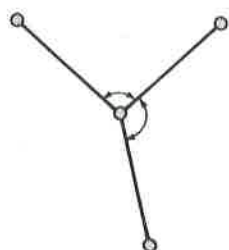
Independent molecule... important role in determining bonded interactions... They are 'through-space' interactions with an inverse power of the distance between the two groups, one of which is... interactions.

4.9 Electrostatics

4.9.1 The Central

Electronegative elements... rise to an unequal distribution of... represented in a number of... point charges through... static properties of the... often referred to as... between two molecules... as a sum of interactions

N_A and N_B are the number of... representation and... detail in Section 4.9.2... electrostatic interactions... (least) capable of predicting... interactions. This is the... or multipoles: the charge... 2.7.3. These moments... (dipole), Θ (quadrupole), electric moment. Their lowest non-zero... non-zero moment. N ... non-zero moment. The... the octopole. Each... distribution of charge... appropriate distances... octopole by eight charges... molecule requires all



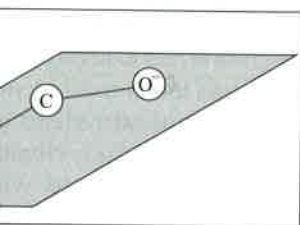
Bend – bend

in force fields. (Adapted from Dinur
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the length of the C–H bond
–H bond is perpendicular to
between the σ orbital of the C–H
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bond and a greater contribu-
tion to the hydrogen
ions suggested that the bond
length was incorporated within

(4.18)

one where the central bond
debate about the existence
pure X-ray crystallographic
calculations certainly



a lengthening of the C–H bond

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:

$$\psi = \sum_{i=1}^{N_A} \sum_{j=1}^{N_B} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \quad (4.19)$$

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,

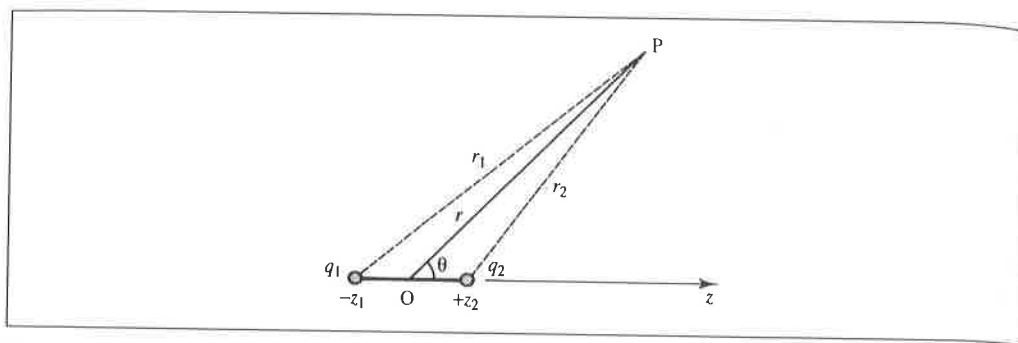


Fig. 4.15: The electrostatic potential due to two point charges.

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:

$$\phi(r) = \frac{1}{4\pi\epsilon_0} \left(\frac{q_1}{r_1} + \frac{q_2}{r_2} \right) \quad (4.20)$$

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

$$\phi(r) = \frac{1}{4\pi\epsilon_0} \left(\frac{q_1}{\sqrt{r^2 + z_1^2 + 2rz_1 \cos \theta}} + \frac{q_2}{\sqrt{r^2 + z_2^2 - 2rz_2 \cos \theta}} \right) \quad (4.21)$$

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

$$\phi(r) = \frac{1}{4\pi\epsilon_0} \left(\frac{q_1 + q_2}{r} + \frac{(q_2 z_2 - q_1 z_1) \cos \theta}{r^2} + \frac{(q_1 z_1^2 + q_2 z_2^2)(3 \cos^2 \theta - 1)}{2r^3} + \dots \right) \quad (4.22)$$

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

$$\phi(r) = \frac{1}{4\pi\epsilon_0} \left(\frac{q}{r} + \frac{\mu \cos \theta}{r^2} + \frac{\Theta(3 \cos^2 \theta - 1)}{2r^3} + \dots \right) \quad (4.23)$$

Thus $(q_1 + q_2)$ is the charge; $(q_2 z_2 - q_1 z_1)$ is the dipole; $(q_1 z_1^2 + q_2 z_2^2)$ 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:

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

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:

$$\mu = \sum q_i \mathbf{r}_i \quad (4.25)$$

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:

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

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:

$$\Theta = \frac{1}{2} \begin{pmatrix} \sum_i q_i (3x_i^2 - r_i^2) & 3 \sum_i q_i x_i y_i & 3 \sum_i q_i x_i z_i \\ 3 \sum_i q_i x_i y_i & \sum_i q_i (3y_i^2 - r_i^2) & 3 \sum_i q_i y_i z_i \\ 3 \sum_i q_i x_i z_i & 3 \sum_i q_i y_i z_i & \sum_i q_i (3z_i^2 - r_i^2) \end{pmatrix} \quad (4.27)$$

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

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

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):

$$\Theta = \begin{pmatrix} \Theta_{\alpha\alpha} & 0 & 0 \\ 0 & \Theta_{\beta\beta} & 0 \\ 0 & 0 & \Theta_{\gamma\gamma} \end{pmatrix} \quad (4.29)$$

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

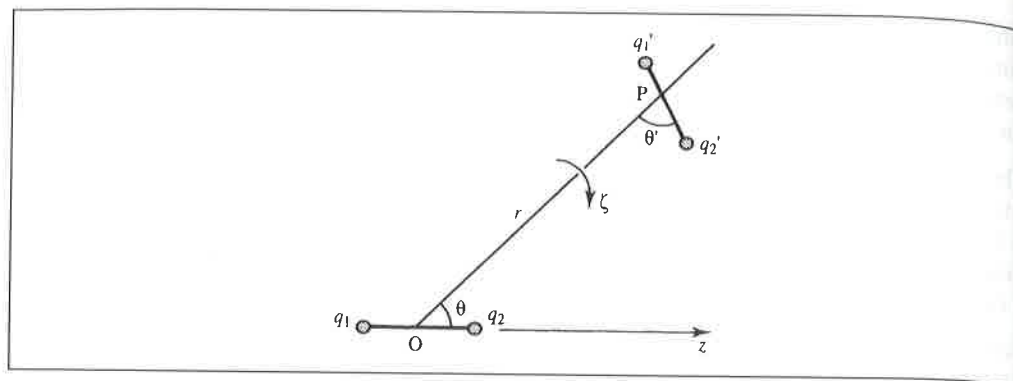


Fig. 4.16: The relative orientation of two dipoles.

molecules can be described in terms of four parameters (the distance joining their centres of mass and three angles as shown in Figure 4.16). The electrostatic interaction between the two molecules is calculated by multiplying each charge by the potential at that point and adding the result for each charge. The following expression is the result [Buckingham 1959]:

$$V(q, q') = \frac{1}{4\pi\epsilon_0} \left\{ \begin{aligned} &\frac{qq'}{r} \\ &+ \frac{1}{r^2} (q\mu' \cos \theta + q'\mu \cos \theta') \\ &+ \frac{\mu\mu'}{r^3} (2 \cos \theta \cos \theta' + \sin \theta \sin \theta' \cos \zeta) \\ &+ \frac{1}{2r^3} [q\Theta' (3 \cos^2 \theta' - 1) + q'\Theta (3 \cos^2 \theta - 1)] \\ &+ \frac{3}{2r^4} [\mu\Theta' \{ \cos \theta (3 \cos^2 \theta' - 1) + 2 \sin \theta \sin \theta' \cos \theta' \cos \zeta \} \\ &\quad + \mu'\Theta \{ \cos \theta' (3 \cos^2 \theta - 1) + 2 \sin \theta' \sin \theta \cos \theta \cos \zeta \}] \\ &+ \frac{3\Theta\Theta'}{4r^5} [1 - 5 \cos^2 \theta - 5 \cos^2 \theta' + 17 \cos^2 \theta \cos^2 \theta' \\ &\quad + 2 \sin^2 \theta \sin^2 \theta' \cos^2 \zeta + 16 \sin \theta \sin \theta' \cos \theta \cos \theta' \cos \zeta] \\ &+ \dots \end{aligned} \right\} \quad (4.30)$$

The energy of interaction between two charge distributions is thus an infinite series that includes charge-charge, charge-dipole, dipole-dipole, charge-quadrupole, dipole-quadrupole interactions, quadrupole-quadrupole terms, and so on. These terms depend on different inverse powers of the separation r . If the molecules are neutral (i.e. $q = q' = 0$) then the leading term in the expansion is that due to the dipole-dipole interaction, which varies as r^{-3} . This is a key result, for the range of the dipole-dipole interaction (r^{-3}) is much less than that of the Coulomb interaction (r^{-1}), Figure 4.17. This will be important in later chapters, where we shall collect atoms together into neutral groups. The electrostatic interaction

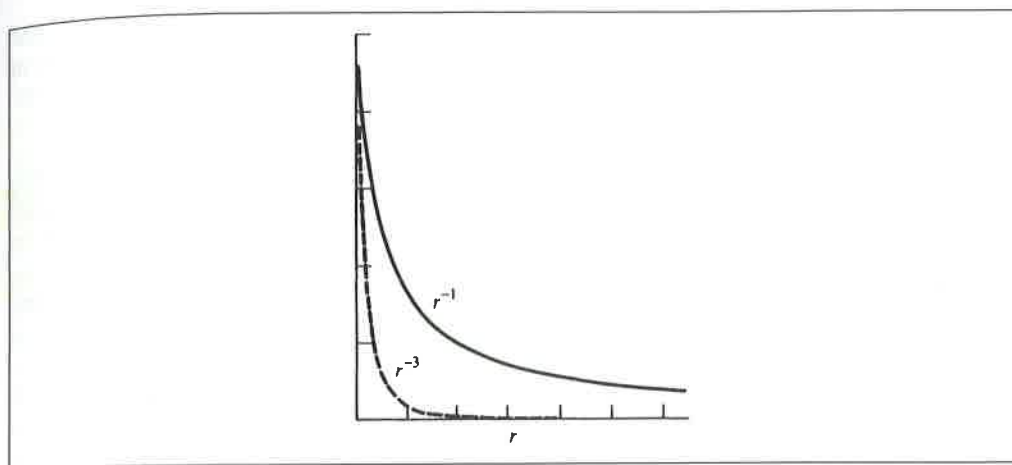


Fig. 4.17: The charge-charge energy decays much more slowly ($\propto r^{-1}$) than the dipole-dipole energy ($\propto r^{-3}$).

between these groups then decays as r^{-3} rather than the r^{-1} dependence of each individual charge-charge interaction. This can be seen in Figure 4.17, in which the functions r^{-1} and r^{-3} have been plotted as a function of distance. Even when the dipole-dipole interaction energy has fallen off almost to zero the charge-charge interaction energy is still significant. In general, the interaction energy between two multipoles of order n and m decreases as $r^{-(n+m+1)}$. It should be emphasised again that these expressions are only valid when the separation of the two molecules, r , is much larger than the internal dimensions of the molecules. The favourable arrangements for the various multipoles are shown in Figure 4.18.

A central multipole expansion therefore provides a way to calculate the electrostatic interaction between two molecules. The multipole moments can be obtained from the wavefunction and can therefore be calculated using quantum mechanics (see Section 2.7.3) or can be determined from experiment. One example of the use of a multipole expansion is

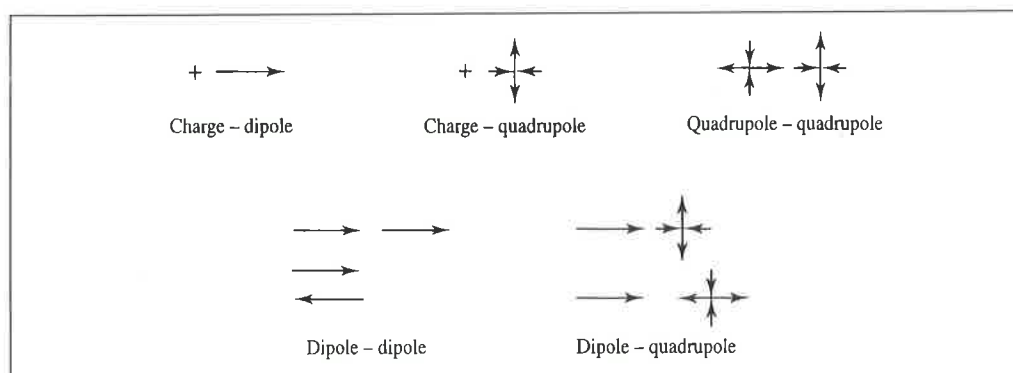


Fig. 4.18: The most favourable orientations of various multipoles. (Figure adapted from Buckingham A D 1959. *Molecular Quadrupole Moments*. Quarterly Reviews of the Chemical Society 13:183-214.)

the benzene model of Claessens, Ferrario and Ryckaert [Claessens *et al.* 1983]. Benzene has no charge and no dipole moment, but it does have a sizeable quadrupole. The inclusion of the quadrupole was found to give clearly superior results in molecular dynamics simulations of the liquid state over models that lacked any electronic contribution.

The main advantage of the multipolar description for calculating the electrostatic interactions between molecules is its efficiency. For example, the charge-charge interaction energy between two benzene molecules would require 144 individual charge-charge interactions with a partial atomic charge model rather than the single quadrupole-quadrupole term. Unfortunately, the multipole expansion is not applicable when the molecules are separated by distances comparable with the molecular dimensions. The formal condition for convergence of the multipolar interaction energy is that the distance between two interacting molecules should be larger than the sum of the distances from the centre of each molecule to the furthest part of its charge distribution. If a sphere is constructed around each molecule, positioned on its centre of mass, with a radius that encompasses all of the charge distribution, then the multipole expansion for the interaction between two molecules will converge if these spheres do not intersect. Even if one requires the sphere to encompass just the nuclei in a molecule (i.e. ignoring the fact that the charge distribution around a molecule extends to infinity) there may still be problems. For example, the convergence sphere for a molecule such as butane would extend beyond the van der Waals radii in some directions, enabling other molecules to penetrate the convergence sphere, as illustrated in Figure 4.19. Another problem is that the multipolar expansion may be slow to converge. The multipolar expansion is often located at the centre of mass, but this may not be the best choice to achieve the most rapid convergence.

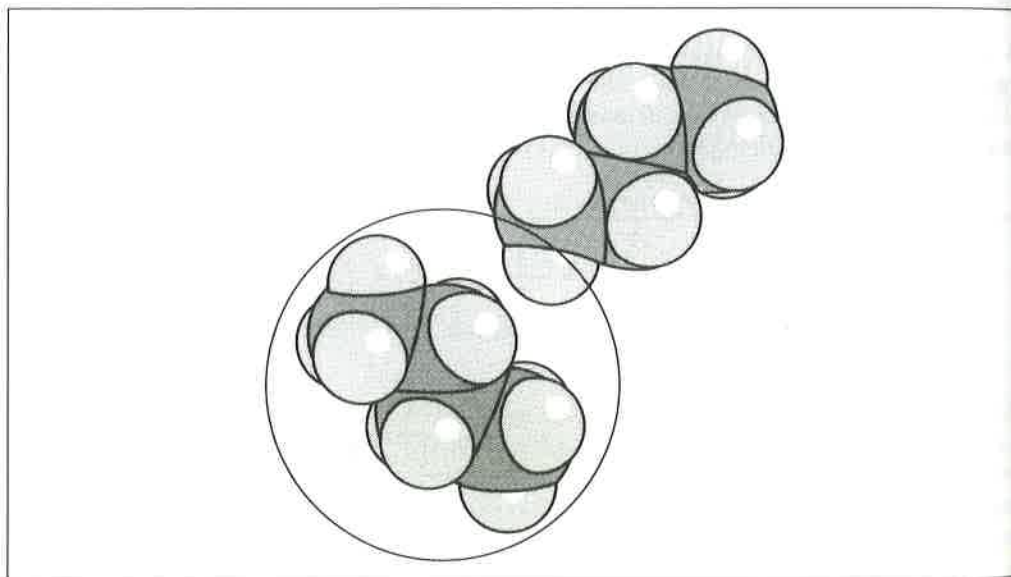


Fig. 4.19: The convergence sphere of the multipole expansion for a molecule such as butane may be penetrated by another molecule.

ns *et al.* 1983]. Benzene has a quadrupole. The inclusion of molecular dynamics simulation contribution.

ing the electrostatic interaction charge-charge interaction individual charge-charge interaction quadrupole-quadrupole interaction when the molecules are ions. The formal condition distance between two interactions from the centre of each molecule is constructed around a sphere that encompasses all of the interaction between two molecules is the sphere to encompass the charge distribution around a molecule. For example, the convergence of the van der Waals radii in the convergence sphere, as the expansion may be slow or fast, but this may



tane may be penetrated by

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:

$$\Theta = 2q(l/2)^2 \quad (4.31)$$

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

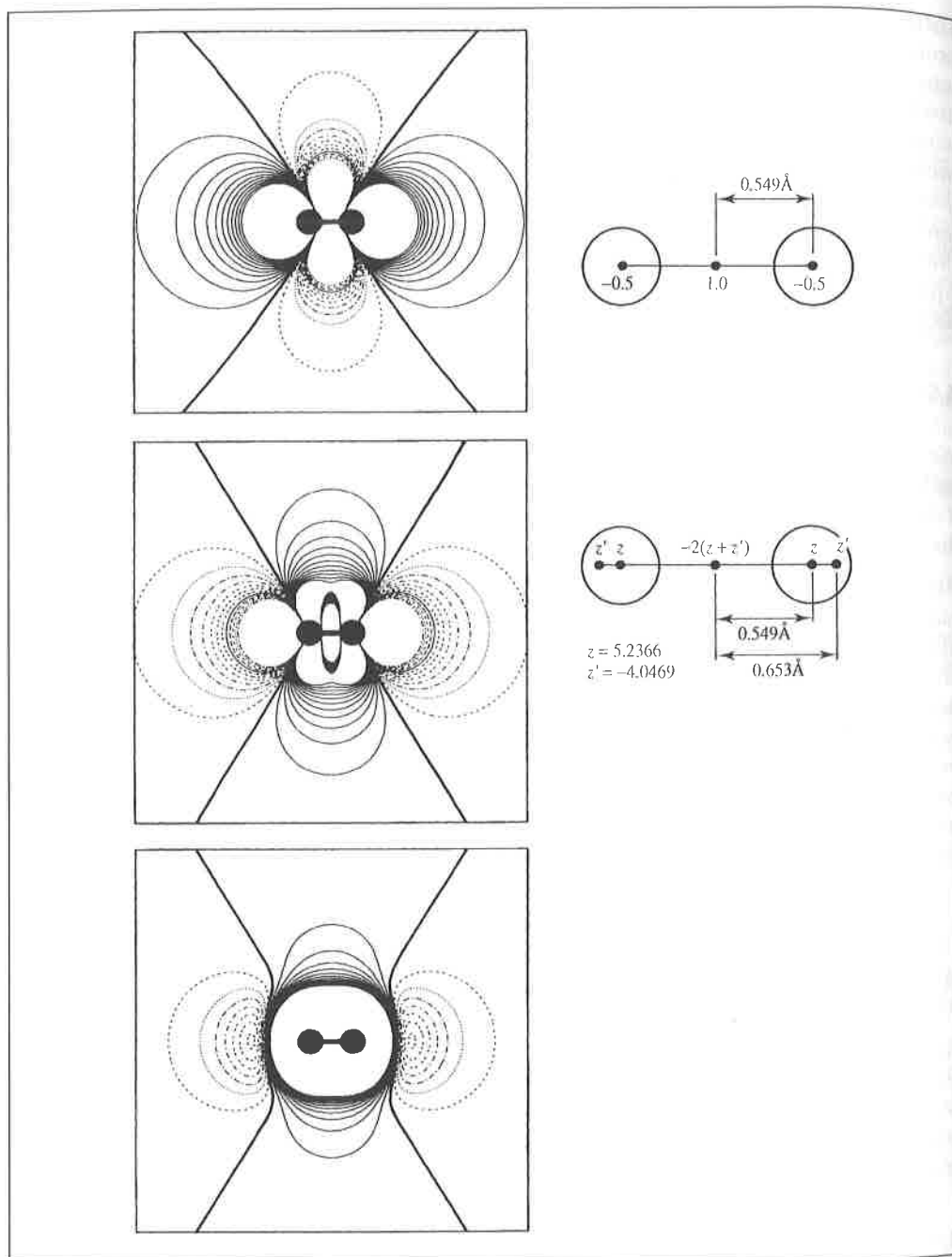
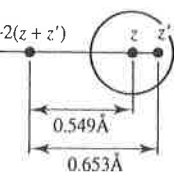
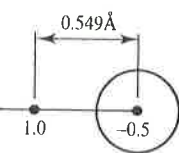


Fig. 4.20: Two charge models for N_2 with the electrostatic potentials that they generate. Also shown is the electrostatic potential calculated using ab initio quantum mechanics (6-31G* basis set.) Negative contours are dashed and the zero contour is bold.



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electric moments can be calculated exactly if the geometry is known. For example, the experimentally determined dipole moment of HF (1.82 D) can be reproduced by placing equal but opposite charges of $0.413e$ on the two atomic nuclei (assuming a bond length of 0.917 \AA). The tetrahedral arrangement of the hydrogens about the carbon in methane means that each hydrogen atom has an identical charge equal to one quarter the charge on the carbon. The molecule is electrically neutral with zero dipole and quadrupole moments but a non-zero octopole moment, which can be reproduced using a hydrogen charge of approximately $0.14e$.

In some cases the atomic charges are chosen to reproduce thermodynamic properties calculated using a molecular dynamics or Monte Carlo simulation. A series of simulations is performed and the charge model is modified until satisfactory agreement with experiment is obtained. This approach can be quite powerful despite its apparent simplicity, but it is only really practical for small molecules or simple models.

The electrostatic properties of a molecule are a consequence of the distribution of the electrons and the nuclei and thus it is reasonable to assume that one should be able to obtain a set of partial atomic charges using quantum mechanics. Unfortunately, the partial atomic charge is not an experimentally observable quantity and cannot be unambiguously calculated from the wavefunction. This explains why numerous ways to determine partial atomic charges have been proposed, and why there is still considerable debate as to the 'best' method to derive them. Indirect comparisons of the various methods are possible, usually by calculating appropriate quantities from the charge model and then comparing the results with either experiment or quantum mechanics. For example, one might examine how well the charge model reproduces the experimental or quantum mechanical multipole moments or the electrostatic potential around the molecule.

We have already encountered in Section 2.7.5 the population analysis method for calculating partial atomic charges. Such sets of charges (commonly referred to as *Mulliken charges* when obtained from that particular partitioning scheme) are often considered to be inappropriate for accurately representing the interactions between molecules. This is because Mulliken charges are primarily dependent upon the constitution of the molecule – how the atoms are bonded together – rather than being designed to reproduce the properties that determine how molecules interact with each other, such as the electrostatic potential. The importance of the electrostatic potential in intermolecular interactions has resulted in much interest in schemes that calculate charges consistent with this particular property.

4.9.4 Charges Derived from the Molecular Electrostatic Potential

The electrostatic potential at a point is the force acting on a unit positive charge placed at that point. The nuclei give rise to a positive (i.e. repulsive) force, whereas the electrons give rise to a negative potential. The electrostatic potential is an observable quantity that can be determined from a wavefunction using Equations (2.222) and (2.223):

$$\phi(\mathbf{r}) = \phi_{\text{nucl}}(\mathbf{r}) + \phi_{\text{elec}}(\mathbf{r}) = \sum_{A=1}^M \frac{Z_A}{|\mathbf{r} - \mathbf{R}_A|} - \int \frac{d\mathbf{r}' \rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} \quad (4.32)$$

The electrostatic potential is a continuous property and is not easily represented by an analytical function. Consequently, it is necessary to derive a discrete representation for use in numerical analysis. The objective is to derive the set of partial charges (usually partial atomic charges) that best reproduces the quantum mechanical electrostatic potential at a series of points surrounding the molecule. A solution to this problem was suggested by Cox and Williams [Cox and Williams 1981]. The electrostatic potential at each of the chosen points is calculated from the wavefunction. A least-squares fitting procedure is then employed to determine the set of partial atomic charges that best reproduces the electrostatic potential at the points, subject to the constraint that the sum of the charges should be equal to the net charge on the molecule. Symmetry conditions may also be imposed to ensure that the charges on symmetrically equivalent atoms are equal. It is also possible to require the atomic charges to reproduce other electrostatic properties of the molecules such as the dipole moment. The fitting procedure minimises the sum of squares of the differences in the electrostatic potential. Thus, if the electrostatic potential at a point is ϕ_i^0 and if the value from the charge model is ϕ_i^{calc} , then the objective is to minimise the following function:

$$R = \sum_{i=1}^{N_{\text{points}}} w_i (\phi_i^0 - \phi_i^{\text{calc}})^2 \quad (4.33)$$

N_{points} is the number of points and w_i is a weighting factor that enables different points to be given different degrees of 'importance' in the fitting process. One of the charges is dependent on the values of the others (because the sum must equal Z , the molecular charge). This N th charge has a value given by:

$$q_N = Z - \sum_{j=1}^{N-1} q_j \quad (4.34)$$

The electrostatic potential due to the charges q_j at the point i is given by Coulomb's law:

$$\phi_i^{\text{calc}} = \sum_{j=1}^{N-1} \frac{q_j}{4\pi\epsilon_0 r_{ij}} + \frac{Z - \sum_{j=1}^{N-1} q_j}{4\pi\epsilon_0 r_{iN}} \quad (4.35)$$

r_{ij} is the distance from the charge j to the point i . At a minimum value of the error function, R , the first derivative is equal to zero with respect to all charges q_k :

$$\frac{\partial R}{\partial q_k} = -2 \sum_{i=1}^{N_{\text{points}}} w_i (\phi_i^0 - \phi_i^{\text{calc}}) \left(\frac{\partial \phi_i^{\text{calc}}}{\partial q_k} \right) = 0 \quad (4.36)$$

This equation can be written in the following form:

$$\sum_{i=1}^{N_{\text{points}}} w_i \left(\phi_i^0 - \frac{Z}{r_{iN}} \right) \left(\frac{1}{r_{ik}} - \frac{1}{r_{iN}} \right) = \sum_{j=1}^{N-1} \left[\sum_{i=1}^{N_{\text{points}}} w_i \left(\frac{1}{r_{ik}} - \frac{1}{r_{iN}} \right) \left(\frac{1}{r_{ij}} - \frac{1}{r_{iN}} \right) \right] \frac{q_j}{4\pi\epsilon_0} \quad (4.37)$$

When expressed in this way, then the set of equations can be recast as a matrix equation of the form $\mathbf{A}\mathbf{q} = \mathbf{a}$. The charges \mathbf{q} are then determined using standard matrix methods via $\mathbf{q} = \mathbf{A}^{-1}\mathbf{a}$.

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$$\left(\frac{1}{r_{ij}} - \frac{1}{r_{iN}} \right) \frac{q_j}{4\pi\epsilon_0} \quad (4.37)$$

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The points i ($1, 2, \dots, N_{\text{points}}$) where the potential is fitted can be chosen in a variety of ways but should be taken from the region where it is most important to model intermolecular interactions correctly. This region is just beyond the van der Waals radii of the atoms involved. Cox and Williams selected points from a regular grid in a shell defined by two surfaces, one corresponding to the union of the van der Waals radii plus 1.2 \AA and the others approximately 1 \AA beyond that. The CHELP procedure of Chirlian and Francel [Chirlian and Francel 1987] uses spherical shells, 1 \AA apart, centred on each atom with points symmetrically distributed on the surface. Any points within the van der Waals radius of any atom in the system are discarded and the shells extend to 3 \AA from the van der Waals surface of the molecule. The CHELP method employs a Lagrange multiplier method to find the atomic charges, rather than an iterative least-squares procedure. This minimises the error function R (Equation (4.33)) subject to the constraint that the charges sum to the total molecular charge. Such an analysis yields a set of $N + 1$ equations in $N + 1$ unknowns and can be solved using standard matrix methods. The CHELPG algorithm of Breneman and Wiberg [Breneman and Wiberg 1990] combines the regular grid of points of Cox and Williams with the Lagrange multiplier method of Chirlian and Francel as the results from CHELP were found to change if the molecule was reoriented in the coordinate system. In CHELPG a cubic grid of points (spaced $0.3\text{--}0.8 \text{ \AA}$ apart) is used and all grid points that lie within the van der Waals radius of any atom are discarded, together with all points that lie further than 2.8 \AA away from any atom.

The algorithm of Singh and Kollman used to derive the charges in the 1984 AMBER force field uses points on a series of molecular surfaces, constructed using gradually increasing van der Waals radii for the atoms [Singh and Kollman 1984]. The points at which the potential was fitted were located on these shells. For the 1995 AMBER force field a modified version of this electrostatic potential method was employed (termed 'restrained electrostatic potential fit', or RESP [Bayly *et al.* 1993]). The RESP algorithm uses hyperbolic restraints on non-hydrogen atoms. These restraints have the effect of reducing the charges on some atoms, particularly buried carbon atoms, which can be assigned artificially high charges in standard electrostatic potential fitting methods. The RESP charges also vary less with the molecular conformation.

4.9.5 Deriving Charge Models for Large Systems

Molecular mechanics is used to model systems containing thousands of atoms such as polymers. How then can charges be derived for such species? Clearly one cannot routinely perform quantum mechanical calculations on a molecule with so many atoms and so it must be broken into fragments of a suitable size. In some cases the fragments might appear relatively easy to define; for example, many polymeric systems are constructed by connecting together chemically defined monomeric units. The atomic charges for each monomer should be obtained from calculations on suitable fragments that recreate the immediate local environment of the fragment in the larger molecule. For example, partial atomic charges for amino acids are often obtained from calculations on a 'dipeptide' fragment (see Figure 4.21), which is more akin to the environment within a protein than in an isolated amino acid.

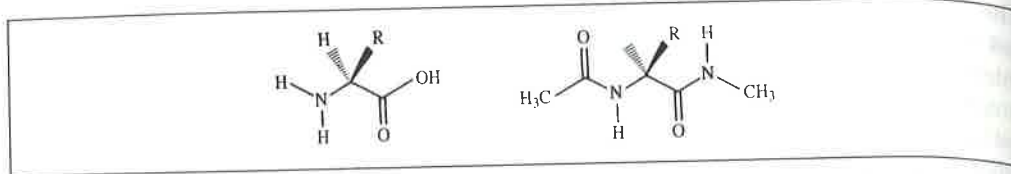


Fig. 4.21: The charges used for calculations on proteins are best derived using a suitable fragment for each amino acid that reflects the environment within the protein (right), rather than the isolated amino acid (left).

The charge sets obtained from electrostatic potential fitting can be highly dependent upon the basis set used to derive the wavefunction. Moreover, the charges do not always improve if a larger basis set is used. It is generally considered that the 6-31G* basis set gives reasonable results for calculations relevant to condensed phases. In many cases it is possible to scale the results of a calculation using a small basis set or even a lower level of theory (such as a semi-empirical calculation) to obtain results comparable with those of a high-level calculation. Of the various semi-empirical methods available, MNDO appears to give the best correspondence with the charges derived from *ab initio* calculations, and scaling factors have been determined by several research groups [Ferenczy *et al.* 1990; Luque *et al.* 1990; Bezler *et al.* 1990]. An additional complicating factor is that the charges obtained from electrostatic potential fitting will often depend upon the conformation for which the quantum mechanical calculation was performed [Williams 1990]. One solution is to perform a series of charge calculations for different conformations and then use a charge model in which each charge is weighted according to the relative population of that particular conformation as calculated from the Boltzmann distribution [Reynolds *et al.* 1992]. In a few charge models the charges vary continuously with the conformation [Rappé and Goddard 1991; Dinur and Hagler 1995].

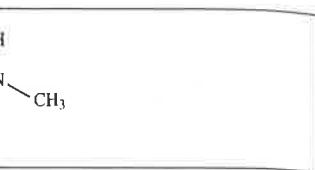
4.9.6 Rapid Methods for Calculating Atomic Charges

Some methods calculate atomic charges solely from information about the atoms present in the molecule and the way in which the atoms are connected. The great advantage of such methods is that they are very fast and can be used to calculate the charge distributions for large numbers of molecules (e.g. in a database). We will consider the Gasteiger and Marsili method [Gasteiger and Marsili 1980] as an example.

The Gasteiger–Marsili approach uses the concept of the *partial equalisation of orbital electronegativity*. Electronegativity is a concept well known to chemists, being defined by Pauling as ‘the power of an atom to attract electrons to itself’. Mulliken subsequently defined the electronegativity of an atom A as the average of its ionisation potential I_A and its electron affinity E_A :

$$\chi_A = \frac{1}{2}(I_A + E_A) \quad (4.38)$$

As Mulliken pointed out, the ionisation potential and electron affinity are specific to a given valence state of an atom, and therefore the electronegativities of an atom’s valence states would not be expected to be the same. This idea can be extended to the concept of orbital



variable fragment for each amino acid (left).

can be highly dependent upon charges do not always improve 6-31G* basis set gives reasonable results in many cases it is possible to obtain a lower level of theory comparable with those of a high-quality available, MNDO appears to give reasonable *ab initio* calculations, and scaling factors are used (Rappé *et al.* 1990; Luque *et al.* 1992). It is found that the charges obtained from MNDO are in good conformation for which the charges are used. One solution is to perform a charge model then use a charge model in the calculation of that particular conformation [Rappé and Goddard 1992]. In a few cases, the charges obtained from MNDO are in good conformation [Rappé and Goddard 1992].

about the atoms present in the molecule. The great advantage of such a method is that the charge distributions for the atoms can be considered the Gasteiger and Marsili method.

equalisation of orbital electronegativities, being defined by Pauling (1960) and subsequently defined the electronegativity I_A and its electron

(4.38)

affinity are specific to a given atom of an atom's valence states and are related to the concept of orbital

electronegativity, which is the electronegativity of a specific orbital in a given valence state. For example, an sp orbital has a higher electronegativity than an sp^3 orbital. The orbital electronegativity will also depend on the occupancy of the orbital; an empty orbital will be better able to attract an electron than an orbital with a single electron, which in turn will be better than an orbital with two electrons. The electronegativity of an orbital will also be affected by the charges in other orbitals. Gasteiger and Marsili assumed a polynomial relationship between the orbital electronegativity $\chi_{\mu A}$ of an orbital ϕ_μ in atom A and the charge Q_A on the atom A:

$$\chi_{\mu A} = a_\mu + b_{\mu A} Q_A + c_{\mu A} Q_A^2 \quad (4.39)$$

Values of the coefficients a , b and c were derived for common elements in their usual valence states (for example, for carbon there are different values for sp^3 , sp^2 and sp valence states).

Electrons flow from the less electronegative elements to the more electronegative ones. This flow of electrons results in a positive charge on the less electronegative atoms and a negative charge on the more electronegative atoms, and as such the flow acts to equalise the electronegativities. Total equalisation of electronegativity does not, however, lead to chemically sensible results. This effect is modelled in the Gasteiger and Marsili approach by an iterative procedure, in which less and less charge is transferred between bonded atoms at each step. The electron charge transferred from an atom A to an atom B (where B is more electronegative than A) in iteration k is given by:

$$Q^{(k)} = \frac{\chi_B^{(k)} - \chi_A^{(k)}}{\chi_A^+} \alpha^k \quad (4.40)$$

In Equation (4.40), $Q^{(k)}$ is the charge (in electrons) transferred; $\chi_A^{(k)}$ and $\chi_B^{(k)}$ are the electronegativities of the atoms A and B; χ_A^+ is the electronegativity of the cation of the less electronegative atom and α is a damping factor which is raised to the power k . Gasteiger and Marsili set α to $\frac{1}{2}$. The charge on each atom is initially assigned its formal charge. In each iteration, the electronegativities are calculated using Equation (4.39) and hence the charge to be transferred. The total charge on an atom at the end of each iteration is thus obtained by adding the charge transferred from all bonds to the atom to the value of the charge from the previous iteration. The damping factor α^k reduces the influence of the more electronegative atoms. This influence decreases with each iteration. With a damping factor of $\frac{1}{2}$ rapid convergence is achieved, usually within four or five steps.

A somewhat related method is the charge equilibration method of Rappé and Goddard [Rappé and Goddard 1991]. This is employed in the 'Universal Force Field' (UFF) [Rappé *et al.* 1992] as a general method for calculating charge distributions over a very wide range of molecules (in principle, the entire periodic table). An additional feature of the method is that the charges are dependent upon the molecular geometry and so can change during the course of a calculation such as a molecular dynamics simulation. The starting point for this approach is a series expansion of the energy of an isolated atom in terms of the charge:

$$v_A(q) = v_{A0} + q_A \left(\frac{\partial v}{\partial q} \right)_{A0} + \frac{1}{2} q_A^2 \left(\frac{\partial^2 v}{\partial q^2} \right)_{A0} + \dots \quad (4.41)$$

Truncating this expansion after second-order terms and considering three specific states (for charges of 0, +1 and -1) leads to:

$$v_{\Lambda}(0) = v_{\Lambda 0} \quad (4.42)$$

$$v_{\Lambda}(+1) = v_{\Lambda 0} + q_{\Lambda} \left(\frac{\partial v}{\partial q} \right)_{\Lambda 0} + \frac{1}{2} q_{\Lambda}^2 \left(\frac{\partial^2 v}{\partial q^2} \right)_{\Lambda 0} \quad (4.43)$$

$$v_{\Lambda}(-1) = v_{\Lambda 0} - q_{\Lambda} \left(\frac{\partial v}{\partial q} \right)_{\Lambda 0} + \frac{1}{2} q_{\Lambda}^2 \left(\frac{\partial^2 v}{\partial q^2} \right)_{\Lambda 0} \quad (4.44)$$

Now the energy of the positive species is the ionisation potential (*IP*) and the energy of the negative species is minus the electron affinity (*EA*). Combining these results gives:

$$\left(\frac{\partial v}{\partial q} \right)_{\Lambda 0} = \frac{1}{2} (IP + EA) = \chi_{\Lambda}^0 \quad (4.45)$$

$$\left(\frac{\partial^2 v}{\partial q^2} \right)_{\Lambda 0} = IP - EA \quad (4.46)$$

As usual, χ_{Λ} is the electronegativity. Rappé and Goddard suggested that for a neutral atom with a singly occupied orbital the difference between the ionisation potential and the electron affinity would correspond to the Coulomb repulsion between two electrons placed in that orbital (the orbital would be unoccupied in the positive ion and doubly occupied in the negative species). Writing this difference as $J_{\Lambda\Lambda}^0$ (referred to as the *idempotential*) leads to:

$$v_{\Lambda}(q) = v_{\Lambda 0} + \chi_{\Lambda}^0 q_{\Lambda} + \frac{1}{2} J_{\Lambda\Lambda}^0 q_{\Lambda}^2 \quad (4.47)$$

Both the electronegativity and the idempotential can be derived from atomic data, though such atomic data generally need to be corrected for use in molecular systems. In order to use these equations to derive a set of charges for a molecule we first consider the total electrostatic energy of the system:

$$\mathcal{V}(q_1 \cdots q_N) = \sum_{i=1}^N (v_{\Lambda 0} + \chi_{\Lambda}^0 q_{\Lambda} + \frac{1}{2} J_{\Lambda\Lambda}^0 q_{\Lambda}^2) + \sum_{\Lambda=1}^N \sum_{B=\Lambda+1}^N q_{\Lambda} q_B J_{\Lambda B} \quad (4.48)$$

In this equation $J_{\Lambda B}$ represents a formulation of the Coulomb energy between charges q_{Λ} and q_B . For well-separated atoms a simple $1/r$ dependency is used. However, this simple Coulomb law is not appropriate for atoms whose charge distributions overlap. In such circumstances (which particularly arise for bonded atoms) there is a significant shielding correction. This shielding correction is a Coulomb integral (Equation (2.107)), with the atomic density being described using a single Slater type orbital whose precise form depends on the nature (ns, np or nd) of the outer valence orbital together with the covalent radius.

In order to derive the actual charges we first incorporate the factors $J_{\Lambda\Lambda}^0$ (the limiting value of $J_{\Lambda\Lambda}$ as the distance tends to zero) into the double summation in Equation (4.48):

$$\mathcal{V}(q_1 \cdots q_N) = \sum_{\Lambda=1}^N (v_{\Lambda 0} + \chi_{\Lambda}^0 q_{\Lambda}) + \frac{1}{2} \sum_{\Lambda=1}^N \sum_{B=1}^N q_{\Lambda} q_B J_{\Lambda B} \quad (4.49)$$

dering three specific states (for

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$$\left(\frac{r'}{2}\right)_{A0}$$

(4.43)

$$\left(\frac{r'}{2}\right)_{A0}$$

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$$\sum_{B=1}^N q_A q_B J_{AB} \quad (4.49)$$

We can then take the derivative of the energy with respect to q_A , which leads to:

$$\frac{\partial \psi}{\partial q_A} = \chi_A^0 + \sum_{A=1}^N q_B J_{AB} = \chi_A^0 + J_{AA}^0 q_A + \sum_{B=1; B \neq A}^N q_B J_{AB} \quad (4.50)$$

The derivative of the energy with respect to the charge is an atomic chemical potential; at equilibrium these chemical potentials will all be equal. The electrons move from regions of low electronegativity (high electrochemical potential) to regions of high electronegativity (low electrochemical potential). A further constraint is that the sum of the atomic charges must sum to the total charge on the molecule. These conditions enable a set of simultaneous equations to be written (subject to per-element limits on the charge on any given atom).

The presence of the $q_A q_B$ term with its implied distance dependency means that the charges depend upon the molecular geometry. Thus, should the conformation of a molecule change the atomic charges will also change. Just three parameters are required for each atom in the system (the electronegativity, the idempotential and the covalent radius).

4.9.7 Beyond Partial Atomic Charge Models

Most of the charge models that we have considered so far place the charge on the nuclear centres. Atom-centred charges have many advantages. For example, the electrostatic forces due to charge-charge interactions then act directly on the nuclei. This is important if one wishes to calculate the forces on the nuclei as is required for energy minimisation or a molecular dynamics simulation. Nuclear-centred charges do nevertheless suffer from some drawbacks. In particular, they assume that the charge density about each atom is spherically symmetrical. However, an atom's valence electrons are often distributed in a far from spherical manner, especially in molecules that contain features such as lone pairs and π electron clouds above aromatic ring systems.

4.9.8 Distributed Multipole Models

One way to represent the anisotropy of a molecular charge distribution is to use *distributed multipoles*. In this model, point charges, dipoles, quadrupoles and higher multipoles are distributed throughout the molecule. These distributed multipoles can be determined in various ways but the distributed multipole analysis (DMA) model of A J Stone [Stone 1981; Stone and Alderton 1985] is probably the best-known example. The DMA method calculates the multipoles from a quantum mechanics wavefunction defined in terms of Gaussian basis functions. As we saw in Section 2.6, the overlap between two Gaussian functions can be represented by another Gaussian located at a point (P) along the line that connects them. Each product of basis functions $\phi_\mu \phi_\nu$ thus corresponds to a charge density at P. This density can be expressed as a multipole expansion about P. The highest multipole moment in the local expansion depends upon the basis set used; no multipole moment higher than the sum of the angular quantum numbers of the basis set is possible. Thus, when using a basis set that contains just s and p functions there will be local multipoles no higher than the quadrupole. The crucial feature is that the local multipole expansion

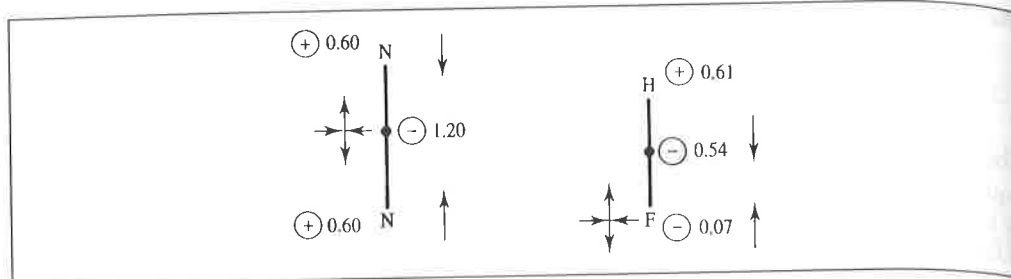


Fig. 4.22: Distributed multipole models for N_2 and HF. (Figure adapted from Stone A J and M Alderton 1985, *Distributed Multipole Analysis Methods and Applications*, Molecular Physics 56:1047–1064.)

about P can be represented as a multipole expansion about another nearby point S. In the distributed multipole approach, a set of site points is chosen and then the local multipole expansion for each pair of basis functions is 'moved' from the relevant point P to one of the sites S.

There are no limitations on the number or location of the multipole sites S; a natural set to use is obtained by placing a site point on each atomic nucleus. In some applications (especially for small molecules) additional sites are defined at the centres of bonds. For example, Stone derived a distributed multipole model for nitrogen from a Dunning [5s4p2d] basis set with two polarisation functions. This model contains charges of +0.60 on the nuclei and a charge of -1.20 at the centre of the bond, together with a dipole on each of the two nuclei and a quadrupole located at the centre of the bond (see Figure 4.22). For HF charges are placed on the two nuclei and at the centre of the bond with a dipole and a quadrupole on the fluorine and a small dipole at the centre of the bond (Figure 4.22). In larger molecules not every atom may be given a site, such as hydrogen atoms bonded to apolar atoms. It is also possible to restrict the order of the multipole expansion at a given atom so that, for example, only a charge component would be present on a polar hydrogen with the higher moments being represented by multipoles on the atom to which it is bonded. An important consideration when choosing the multipole sites is that, when a local multipole expansion is moved, the resulting multipole expansion is no longer a truncated series. However, the smaller the distance between P and the corresponding site point S, the quicker the series converges. In practice, therefore, each local multipole moment expansion is either moved to the nearest site point or is divided between the two nearest site points when they are equally close. With a basis set that contains just s and p functions and multipole sites at the atomic nuclei, it is usually found that the distributed multipole series converges rapidly after the quadrupole term. The multipoles themselves can vary considerably with the basis set used to perform the *ab initio* calculation, but the various electronic properties derived from them usually do not change much.

The distributed multipole model automatically includes non-spherical, anisotropic effects due to features such as lone pairs or π electrons. The original applications of the DMA approach were to small molecules such as diatomics and triatomics. The method has since been used to develop models for nuclei acids and for peptides and has even been applied to the undecapeptide cyclosporin [Price *et al.* 1989], which contains 199 atoms (the

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quantum mechanical calculation on this molecule used 1000 basis functions). However, distributed multipole models have not yet been widely incorporated into force fields, not least because of the additional computational effort required. It can be complicated to calculate the atomic forces with the distributed multipole model; in particular, multipoles that are not located on atoms generate torques, which must be analysed further to determine the forces on the nuclei.

4.9.9 Using Charge Schemes to Study Aromatic-Aromatic Interactions

The attractive interactions between molecules containing π systems have long been studied by theoreticians and experimentalists. Such systems are involved in a variety of phenomena, including the stacking of the nucleic acid bases in DNA, the packing of aromatic molecules in crystals and interactions between amino acid side chains in proteins. A variety of orientations are observed for aromatic dimers, ranging from edge-on, T-shaped structures to face-to-face structures (Figure 4.23). Within these two families the molecules can move relative to each other, so that, for example, in a face-to-face arrangement the atoms are overlaid or are staggered. In the T-shaped structure the large quadrupole moments of the benzene molecules adopt their most favourable orientation.

One very simple model of the interactions in such systems was devised by Hunter and Saunders [Hunter and Saunders 1990], who wanted to explain the stacking behaviour of aromatic systems such as the porphyrins shown in Figure 4.24. It is experimentally observed that these molecules adopt a cofacial arrangement with their centres offset as shown. Hunter and Saunders placed point charges not only at the nuclei but also at locations above and below each atom, perpendicular to the plane of the ring. Thus in benzene each carbon atom was given a charge of $+1$ and also had two associated charges of $-\frac{1}{2}$ above and below the ring (Figure 4.25). The electrostatic interaction between two ring systems is

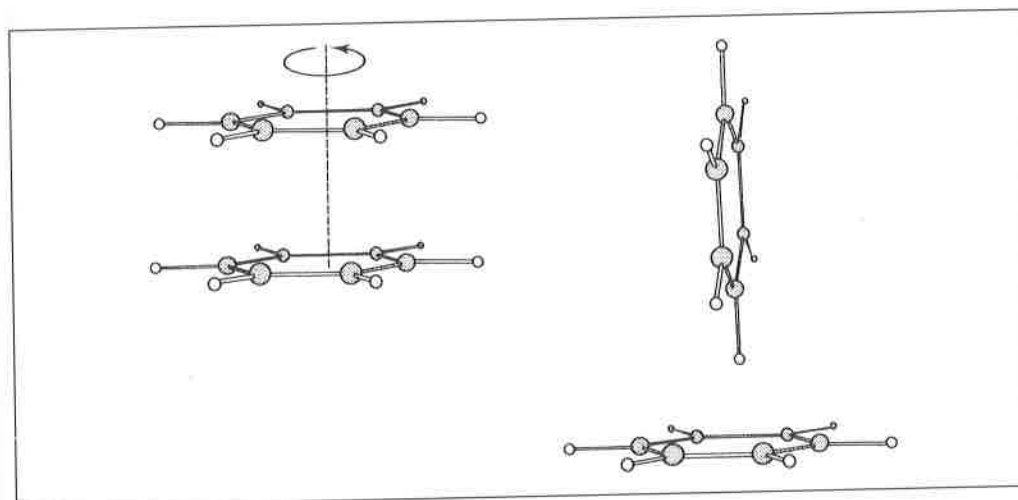


Fig. 4.23: Face-to-face (left) and T-shaped (right) orientations of the benzene dimer.

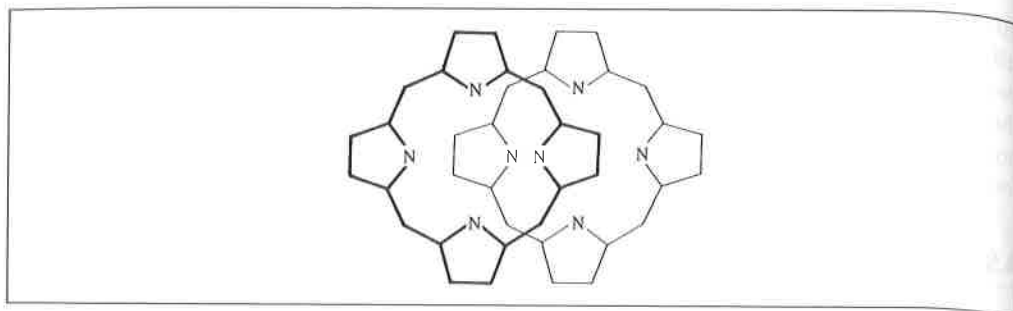


Fig. 4.24: Porphyrin system typical of those studied by Hunter and Saunders [Hunter and Saunders 1990].

calculated in the usual way by summing the charge-charge interactions using Coulomb's law. A major advantage of the Hunter-Saunders approach is its computational simplicity. Moreover, it can be extended to cover a wide range of atom types and so applied to many systems [Vinter 1994] with particular emphasis on simulating DNA [Hunter 1993, Packer *et al.* 2000]. Hunter and Saunders summarised the results of their investigations on porphyrins in three rules:

1. π - π repulsion dominates in a face-to-face geometry;
2. π - σ attraction dominates in an edge-on geometry;
3. π - σ attraction dominates in an offset π -stacked geometry.

The interactions between aromatic systems have also been studied using point charge models, central multipoles and distributed multipoles. Fowler and Buckingham examined homodimers of *sym*-triazine and 1,3,5-trifluorobenzene (Figure 4.26) [Fowler and Buckingham 1991]. They were particularly keen to calculate how the electrostatic energy changed as the rings were twisted in the face-to-face geometry. All but one of the energy models suggested that the staggered orientations were the arrangements of minimum energy, but the energy difference between the eclipsed and staggered structures varied widely, depending upon the model. The central multipole model was found to be ineffective due to convergence problems. Three different point-charge models were considered, all of

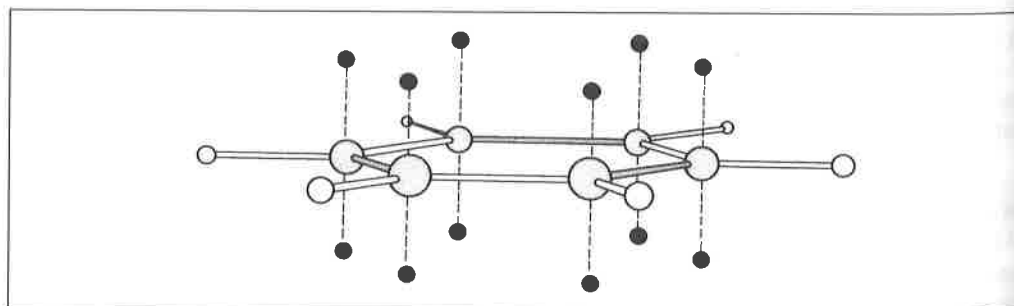


Fig. 4.25: Anisotropic model of benzene developed by Hunter and Saunders [Hunter and Saunders 1990].

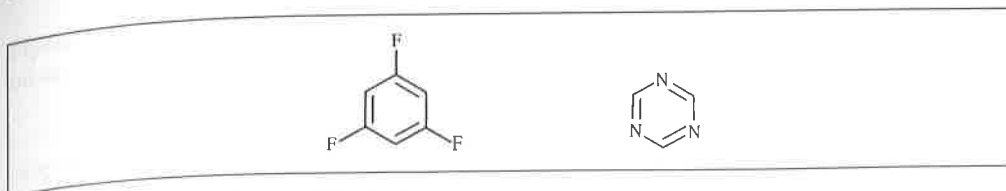


Fig. 4.26: Sym-triazine and 1,3,5-trifluorobenzene.

which gave acceptable energy curves. The distributed multipole model also performed well, being comparable to the most accurate of the point-charge models.

4.9.10 Polarisation

Our discussion of electronic effects has concentrated so far on 'permanent' features of the charge distribution. Electrostatic interactions also arise from changes in the charge distribution of a molecule or atom caused by an external field, a process called *polarisation*. The primary effect of the external electric field (which in our case will be caused by neighbouring molecules) is to induce a dipole in the molecule. The magnitude of the induced dipole moment μ_{ind} is proportional to the electric field E , with the constant of proportionality being the polarisability α :

$$\mu_{\text{ind}} = \alpha E \quad (4.51)$$

The energy of interaction between a dipole μ_{ind} and an electric field E (the induction energy) is determined by calculating the work done in charging the field from zero to E , using the following integral:

$$v(\alpha, E) = - \int_0^E dE \mu_{\text{ind}} = - \int_0^E dE \alpha E = -\frac{1}{2} \alpha E^2 \quad (4.52)$$

In strong electric fields contributions to the induced dipole moment that are proportional to E^2 or E^3 can also be important, and higher-order moments such as quadrupoles can also be induced. We will not be concerned with such contributions.

For isolated atoms, the polarisability is isotropic – it does not depend on the orientation of the atom with respect to the applied field, and the induced dipole is in the direction of the electric field, as in Equation (4.51). However, the polarisability of a molecule is often anisotropic. This means that the orientation of the induced dipole is not necessarily in the same direction as the electric field. The polarisability of a molecule is often modelled as a collection of isotropically polarisable atoms. A small molecule may alternatively be modelled as a single isotropic polarisable centre.

Let us consider the electric field due to a dipole μ aligned along the z axis. The magnitude of the electric field at a point P due to the dipole (see Figure 4.27) is:

$$E(r, \theta) = \frac{\mu \sqrt{1 + 3 \cos^2 \theta}}{4\pi\epsilon_0 r^3} \quad (4.53)$$

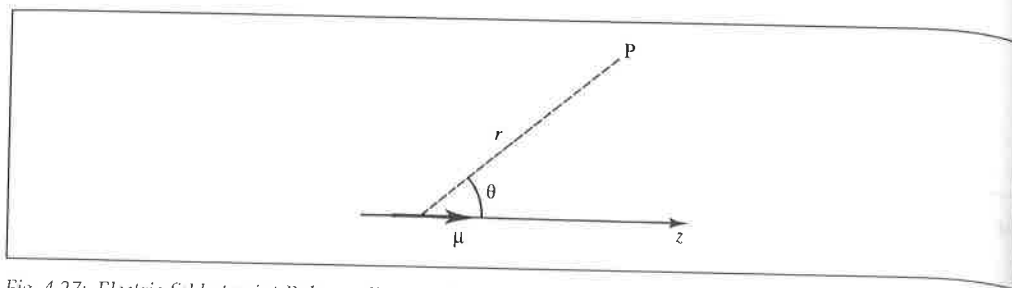


Fig. 4.27: Electric field at point P due to dipole at the origin.

The induction energy with another molecule of polarisability α placed at P is therefore

$$v(r, \theta) = -\alpha \mu^2 \frac{1 + 3 \cos^2 \theta}{(4\pi\epsilon_0 r^3)^2} \quad (4.54)$$

The interaction between a dipole and an induced dipole is independent of the disorienting effect of thermal motion, whereas the dipole-dipole interaction between two permanent dipoles does vary with the relative orientation of the two dipoles. This is because the induced dipole follows the direction of the permanent dipole even as the molecules change their orientations as a consequence of molecular collisions.

An important consideration when modelling polarisation effects is that the dipole induced on a molecule (A) will affect the charge distribution of another molecule (B). The electric field at A due to the dipole(s) on B will in turn be affected. The presence of other molecules can also influence the interaction. Consider the polarisation interaction between a polar molecule and a neighbour (Figure 4.28). A third molecule may reduce the size of the electric field on the second molecule and so lower the induction energy. This type of three-body effect will be particularly significant when polarisable atoms are close to polar groups. Polarisation is a cooperative effect and, as such, is modelled using a set of coupled equations which are typically solved iteratively. Initially, the induced dipoles are set to zero. An initial approximation to each induced dipole is then calculated from the permanent charges (i.e. partial atomic charges). The electric field due to these induced dipoles is then added to the electric field from the permanent charges. This gives a refined value of the electric field from which a new induced dipole can be determined. The calculation continues until the induced dipoles do not change significantly between iterations.

A variety of schemes for including polarisation into molecular mechanics force fields have been devised. One approach is to model the polarisation effects at the atomic level, with

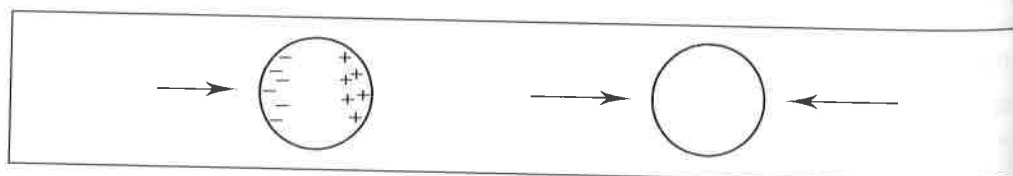


Fig. 4.28: The polarisation interaction between a dipole and a polarisable molecule can be affected by the presence of a second dipole (right) and is therefore a many-body effect.

dipoles being induced on each atom [Dang *et al.* 1991]. The magnitude of the dipole induced on an atom i is given by:

$$\mu_{\text{ind},i} = \alpha_i E_i \quad (4.55)$$

α_i is the atomic polarisability, assumed to be isotropic. Appropriate values of α_i have been determined for various systems. The electric field, 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:

$$E_i = \sum_{j \neq i} \frac{q_j \mathbf{r}_{ij}}{r_{ij}^3} + \sum_{j \neq i} \frac{\mu_j}{r_{ij}^3} \left(3 \frac{\mathbf{r}_{ij} \mathbf{r}_{ij}}{r_{ij}^2} - \mathbf{1} \right) \quad (4.56)$$

\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

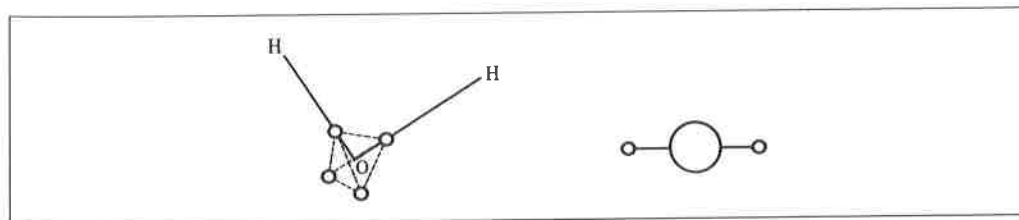


Fig. 4.29: Polarisable models of water and ions developed by Sprik and Klein. (Figure adapted from Sprik M 1993. *Effective Pair Potentials and Beyond*. In *Computer Simulation in Chemical Physics*, Allen M P, D J Tildesley (Editors). Dordrecht, Kluwer).

manner during the simulation rather than having to determine a new set of charges at each iteration of the procedure. This fluctuating charge model includes intramolecular interactions and so the traditional Coulombic $1/r$ expression is not appropriate. Rather, the charges are replaced by charge distributions (formulated as Slater s orbitals) whose interaction is calculated using a Coulomb integral expression. This interaction is effectively identical to the standard Coulomb expression for intermolecular interactions, only differing for the intramolecular contribution.

One feature of this oscillating charge model is that it requires rather less computational effort than traditional polarisation models. It also implicitly preserves the higher-order multipole terms, which need to be explicitly incorporated in some of the alternative approaches. Ions are represented by two partial charges (which sum to the required integral ionic charge) which are connected by a harmonic spring. The mass of one of these two species is made much greater than the other so that the heavier site remains near the centre of mass as the spring oscillates. This particular model has been used for simulations of pure liquid water [Rick *et al.* 1994], the solvation of amides [Rick and Berne 1996] and to investigate the effects of polarisability on the hydration of the chloride ion in water clusters [Stuart and Berne 1996]. These calculations predicted that the chloride ions were located on the outside of the clusters, even when they contained more than 100 water molecules. This was in contrast to equivalent calculations using a non-polarisable model, the difference being attributed to the presence of fluctuations in the dipole strengths of the water molecules in the cluster, which are, as a consequence, more mobile.

Due to the computational expense, polarisation effects are often included in a calculation only when their effect is likely to be significant, such as simulations of ionic solutions. These systems usually contain atoms or ions and small molecules only. It is important to be aware of the following problem when using atomic polarisabilities. Consider a diatomic molecule. The application of an external field will induce dipoles on both atoms. The dipole on one atom will also contribute to the electric field at the other atom, and thereby influence its induced dipole, but the model takes no account of the fact that the charge distributions on the two atoms are inherently linked. For this reason (and for reasons of computational efficiency) it is common to treat small molecules such as water as single polarisable centres when calculating polarisation effects.

4.9.11 Solvent Dielectric Models

All of the formulae that we have written for electrostatic energies, potentials and forces have included the permittivity of free space, ϵ_0 . This is as one would expect for species acting in a vacuum. However, under some circumstances a different dielectric model is used in the equations for the electrostatic interactions. This is often done when it is desired to mimic solvent effects, without actually including any explicit solvent molecules. One effect of a solvent is to dampen the electrostatic interactions. A very simple way to model this damping effect is to increase the permittivity, most easily by using an appropriate value for the relative permittivity in the Coulomb's law equation (i.e. $\epsilon = \epsilon_0 \epsilon_r$). An alternative approach is to make the dielectric dependent upon the separation of the charged species; this gives rise

determine a new set of charges at each model includes intramolecular interaction is not appropriate. Rather, the interaction is formulated as Slater s orbitals) whose expression. This interaction is effectively intramolecular interactions, only differing

requires rather less computational effort than the higher-order multipole expansion of the alternative approaches. Ions are assigned to the required integral ionic charge) of one of these two species is made remains near the centre of mass as the model for simulations of pure liquid water [Berne 1996] and to investigate the effects of ions in water clusters [Stuart and Berne 1996]. Ions were located on the outside of water molecules. This was in contrast to the model, the difference being attributed to the distribution of the water molecules in the cluster,

are often included in a calculation such as simulations of ionic solutions. All molecules only. It is important to consider polarisabilities. Consider a diatomic molecule with dipoles on both atoms. The dipole moment of one atom, and thereby influence the other atom, and thereby influence the fact that the charge distributions are different (and for reasons of computational efficiency) is water as single polarisable centres

energies, potentials and forces have been calculated. One would expect for species acting in a dielectric model is used in the calculation done when it is desired to mimic the behaviour of solvent molecules. One effect of a dielectric is to dampen the interaction between charges in a simple way to model this damping by using an appropriate value for the dielectric constant ($\epsilon = \epsilon_0 \epsilon_r$). An alternative approach is to use a distance-dependent dielectric; this gives rise

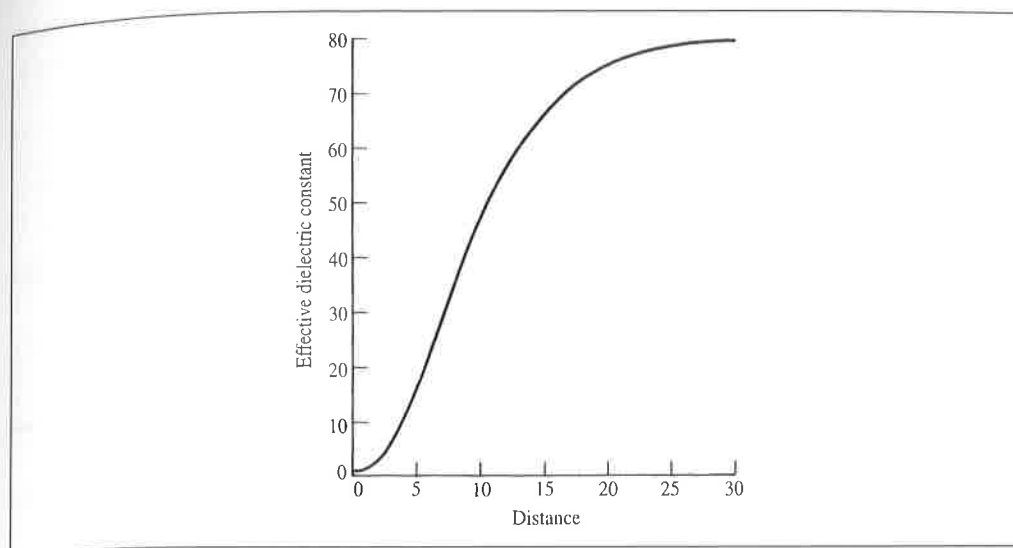


Fig. 4.30: A sigmoidal dielectric model smoothly varies the effective permittivity from 80 to 1 as shown.

to the so-called distance-dependent dielectric models. The simplest implementation of a distance-dependent dielectric is to make the relative permittivity proportional to the distance. The interaction energy between two charges q_i and q_j then becomes:

$$w(r) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r^2} \quad (4.57)$$

The simple distance-dependent dielectric has no physical basis and so it is not generally recommended, except when no alternative is possible. More sophisticated distance-dependent functions can also be employed. Many of these have an approximately sigmoidal shape in which the relative permittivity is low at short distances and then rises towards the bulk value at long distances. One example of such a function is [Smith and Pettit 1994]:

$$\epsilon_{\text{eff}}(r) = \epsilon_r - \frac{\epsilon_r - 1}{2} [(rS)^2 + 2rS + 2] e^{-rS} \quad (4.58)$$

The value of ϵ_{eff} varies from a value of 1 at zero separation to ϵ_r (the bulk permittivity of the solvent) at large distances, in a manner determined by the parameter S (which is typically given a value between 0.15 \AA^{-1} and 0.3 \AA^{-1} ; Figure 4.30). Sigmoidal functions give better behaviour than the simple distance-dependent dielectric model. However, it may be difficult to choose the appropriate value for the bulk dielectric ϵ_r when performing calculations on large solutes, as the shortest distance between two charges may be through the solute molecule rather than through the solvent (Figure 4.31).

The polarisation term can be a major contributor to the free energy of solvation of a solute, and a variety of schemes have been devised to incorporate such effects where the solvent is modelled as a continuum. We shall discuss these methods in more detail in Sections 11.9–11.12.

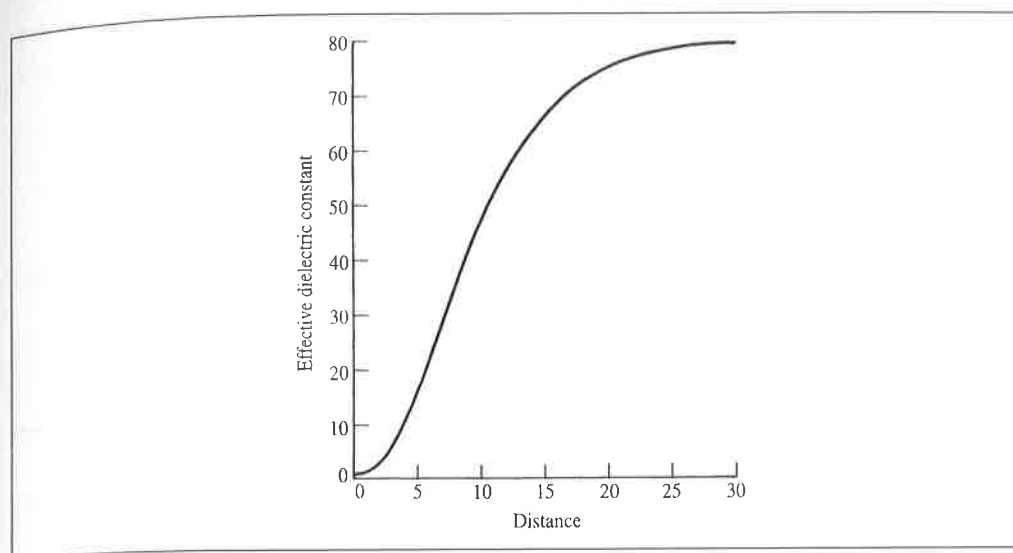


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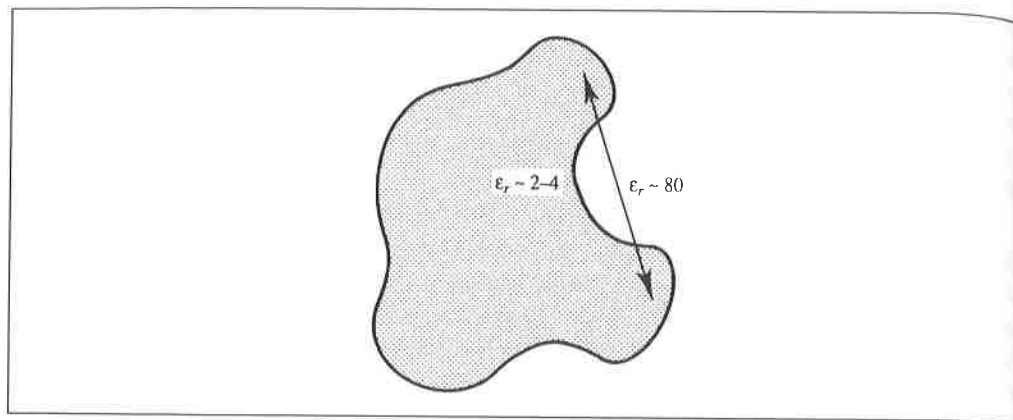


Fig. 4.31: A line joining two points may pass through regions of different permittivity.

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 \AA 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

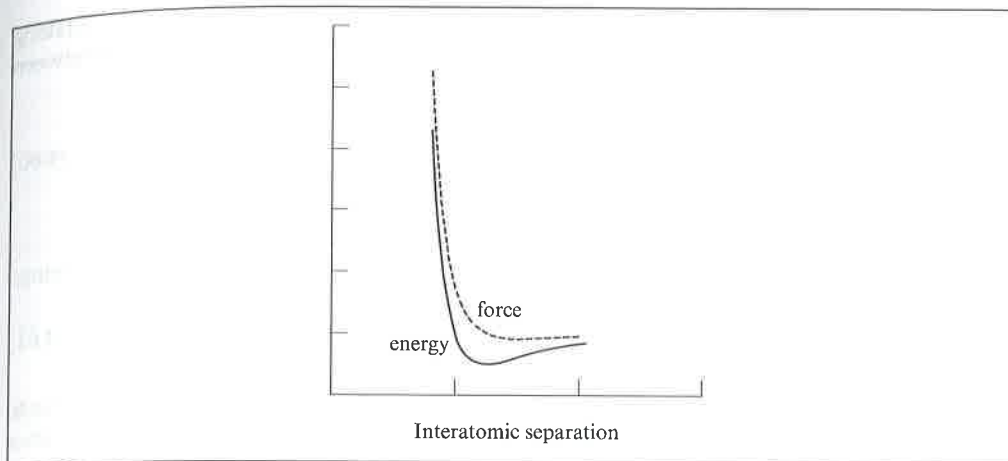


Fig. 4.32: The interaction energy and the force between two argon atoms.

interactions in a system. Elements of a rare gas atom dipole interactions. But could rare gases have behaviour? Deviations from s, thus the forces that forces.

using a molecular beam with the separation in a behaviour. The essential at infinite distance (and variation is reduced, the approximately 3.8 Å for ses further. The force potential energy with elements have been used including gas imperfec-transport properties.

between attractive and repulsive forces act at London first showed anics [London 1930] The dispersive force

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:

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

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

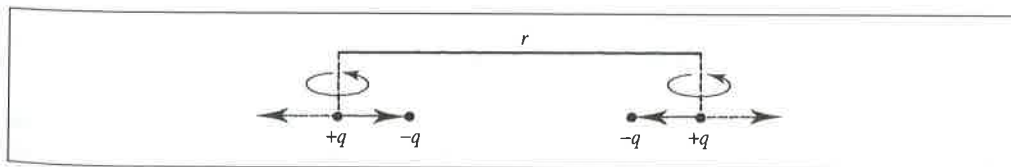


Fig. 4.33: The Drude model for dispersive interactions. (Figure adapted from Rigby M, E B Smith, W A Wakeham and G C Maitland 1986. *The Forces Between Molecules*. Oxford, Clarendon Press.)

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):

$$v(r) = -\frac{\alpha^4 \hbar \omega}{2(4\pi\epsilon_0)^2 r^6} \quad (4.60)$$

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:

$$v(r) = -\frac{3\alpha^4 \hbar \omega}{4(4\pi\epsilon_0)^2 r^6} \quad (4.61)$$

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:

$$v(r) = \frac{C_6}{r^6} + \frac{C_8}{r^8} + \frac{C_{10}}{r^{10}} + \dots \quad (4.62)$$

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 \AA , 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 energy curve.

expression that can be evaluated. The value of the constant ϵ is determined by the van der Waals interaction energy at the following form:

The Lennard-Jones potential energy curve is shown graphically in terms of the internuclear distance r . At this separation the distance is zero and the energy can thus also be written as:

or

A is equal to ϵ .

The Lennard-Jones potential energy curve shows the repulsive part of the curve as a dashed line. The r^{-6} variation is the theoretical treatment of the strong theoretical

as the molecules approach (along the interaction energy between by (see Appendix 4.1):

(4.60)

n varies as $1/r^6$.

dimensions, the result being:

(4.61)

if higher-order terms, due to are included as well as other de model is more properly

(4.62)

ive interaction. Despite its just the C_6 term is included % too small.

ween a pair of argon atoms um mechanical origin and normally prohibits any two umbers. The interaction is repulsive forces are often ces. The effect of exchange ns by forbidding them to e reduced electron density opletely shielded nuclei. At as $1/r$ due to this nuclear lly, as $\exp(-2r/a_0)$, where

ns and molecules can be ns are far from trivial, d we require a means to ising a simple empirical

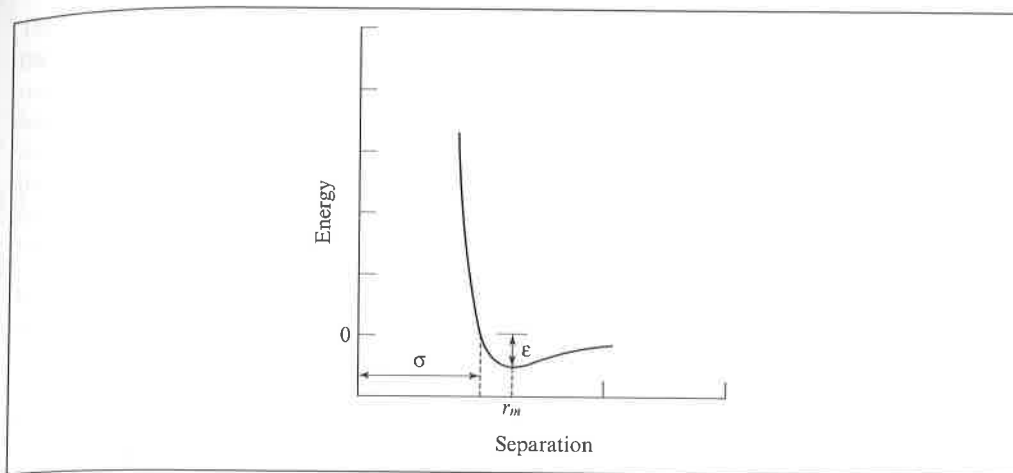


Fig. 4.34: The Lennard-Jones potential.

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:

$$v(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] \quad (4.63)$$

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. $\partial v / \partial r = 0$), from which it can easily be shown that $r_m = 2^{1/6}\sigma$. We can thus also write the Lennard-Jones 12-6 potential function as follows:

$$v(r) = \epsilon \{ (r_m/r)^{12} - 2(r_m/r)^6 \} \quad (4.64)$$

or

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

A is equal to ϵr_m^{12} (or $4\epsilon\sigma^{12}$) and C is equal to $2\epsilon r_m^6$ (or $4\epsilon\sigma^6$).

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

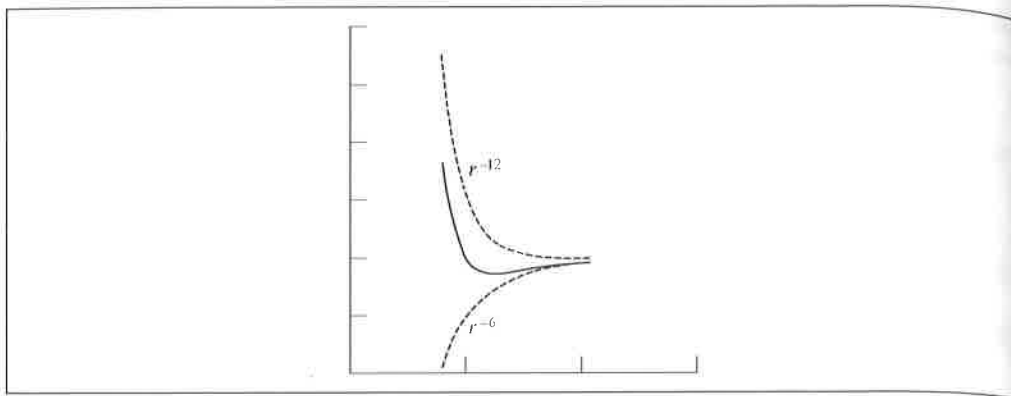


Fig. 4.35: The Lennard-Jones potential is constructed from a repulsive component (αr^{-12}) and an attractive component (αr^{-6}).

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:

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

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:

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

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:

$$v(r) = \varepsilon_{ij} \left(\frac{1.07r_{ij}^*}{r_{ij} + 0.07r_{ij}^*} \right)^7 \left(\frac{1.12r_{ij}^{*7}}{r_{ij}^7 + 0.12r_{ij}^{*7}} - 2 \right) \quad (4.68)$$

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:

$$r_{ii}^* = A_i \alpha_i^{1/4} \quad (4.69)$$

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*:

$$v(r) = \varepsilon \left[\frac{6}{\alpha - 6} \exp[-\alpha(r/r_m - 1)] - \frac{\alpha}{\alpha - 6} \left(\frac{r_m}{r} \right)^6 \right] \quad (4.70)$$

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

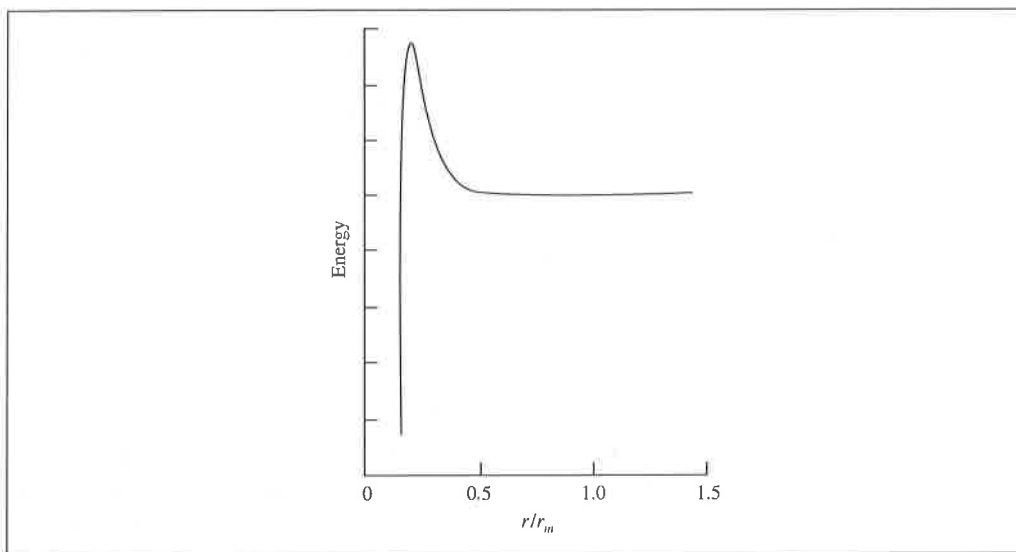


Fig. 4.36: A drawback of the Buckingham potential is that it becomes steeply attractive at short distances.

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

$$w(r) = -2.25\varepsilon(r_m/r)^6 + 8.28 \times 10^5 \varepsilon \exp(-r/0.0736r_m) \quad (4.71)$$

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, 8.28×10^5 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:

$$\sigma_{AB} = \frac{1}{2}(\sigma_{AA} + \sigma_{BB}) \quad (4.72)$$

$$\varepsilon_{AB} = \sqrt{\varepsilon_{AA}\varepsilon_{BB}} \quad (4.73)$$

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

$$r_{AB}^* = R_{AA}^* + R_{BB}^* \quad (4.74)$$

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].

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$$r_{ij}^*/0.0736r_m) \quad (4.71)$$

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(4.74)

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OPLS force field falls into

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

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

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:

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

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:

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

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

$$\epsilon_{ij} = \frac{1}{2} \frac{kG_i G_j C_{6ij}}{r_{ij}^{*6}} = \frac{181.16 G_i G_j \alpha_i \alpha_j}{(\alpha_i/N_i)^{1/2} + (\alpha_j/N_j)^{1/2}} \frac{1}{r_{ij}^{*6}} \quad (4.78)$$

Here, k is a factor which converts to units (kcal/mol in this case where the distances are in Å and the polarisabilities in Å³). 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