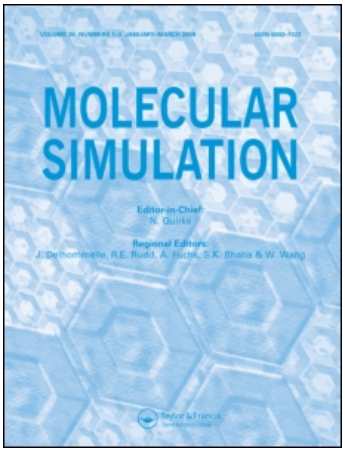


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# Is the Isotropic Atom—Atom Model Potential Adequate?

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# IS THE ISOTROPIC ATOM–ATOM MODEL POTENTIAL ADEQUATE?*

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We discuss some of the problems that have frustrated the development of reliable model intermolecular potentials for polyatomic molecules. In particular, the usual assumption of an isotropic atom–atom model potential is analysed, and evidence for its inadequacies is presented. A new approach to designing model potentials, an anisotropic site–site model, is introduced by describing several applications to both small and organic molecules, including molecular dynamics and Monte Carlo simulations. The anisotropy required in an atom–atom potential can be directly linked to the non-spherical features in the valence electron distribution, such as lone pairs and $\pi$ electrons. An accurate electrostatic model for these effects can be constructed from a distributed multipole analysis of the *ab initio* wavefunction. The empirically required forms of anisotropy in the repulsion potential can also be qualitatively linked to the molecular electron density difference map. Thus, consideration of the molecular bonding can be a useful indication of how to construct adequate model intermolecular pair potentials.

KEY WORDS: Intermolecular potentials, molecular simulation, distributed multipole analysis, atom–atom potential



## 1. INTRODUCTION

A major concern for anyone involved in molecular simulations of real materials is whether the model intermolecular pair potential, the fundamental scientific input, is sufficiently accurate for the conclusions of the study to be valid. This often leads to interesting details of the simulation results being discussed with the caveat that they could be artifacts of the model potential. The current advances in computer technology are rapidly removing the computational constraints on simulation work, and so our justified lack of confidence in model potentials is now the major barrier to progress in this field.

Simulations of the physical properties of argon enjoy almost unique confidence in the model potential, as the state-of-the-art potentials [1] can account for a very wide range of experimental data. Thus the errors in the model for the forces on the atoms that can be used in simulations are probably at the level of the many-body terms. However, the form of the Barker-Pompe model potential that can represent the argon intermolecular potential,

$$U(R)/\varepsilon = \exp[\alpha(1 - R/\varrho)] \sum_{i=0}^{5} A_i(R/\varrho - 1)^i + \sum_{j=0}^{2} C_{2j+6}/(\delta + (R/\varrho)^{2j+6}), \quad (1)$$

contains 11 parameters in addition to the well depth $\varepsilon$ and minimum energy separation $\varrho$, indicating that a large number of potential parameters are required to give the model potential sufficient flexibility to describe the actual pair potential. Since the

*Invited Article

intermolecular potential for a polyatomic molecule is also a function of the relative orientation, introducing up to five additional variables, and the molecule may contain more than one type of atom, it seems likely that, when potentials for polyatomics reach the same accuracy as the argon potential, they will contain dozens of parameters.

The intermolecular potentials of polyatomics include additional effects arising from the fact that the molecules are not spherical, namely the long-range electrostatic interaction between the undistorted molecular charge clouds, and the induction energy arising from the distortion (polarization) of one molecular charge cloud in the electric field arising from the other. The importance of the electrostatic energy, which can dominate the orientation dependence of the potential, has recently been highlighted by advances in our ability to model electrostatic interactions, which are discussed in §3. The induction energy is highly non-additive, making it impossible for this contribution to be modelled accurately within the pairwise additivity approximation. Hence most simulations use "effective" potentials, which have been fitted to some condensed phase data, and will include some imprecisely defined contribution from the many-body terms.

A further problem in determining accurate and reliable potentials for polyatomics is that extracting information about the potential from experimental data is more difficult than for monatomics. Some data, such as the second virial coefficients, depend on some orientational average of the potential, and so could be reproduced well by a potential with completely the wrong orientation dependence. Other experimental properties that depend on the dynamics of molecular collisions, such as transport data, are much more difficult to calculate for polyatomics than for atoms because of the possibility of inelastic collisions. Approximate calculations of transport properties can be used to test a proposed potential, but the calculations are too expensive to be used in an iterative fitting procedure. In contrast, the crystal structures of polyatomics have less symmetry than those of the rare gases, and so contain more information that can be used in deriving an effective potential. However, solid state properties sample the potential, and its derivatives, only around a very limited set of relative orientations of the molecules, and so a potential derived from such properties may extrapolate poorly to other orientations unless the model potential has an appropriate functional form.

These problems explain why progress in determining accurate intermolecular potentials for polyatomics is so far behind that for the rare gases. Indeed, a recent careful attempt to derive an intermolecular potential for nitrogen [2] that could reconcile several diverse pieces of experimental and theoretical data was appropriately entitled "Towards an intermolecular potential for nitrogen".

The simulation community should not, however, restrict its attention to systems like argon until comparably reliable potentials are available for other systems. Computer simulation is too powerful a technique to be kept in storage awaiting progress in the quantification of intermolecular forces. Indeed, feedback from the successes and disappointments of simulations provides important pieces of the jigsaw that will eventually form the picture of the accurate potential. Hence, the key question about any simulation is always whether the model potential is good enough for the purposes of the simulation.

Simple potentials will be good enough for many purposes. An isotropic atom–atom Lennard-Jones potential is not much more than a softened version of a hard-sphere model of the molecular shape, with a dispersion term that will tend to optimize the

closeness of the intermolecular packing. However, every undergraduate chemist has learnt a great deal from physical space-filling molecular models that aid thinking in three dimensions. Molecular graphics systems are powerful research tools because they can be used to "build" such models quickly, and allow them to be manipulated without the interference of gravity.

Nevertheless, anyone who plans a simulation of a more subtle property, or is seeking quantitative agreement with experimental data, knows that the first hurdle is either the choice between rival model potentials, or the problem of developing one for the project. The choice between rival model potentials should not be determined solely by the claims of the developers, as those most experienced in the black art of potential development generally have lower expectations of the reliability of their models in other applications. Indeed, the preceding discussion suggests that all polyatomic model potentials are probably rather crude approximations to the true potential for many orientations. More appropriate criteria for choosing between rival model potentials are first whether the potential was fitted to properties sensitive to the same features of the potential as those being studied in the simulation, and secondly whether the form of the model potential is likely to give a reasonable extrapolation to other orientations that might be sampled.

Carbon disulphide provides a salutary example of the problems that can be encountered in transferring potentials between studies. There were two rival isotropic atom–atom Lennard-Jones potentials for $CS_2$, with rather different parameters. One had been used in liquid simulations [3], the second in calculations on the low temperature crystal structure [4]. Both potentials gave reasonable predictions for the crystal phonon frequencies [5] in traditional lattice dynamics calculations. However, the differences between the potentials became apparent when they were used to predict the crystal structure at about 80K [6], using a new molecular dynamics method [7], which allows the shape and volume of the simulation cell to change to balance the spontaneously generated internal stresses and the applied external pressure. The first potential gave a qualitatively correct prediction of the observed *Cmca* structure, but failed to reproduce the anomalous negative thermal expansion coefficient along one crystal axis. The simulation using the second potential immediately transformed from the initial experimental *Cmca* lattice to a radically different structure. It has been proposed that a more realistic potential for $CS_2$ must include anisotropic electrostatic and repulsive forces [8].

The new molecular dynamics method clearly provides a particularly sensitive test of the model potential, and a valuable theoretical method of predicting the phase diagrams of molecular solids. Indeed, the prediction of phase changes to unobserved new structures [9] would be very exciting if only we had confidence in the model potential. However, the conclusions from many simulations of condensed phases is that current models are not good enough for the solid state, and that we need to develop potentials on a firmer theoretical basis.

This article describes our recent work on model intermolecular potentials, which exploits recent advances in the theory of intermolecular forces. We cannot yet offer a recipe for reliable model potentials, or even guarantee that our potential for a given molecule is better than adequate for the application for which it was designed. However, this work explores the inadequacies of the isotropic atom–atom model potential and develops more appropriate functional forms for the intermolecular potentials of polyatomic molecules.

The paper starts with an analysis of the assumptions implicit in the isotropic

atom–atom model. A more general approach to modelling the electrostatic and repulsive potential is described in §3 and §4, with emphasis on the applications that demonstrate the need for anisotropic site–site potentials. The use of such potentials can be computationally efficient, even advantageous (§5), and the approach is particularly promising for organic molecules (§6). The account is qualitative, using the minimum of mathematics and formal intermolecular potential theory (which can be found in the references), because the aim of this paper is to provide practical answers to the question of why an isotropic atom–atom potential may be found inadequate, and providing ideas for better models.

## 2. THE ISOTROPIC ATOM–ATOM MODEL POTENTIAL

Most molecular modelling is based on the assumption that the intermolecular potential between a pair of molecules can be modelled as a sum of interactions between every intermolecular pair of atoms, and that these interactions depend only on the separation of the atoms. A typical model is

$$U = \sum_{kl} B_{\kappa\lambda} \exp(-C_{\kappa\lambda} R_{kl}) - A_{\kappa\lambda}/R_{kl}^6 + q_\kappa q_\lambda / R_{kl}, \tag{2}$$

where atom $k$, of atomic type $\kappa$ is at a distance $R_{kl}$ from atom $l$ of type $\lambda$ in the other molecule. This model has an exponential model for the repulsion, a $R^{-6}$ dispersion term, and a point charge electrostatic model, which are quantified by the derived parameters $B_{\kappa\lambda}$ and $C_{\kappa\lambda}$, $A_{\kappa\lambda}$, and charges $q_\kappa$ and $q_\lambda$, respectively. Other potentials of this type may have a Lennard-Jones repulsion–dispersion model, or be a more complex function of $R_{kl}$ [2]. All these models have an implicit orientation dependence, from using an isotropic inert-gas-like potential between every pair of atoms. This is assuming that molecules interact with each other as if they were a superposition of spherical charge distributions.

This is clearly a good zeroth order approximation, which recognizes that the relative positions of the atoms within the molecule is the major factor in defining the molecular shape. However, it completely neglects the rearrangement of the valence electrons that occurs on bonding. Chemical theories of bonding invoke not only a shifting of electron density into the bonds but also, for some atoms and types of bonding, the formation of $\pi$ and lone pair orbitals. These markedly non-spherical features in the electron density distribution can be clearly seen on electron density difference maps, obtained from high quality X-ray data [10, 11], and are often invoked in theories of organic reactivity and hydrogen bonding.

The remainder of this article is devoted to evidence that the anisotropy of the valence electron distribution can have a sufficiently important effect on the intermolecular potential that it should be considered when designing model potentials, and to describing applications of a formalism for representing these effects efficiently. The isotropic atom–atom model has dominated computer modelling work, and proved adequate for many purposes [12]. However, the literature often hints at the difficulty in finding a "good enough" potential, and notes room for improvement in the accuracy of the predictions. There is no formal record of the number and range of simulation projects abandoned for lack of an adequate potential. Thus, the aim of this article is to encourage those involved in molecular simulation to consider whether the isotropic atom–atom potential is likely to be adequate for their particular study,

and to suggest methods of improving the model potential by adapting the assumed functional form.

## 3. THE ELECTROSTATIC ENERGY

In regions where there is negligible overlap of the molecular charge distributions, the electrostatic contribution to the potential can be considered as arising solely from the rearrangement of the valence electrons from spherical atoms, because a superposition of neutral spherical charge distributions has no long-range electrostatic potential. Hence, an atom-based electrostatic model is intuitively reasonable. However, electrostatic models for small molecules have generally been based on the central multipole expansion, since experimental data can generally provide a value only for the first non-zero total multipole moment. This is the dipole moment for HF, the quadrupole moment for $N_2$ and the octupole moment for $CH_4$.

*Ab initio* calculations are providing increasingly accurate electron density distributions, which can be analysed to obtain either the higher order multipole moments, or alternative models for the electrostatic interactions. An *ab initio* electron density difference map for $Cl_2$ is shown in Figure 1, where the subtraction of spherical atomic charge densities clearly reveals the build-up of the lone pair density at the sides of the atoms. Beside this figure are representations of the electron distribution corresponding to the first few pure multipole moments. A qualitative comparison shows that the total molecular charge density of $Cl_2$ will be poorly represented as a neutral sphere plus a quadrupole, hexadecapole, and the other symmetry allowed central multipoles, as the lone pair density will not be represented accurately by the expansion unless extremely high-order central multipoles are included. In contrast, the electron density around each atom is fairly well modelled by an atomic quadrupole, which gives a rough approximation to the lone pair density, plus a dipole and octupole to refine the description of the bonding region and the lone pair density. Thus, the multipole expansion at each atom would give quite an accurate model for the molecular charge density with relatively few terms.

A quantitative distributed multipole model requires a recipe for dividing up the molecular charge distribution into the contributions to be represented at each expansion site. There are several methods available. The distributed multipole analysis (DMA) of Stone [13] exploits the fact that modern wavefunctions are expanded in terms of Gaussian functions. The charge density is expressed as a sum of contributions from every pair of Gaussian primitives in the basis set. Each product of Gaussian functions can be represented by another Gaussian at a site whose position is determined by their centres and exponents. Thus, the contributions to the charge density from the overlap of two *s*-orbital primitives is equivalent to a point charge at the centre of the product Gaussian, an *s* and a *p* orbital produce a dipole and a charge at that site, and two *p* orbitals generate a point quadrupole, dipole and charge.

The charge density calculated from an *s* and *p* basis set can therefore be exactly represented by a charge, dipole and quadrupole at each atom, summed from the pairs of orbitals that are both centred on that atom, plus a very large number of point charges, dipoles and quadrupoles at sites between the nuclei, representing the charge density contributions from pairs of orbitals on different atoms. Each of the latter contributions can be represented by an infinite multipole expansion at another centre, which is taken to be the nearest of the chosen expansion sites. The qualitative

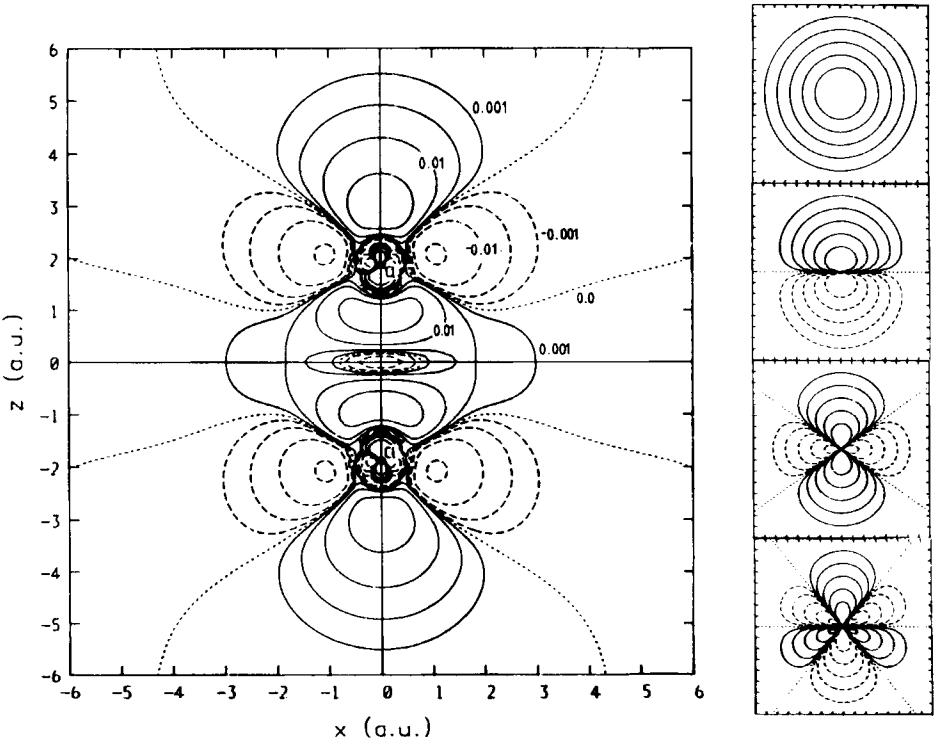


**Figure 1** Chlorine SCF density difference, defined by subtracting spherical atomic charge densities from the molecular charge density calculated using a (*7s6p3d*) basis set. The solid contours are positive, dotted zero and the dashed negative (build-up of electron density). The non-zero contours are at $10^{-3}$, $3 \times 10^{-3}$, $10^{-2}$, $3 \times 10^{-2}$ and $10^{-1}$ atomic units. The figures at the side show pure multipolar distributions corresponding to a charge, dipole, quadrupole and octupole, in descending order [60].



argument above suggests that every atomic centre is a good choice of expansion sites for a distributed multipole model, but this can be supplemented by extra sites in the centre of bonds for high accuracy, or sites on hydrogen atoms can be omitted for computational efficiency. Provided that there are sufficient expansion sites for every contribution to the charge density to be represented at a sufficiently adjacent site, the multipoles above quadrupole that appear in the final distributed multipole analysis will be small.

We can use the sets of distributed multipoles at each site to evaluate the long range electrostatic energy of two (or more) molecules, by summing all the terms in the multipole expansion of the electrostatic energy up to $R^{-5}$ (to include the quadrupole–quadrupole contribution), between every intermolecular pair of sites. The formulae for all terms in the multipole expansion for two interaction sites with no symmetry (i.e. all possible multipoles) up to $R^{-5}$ have been given in a simple, explicit form suitable for use in model potentials [14], along with the derivation of the associated forces and torques. Thus, a distributed multipole analysis of an *ab initio* wavefunction can be used to generate an anisotropic atom–atom electrostatic model that will represent the effects of features such as equitorial lone pairs or $\pi$ electrons by a

significant atomic quadrupole, or an axial lone pair by a significant atomic dipole, without requiring the input of any assumptions about the bonding.

The distributed multipole analysis program is incorporated into the CADPAC suite of *ab initio* programs [15], and the distributed multipole analysis of the wavefunction requires a tiny fraction of the time required to calculate the wavefunction. This method suffers from the disadvantage that the distributed multipoles are fairly sensitive to the basis set, since the division of the charge density is determined by the basis set, which is very overcomplete for an accurate wavefunction. One alternative method [16] partitions the charge density by the zero-flux surfaces between the atoms, which is a more absolute criterion, but this suffers from poor convergence [13] and the overwhelming practical disadvantage of being extremely expensive to compute, and so has only been applied to small molecules. However, Spackman [17] has found that electrostatic energies calculated from various sets of distributed multipoles derived by different partitioning schemes and various reasonable quality wavefunctions are in good agreement, provided that multipoles up to quadrupole or higher are included. Similarly, the distributed multipoles are all qualitatively consistent with the chemical bonding picture of the charge density of the molecules. Indeed, low temperature X-ray diffraction work can also provide experimental atomic multipole moments for calculating the electrostatic interactions in the crystal [18].



Thus, an atom-based distributed multipole model can be used to give a new level of accuracy to model long-range electrostatic potentials. The accuracy is primarily limited by the quality of the wavefunction, since the error in truncating the multipole expansion can be reduced by adding more sites or using more terms, until the desired level of convergence is achieved. This type of model can be contrasted with both the point charge model commonly used for organic molecules, and the central multipole expansion, which is more popular for small molecules.

A point charge model is essentially a brutally truncated distributed multipole model, and thus the generally perceived inadequacies of Mulliken analysis point charge models can be directly attributed to their neglect of the electrostatic contribution from the atomic dipoles, quadrupoles etc. These errors can be partially absorbed by using point charges that have been fitted to the electrostatic potential outside the molecule [19]. However, various schemes for potential-derived point charge models have found, either as an empirical necessity, as in the case of the azabenzenes [20], or from a theoretical analysis of the problem [21], that extra sites are needed to describe the potential arising from bonding features such as lone pairs. The efficiency of the point charge model will therefore depend on the bonding in the molecule and the accuracy required, but the use of point charges at only atomic sites will generally be a rather crude model.

The central multipole model is a distributed multipole model in the limit of only one site, and so suffers from poor convergence properties for the reasons outlined above. Even if a very high-order expansion could be used, the central multipole model is unsuitable for modelling the condensed phases of all but the most spherical molecules, as these may sample orientations where the expansion is formally and practically divergent [22]. In contrast, an atomic sites distributed multipole model is practically convergent at all physically accessible orientations [22]. (This assumes that the penetration term, which describes the modification of the electrostatic interaction by the overlap of the molecular charge distributions, is treated separately.)

The use of a distributed multipole model for the electrostatics is theoretically desirable, but is it worth using in simulations, where some weight is always given to

keeping the model potential simple to save computer time? The answer, which will depend on the molecule concerned and the aim of the simulation, is suggested by looking at the results of molecular modelling work that has employed distributed multipole models.

One highly desirable property of a model potential is that it should predict the correct dimer structure. Buckingham and Fowler [23] have shown that the electrostatic interaction is very important in accounting for the variety of structures adopted by the van der Waals complexes of small polyatomics. This was done by using a distributed multipole model to determine the minimum in the electrostatic energy of the complexes subject to the constraint that the molecules could not approach closer than allowed by the Pauling van der Waals radii of the non-hydrogenic atoms. This simple model correctly predicted the relative orientation of the two molecules within 29 van der Waals complexes, most of which were hydrogen bonded.

The structures of these complexes can be qualitatively rationalized by the Legon-Millen rule, which states that hydrogen bonds will tend to form to regions of high electron density in the proton acceptor, such as lone pairs and $\pi$ bonds. Buckingham and Fowler's results show that this rule of thumb can be accounted for by the electrostatic attraction to these regions of high electron density, but this is only apparent when the electrostatic potential around these features is modelled accurately. For example, HCN $\cdots$ HF is linear because the axial lone pair on nitrogen gives it a significant atomic dipole, whereas the HF dimer is bent because the equitorial lone pair density on F produces a significant atomic quadrupole, and the acetylene HF complex is T-shaped as the DMA represents the $\pi$ electron density.

The success of this simple model has been analysed using *ab initio* perturbation theory [24], which showed that, for many van der Waals complexes, the electrostatic energy dominates the orientation dependence of the potential, as the angular variations in the exchange–repulsion and charge transfer terms tend to cancel. This distributed multipole electrostatic model has been extended by the addition of isotropic atom–atom repulsion–dispersion potentials and used to predict the relative separations and total energies of some hydrogen bonded complexes [17].

Thus, a distributed multipole model is necessary to describe the orientation dependence of strong electrostatic interactions such as hydrogen bonds. However, a simplification of this model may be adequate for some simulations; Dove and Lynden-Bell [25] used a DMA of thiourea to develop a three point-charge model for the electrostatic interaction of the sulphur atom to replace the significant higher multipole moments on $S$ that arise from the lone pair density. This was both necessary and sufficient to enable them to develop a model potential capable of predicting the hydrogen bonding networks found in solid thiourea.

The importance of the electrostatic interaction in controlling the packing of diatomic $X_2$ molecules has been investigated by determining the relative stability of various types of crystal packing as a function of the atomic quadrupole and dipole on each atom [26]. Figure 2 shows the predicted crystal structures for families of model intermolecular pair potentials comprising the electrostatic model (as defined on the axes) and an isotropic exp-6 atom–atom potential. Figures 2a and 2b correspond to two different values of the minimum energy separation $\varrho_0$ between an intermolecular pair of atoms in the repulsion–dispersion potential. The most important feature of these plots is that the optimum structure can change along the lines of constant total quadrupole moment, according to whether the total quadrupole moment arises from dipolar or quadrupolar distortions of the atoms from spherical.

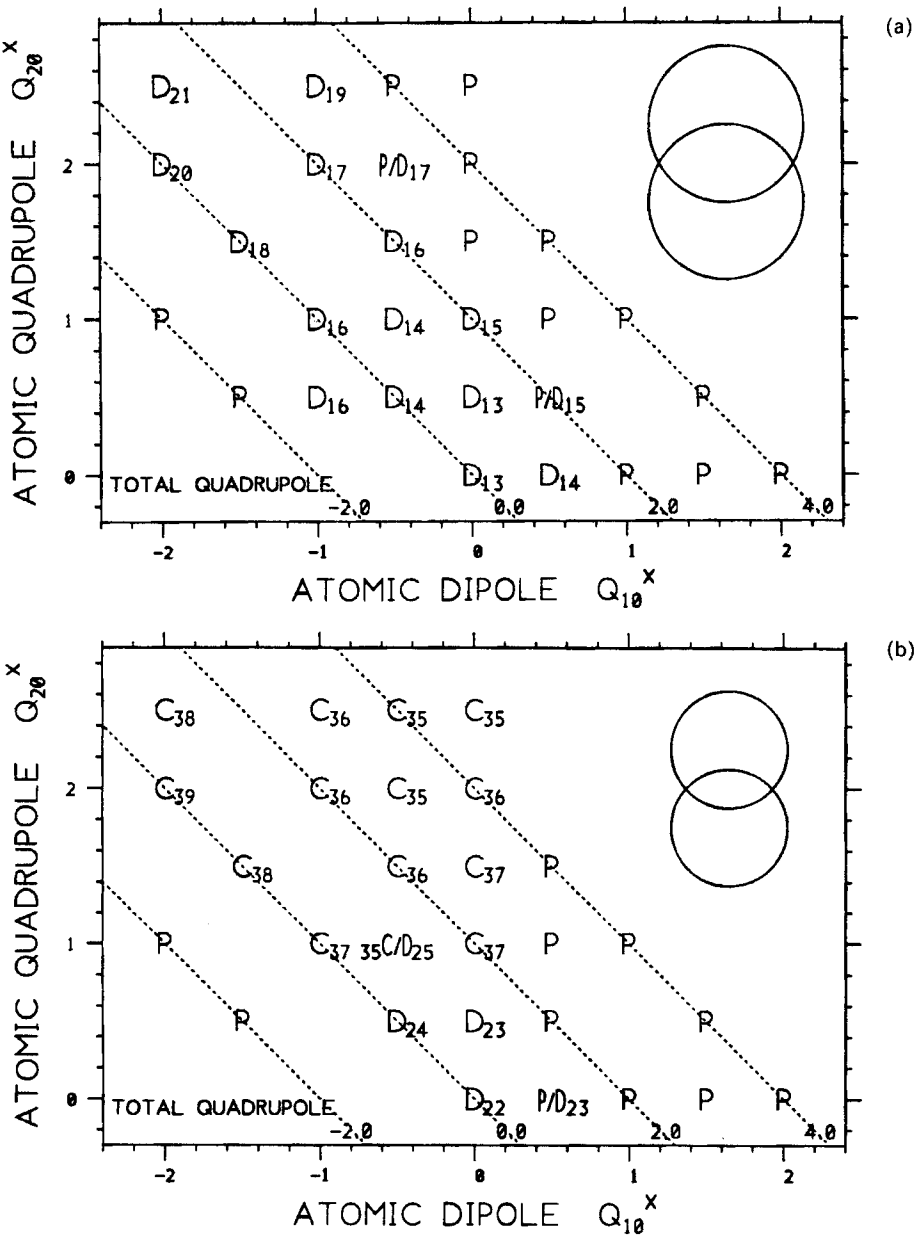


**Figure 2** The structure giving the minimum lattice energy for a diatomic molecule $X_2$, as a function of the dipole and quadrupole electrostatic moment on each atom. The repulsion–dispersion potential is an isotropic exp-6 atom–atom model with $\alpha = 10$ and (a) $\varrho_0 = 2.0$ and (b) $\varrho_0 = 1.5$. All quantities are in reduced units, defined by $\varepsilon = 1$ and the molecular bondlength $d = 1$. The different symmetry structures [26] are denoted *P* for *Pa3*, *R* for $R\bar{3}m$, *C* for *Cmca*, and *D* for *C2/c*. The subscript is the angle of tilt within the molecular rafts $\theta$. The dotted lines are contours of constant total quadrupole moment. When two symbols are shown, e.g. *P*/*D*, the energies of the corresponding structures differ by less than $0.05\varepsilon$.

This explains why English and Venables [27] found that an isotropic atom–atom repulsion–dispersion potential, plus a central quadrupole moment, cannot satisfactorily account for the types of crystal structure adopted by the halogens. Fluorine is the most spherical ($\varrho_0/d \approx 2.2$), with an estimated reduced atomic dipole of approximately $-0.5$ and quadrupole around 2.1, reflecting the equitorial lone pair density. Fluorine adopts the monoclinic *C2/c* structure with an angle of tilt around 18°, as predicted by Figure 2a. The other halogens, $Cl_2$, $Br_2$ and $I_2$ are less spherical ($1.9 \geqslant \varrho_0/d \geqslant 1.5$) and adopt the *Cmca* structure with angles of tilt around 33°, which Figure 2b shows can be accounted for by their total quadrupole moment ($3.5 \geqslant$ dimensionless quadrupole $\geqslant 2$) being dominated by atomic quadrupole distortions. If a central quadrupole moment electrostatic model is used, these molecules would be predicted to have the same cubic *Pa3* structure as $\alpha$-$N_2$.

The calculated lattice frequencies of $N_2$ are also very sensitive to the detailed nature of the molecular charge distribution [28], which has been demonstrated using a five-site point charge electrostatic model that had been fitted to the higher central multipole moments. Since nitrogen is one of the smallest molecules, the accumulated evidence shows that either first central multipole moment, or atomic-site point charge models, will generally be inadequate for simulating the condensed phases of molecules.



Distributed multipole analyses have been obtained for larger molecules, including the azabenzenes [29] and the aromatic hydrocarbons from benzene to coronene [30]. Since the calculations were necessarily at the SCF level using modest basis sets, the electrostatic energies calculated from the DMAs will be less accurate than those used for smaller molecules. Nevertheless, the distributed multipole models generally provide the best available estimate of the electrostatic interactions of these molecules, and also show the systematic trends in the molecular charge distributions very nicely. The DMAs of the azabenzenes [29], with sites on the C and N atoms only, show that each carbon atom donates about a quarter of an electron to each neighbouring nitrogen atom, so that the charges on the carbon atom vary from nothing for benzene and the carbon atoms bonded to two other carbon atoms in pyridine and pyrimidine, to around plus half in *s*-tetrazine. The distributed dipoles have components representing the nitrogen lone pairs, CH bonds and bond polarization effects along CN bonds. Thus the *ab initio* results for the charge distributions of the azabenzenes show a short-range inductive effect, in accord with chemical intuition. However, earlier work that derived point-charge [31] or distributed dipole [32] models, using the total multipole moments of these molecules, used rather different assumptions about the systematics of the charge distributions.

These sets of distributed multipoles were used to study van der Waals complexes involving *s*-tetrazine, benzene, anthracene and perylene [33], using the Buckingham–Fowler [23] approach of determining the minima in the electrostatic energy in accessible orientations. For complexes involving two planar molecules, the repulsion–dispersion potential will strongly favour a parallel-plate sandwich structure, as this optimizes the number of short intermolecular atom–atom contacts. However, the spectroscopic evidence shows that many such complexes do not adopt this structure. The accurate electrostatic model potential was sufficiently successful at qualitatively predicting the diverse observed structures to show that the electrostatic energy did indeed play a major role in determining the structures of these van der Waals complexes. Thus, distributed multipole studies can provide a useful complement to experimental work on the structures of the van der Waals complexes of large

molecules, by suggesting probable structures for the complexes, which are often not intuitively obvious.

Reliable predictions for the separations and orientations of the molecules within van der Waals complexes would require a high quality model for all contributions to the intermolecular potential. Predictions have been made using various isotropic atom–atom potentials (see references within [33]), but the results of these calculations are often sensitive to the assumed electrostatic model. Although a simple systematic point charge model is remarkably good for predicting the total quadrupole moments of the aromatic hydrocarbons [30], a more detailed anisotropic model is needed for close contacts in some orientations. For example, the central parallel-plate structure of the perylene–benzene complex is strongly destabilized by the electrostatic repulsion between the two $\pi$ electron systems. These effects are represented by significant negative quadrupole moments on all carbon atoms in the DMAs. This electrostatic repulsion is underestimated by a factor of four by a point charge model which has only small charges on the interior carbon atoms of perylene. Hence, although total potential calculations using such a point charge model supported the experimental suggestion that the complex adopted the plane parallel-plate structure [34], the theoretical predictions would have been rather inconclusive if a more sophisticated electrostatic model had been used. Similarly, even distinguishing between different T-shaped structures for the benzene dimer is sensitive to the electrostatic model, as an atomic point charge model gives a loss of 1.9 kJ mol$^{-1}$ electrostatic stabilisation when a molecule 4.7 Å above the ring of another is rotated from having the vertex to having the edge pointing into the ring, whereas a DMA calculation corresponding to the same total quadrupole moment predicts a gain of 1.5 kJ mol$^{-1}$.

Hence, the use of a point charge atom–atom electrostatic model can be dangerous for simulating the properties of organic molecules with marked non-spherical features, such as $\pi$ electrons or lone pairs.



## 4. REPULSION POTENTIAL

The deviation of a molecular charge density from a superposition of spherical atomic charge densities will not only determine the electrostatic interactions but will also affect the other contributions to the potential. There is empirical evidence that the repulsive wall around each atom is not spherical from the variation in the effective van der Waals radius of atoms with orientation. Nyburg and Faerman [35] analysed the X···X van der Waals diameter in hundreds of close intermolecular contacts of the form C–X···X–C from the Cambridge Structural Database, as a function of the angles between the X···X vector and the C–X bond vectors. This showed that two iodine atoms can approach each other 0.7 Å closer if they are end on (i.e. C–I···I–C) than side on. The corresponding difference for Cl is 0.4 Å. These differences are consistent with the equitorial lone pair density pushing out the repulsive wall at the sides of the atoms.

An investigation into the effects of anisotropy in the repulsion–dispersion potential on the packing of diatomic $X_2$ molecules [26], used a simple anisotropic extension of the isotropic atom–atom exp-6 potential:

$$U = \sum_{i=1,2;\, j=3,4} \frac{\varepsilon}{(\alpha\varrho_0 - 6)} \left[ 6 \exp\left(-\alpha(R_{ij} - \varrho(\Omega_{ij}))\right) - \frac{\alpha\varrho_0^7}{(R_{ij} - \varrho(\Omega_{ij}) + \varrho_0)^6} \right]. \quad (3)$$

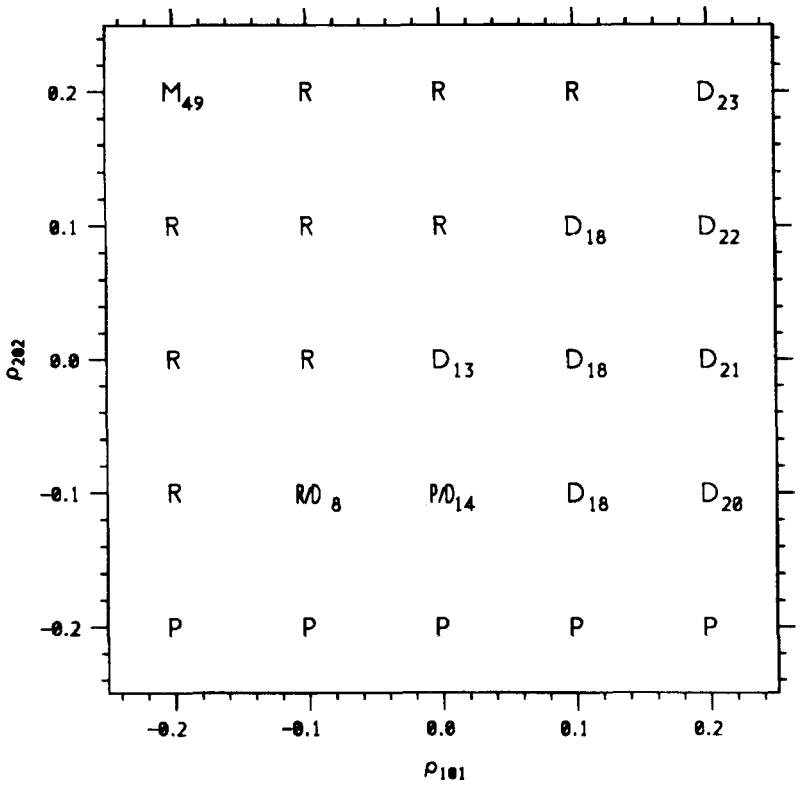


**Figure 3a** The structure giving the minimum lattice energy for a diatomic molecule $X_2$, as a function of the anisotropic distortions in the minimum energy separation $\varrho(\Omega)$ for an atom–atom exp-6 repulsion–dispersion potential with $\alpha = 10$ and $\varrho_0 = 2.0$. All quantities are in reduced units ($\varepsilon = 1$, $d = 1$). The structures [26] are denoted *P* for *Pa3*, *R* for $R\bar{3}m$, *C* for *Cmca*, *D* for *C2/c*, and *M* for *C2/m*. The subscript is the angle of tilt within the molecular rafts $\theta$. When two symbols are shown, e.g. *R/D*, the energies of the corresponding structures differ by less than $0.05\,\varepsilon$.

In this model the minimum energy separation between an intermolecular pair of atoms depends on their relative orientation, as defined by the angles between the unit vectors $\mathbf{z}_1$ and $\mathbf{z}_2$ along the intramolecular bonds, pointing outwards at the atom in question, and the intermolecular X···X vector $R_{ij}\hat{\mathbf{R}}$. (This vector formalism for defining the relative orientation of molecular fragments can also be used to express the orientation dependence of the electrostatic interactions concisely [14].) This study only considered simple anisotropic distortions of the form

$$\varrho(\Omega_{ij}) = \varrho_0 + \varrho_{101}(\mathbf{z}_1.\hat{\mathbf{R}} - \mathbf{z}_2.\hat{\mathbf{R}}) + \varrho_{202}\tfrac{1}{2}(3\mathbf{z}_1.\hat{\mathbf{R}}^2 + 3\mathbf{z}_2.\hat{\mathbf{R}}^2 - 2),$$

where $\varrho_{101}$ and $\varrho_{202}$ are parameters that quantify small ($\leqslant 10\%$) distortions of the form of the first and second Legendre polynomials. This atom–atom potential is of the shifted form $U = \varepsilon(\Omega)F(R - \varrho(\Omega))$ proposed by Stone [36], where the reduced shape of the potential curve is the same for all orientations, but the radical scale is shifted by $\varrho(\Omega)$. Hence a positive value of $\varrho_{101}$ moves the repulsive wall out at the end of the molecule and inwards in the region of the molecular bond, and a negative value of $\varrho_{202}$

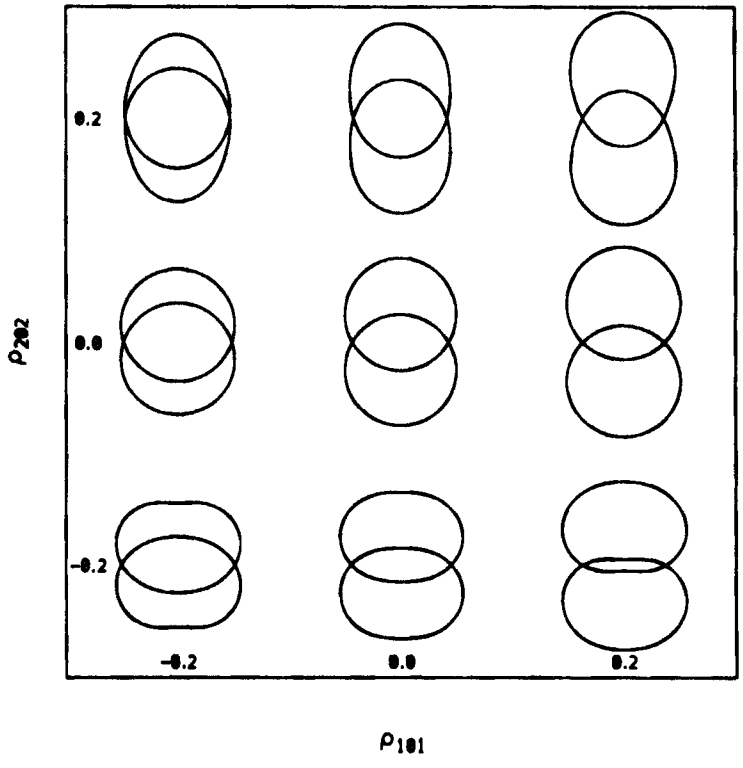


**Figure 3b** The effective molecular shapes corresponding to the distortions in Figure 3a.

moves the repulsive wall inwards at the end and middle of the molecule, and outwards at the sides of the atoms. The effects of these distortions on the effective molecular shape is shown in Figure 3b, which gives the contour of the contribution to the minimum energy separation around each atom. This shows that modest distortions in the charge distribution of each atom can produce quite noticeable changes in the shape of the molecule.

These effective molecular shapes can qualitatively explain the changes in the most stable crystal structure of the molecules as a function of the size and form of the anisotropic distortions $\varrho_{101}$ and $\varrho_{202}$ (Figure 3a). The most spherical molecules adopt the $R\bar{3}m$ structure, which is derived from the atomic close packed face-centered-cubic structure by elongating the atoms into molecules along a three-fold axis, giving close packed rafts of perpendicular molecules. If the molecule has a significant waist, this favours the tilting of the molecules within the rafts, giving the monoclinic $C2/c$ structure. If the molecules are rather squat, this will increase the separation within the close packed rafts of molecules, making these structures less favourable than the $Pa3$ structure, which is derived from the face-centred-cubic atomic structure by elongating along different body diagonals.

This simple study also shows that the main effect of anisotropy in the repulsion–dispersion potential is to change the optimum lattice parameters for the structure, as they are mainly determined by the value of $\varrho(\Omega)$ for the closest intermolecular contacts. This affects the lattice energy as a value of $\varrho(\Omega)$ greater than $\varrho_0$ along a close

contact direction will generally expand the lattice (it could cause a rotation in structures with such degrees of freedom), reducing the dispersion contribution from the next nearest neighbour and further shells of molecules.

One specific point to emerge from this study was that the *Pa3* structure was virtually insensitive to anisotropic distortions of the $\varrho_{202}$ form. Hence any analysis of the crystal structure of $\alpha$-$N_2$ would be insensitive to such distortions. However, there is evidence that this term is important, as an *ab initio* surface for $N_2 \cdots N_2$ [37] could be fitted [38] satisfactorily with an anisotropic atom–atom potential of the form (3), plus an electrostatic model, with

$$\varrho(\Omega)/\text{Å} = 3.907 - 0.086(\mathbf{z}_1.\hat{\mathbf{R}} - \mathbf{z}_2.\hat{\mathbf{R}}) + 0.119\tfrac{1}{2}(3\mathbf{z}_1.\hat{\mathbf{R}}^2 + 3\mathbf{z}_2.\hat{\mathbf{R}}^2 - 2). \quad (4)$$

This form for $\varrho(\Omega)$ reflects the bonding in $N_2$, where the axial lone pair and triple bond give a build up of electron density at the end and middle of the molecule, and a depletion at the sides of the atoms. This explains why the *ab initio* surface could not be represented satisfactorily within the isotropic site–site ansatz [37], as the common expedient of allowing the interaction centres to move off the nuclei is not effective in modelling quadrupolar distortions ($\varrho_{202}$) in the repulsive wall, although it can model dipolar distortions ($\varrho_{101}$) to some degree. The need to use anisotropic repulsion terms to fit an *ab initio* surface has also been demonstrated for $HF \cdots HF$ [39].

The anisotropies in the repulsion, dispersion and electrostatic contributions in an atom–atom intermolecular potential are related by their fundamental cause, the non-spherical features in the electron density of the molecule. A build-up of electron density at a given angle to the molecular bond will give a negative contribution to the atomic multipole moments sampling that orientation, and will also be expected to move out the position of the repulsive wall in that direction, giving a positive contribution to $\varrho(\Omega)$. It may also change the hardness of the repulsive wall and well depth in that orientation, which could be represented by making $\alpha$ and $\varepsilon$ functions of orientation. Work on exploring this link and trying to quantify the anisotropy of the repulsion from the charge density is in progress. However, it is already clear [26] that the electrostatic multipoles and anistropy in the repulsion arising from a particular non-spherical atomic charge distribution have very different effects on the molecular packing. The electrostatic interaction primarily affects the lattice energy, and is the same if the density difference is replaced by its negative (i.e. the signs of all the distributed multipoles are reversed), whereas the repulsion anisotropy primarily affects the lattice parameters. Hence, in order to predict correctly the lattice parameters and energies of different structures for a given molecule, both the electrostatic moments and the anisotropy of the repulsion must be modelled reasonably well, as errors in one component cannot be effectively absorbed by adjusting the other term.

One of the earliest studies of the importance of anisotropy in the repulsion potential was an investigation of the crystal structure of $Cl_2$ [40]. It had been established that an isotropic atom–atom potential, plus any reasonable electrostatic model, would predict that $Cl_2$ would adopt the *Pa3* structure rather than the observed *Cmca* packing. This had been interpreted as demonstrating that intermolecular bonding was sufficiently strong in $Cl_2$ to stabilise the observed structure [41], although it was later pointed out that a reduction in the repulsion in the same direction as the proposed increased attraction would have the same effect [42]. This was demonstrated by the development of an anisotropic atom–atom repulsive potential [40], which, when added to electrostatic terms calculated from a DMA and an isotropic atom–atom dispersion model, gave an excellent quantitative prediction of the experimental crystal

structure, and its stability relative to *Pa3*. The ability to predict the crystal structure required a fairly specific form of anisotropy in the repulsive potential, which can be interpreted as arising from the lone pair electron density. Since this lone pair density appears on the experimental X-ray deformation density map of the solid [10], but there is no detectable peak corresponding to intermolecular bonding, we can conclude that the anisotropy in the repulsion and electrostatic potential, arising from the lone pair density, plays a major role in stabilizing the *Cmca* structure of $Cl_2$.

This work has been extended recently in a molecular dynamics study [43] of liquid chlorine, which shows an unusual asymmetry in the first peak in the experimental structure factor $S(k)$. The original anisotropic atom–atom potential is not completely satisfactory for the liquid [44], which is not unexpected as the potential has a minimum in a relative orientation that was not sampled in the solid [40]. However, a superior anisotropic atom–atom potential, with anisotropy in the dispersion, has recently been developed [43] using lower temperature crystal structure data, and the constraints that no alternative crystal structure had a lower energy, that the potential extrapolated reasonably to unsampled orientations, and that the pressure in the liquid at one state point was reasonable. This potential can also predict the lattice frequencies, liquid structure factor, a diverse range of thermodynamic properties of the liquid, the gaseous structure factor and the second virial coefficients satisfactorily. Since most other proposed potentials for chlorine have had difficulty in simultaneously describing even two of these properties, the success of this model shows that the use of anisotropic atom–atom potentials represents an important advance in our ability to model real polyatomic systems.

However, the empirical development of this potential required both testing various forms of anisotropy in the repulsion–dispersion potential and optimizing the parameters, and since the calculations test only the total potential, it is highly probable that the potential involves some cancellation of errors between the models for the different components. The development of more realistic model potentials for polyatomics would be considerably facilitated by more theoretical guidance on the functional form of the anisotropy of both the repulsion and the dispersion terms, including the modification in the long-range terms at the onset of molecular overlap.



## 5. THE COMPUTATIONAL ADVANTAGES OF USING ANISOTROPIC SITE–SITE POTENTIALS

There has been a marked reluctance to use anisotropic site–site potentials in simulations because of the need to adapt the computer codes, and the belief that such calculations would be prohibitively expensive in computer time. However, some comments on the mathematical formalism used in our formulation of anisotropic potentials, and our preliminary experience in using such potentials in molecular dynamics and Monte Carlo simulations, show that the scheme not only is practical, but can be computationally advantageous.

We have used orientation dependent functions taken from the complete set of expansion functions for any scalar property of the relative orientation of two molecules of arbitrary symmetry, as defined by Stone [45]. Since these $S$ functions are defined using spherical tensor theory, it is straightforward to extract the functions appropriate to the symmetry of the molecular fragment [36]. For example, the $S$ functions that can appear in a model potential for linear molecules are closely related

to products of spherical harmonics. Indeed, the $S$ functions appear as the natural expansion functions for the orientation dependence of the perturbation theory multipole expansion of the long-range electrostatic, induction and dispersion energy [46, 14]. The forces and torques corresponding to any anisotropic potential expressed in terms of $S$ functions can be derived analytically, using spherical tensor theory [45, 14]. The formalism can be used with any set of coordinates that define the relative orientation of the two molecular sites, but we have found the use of the unit vectors that define the local axis system and the direction of the inter-site vector particularly convenient. A molecular dynamics program has already been adapted to use anisotropic site–site potentials for linear molecules [47], using this approach and the analytical expressions for the associated forces and torques, and it is planned to extend the program to nonlinear molecules in the near future.

The molecular dynamics study of $Cl_2$ demonstrated fears that the use of anisotropic functions would be prohibitively expensive in computer time to be groundless [47]. The simulation required only $2\frac{1}{2}$ times the time required for an isotropic atom–atom potential, which is approximately the same increase as would have arisen from the introduction of a third isotropic interaction site at the centre of the bond. Since the number of inter-site vectors increases as the square of the number of sites on the molecule, the usual expedient of adding extra interaction sites to an isotropic atom–atom potential is clearly a more costly and less flexible method of improving the model potential than introducing anisotropic functions.



Anisotropic site–site potentials can also be used to decrease the computational requirements of simulations of organic molecules, by using one site on the carbon atom to model a methyl group etc., and representing the effects of the bonded hydrogen atoms by anisotropy in the potential. This is a reasonable approximation because there is relatively little charge density associated with hydrogen atoms; indeed an isotropic "atom–atom" hydrocarbon potential scheme [48] has the hydrogen interaction sites displaced into the CH bond to model the shift in the charge density. This approach to modelling CH bonds has been tested by using this isotropic "atom–atom" potential [48] to generate an intermolecular potential energy surface for methane. This surface was then fitted [49] with a one site carbon–carbon potential, which included anisotropic functions appropriate to tetrahedral symmetry, of the form:

$$U = \exp[-\alpha(R - \varrho(\Omega))] - A/R^6, \tag{5}$$

where

$$\begin{aligned}\varrho(\Omega) = {} & \varrho_0 + \varrho_3 3\sqrt{3}[(\mathbf{x}_1.\hat{\mathbf{R}})(\mathbf{y}_1.\hat{\mathbf{R}})(\mathbf{z}_1.\hat{\mathbf{R}}) - (\mathbf{x}_2.\hat{\mathbf{R}})(\mathbf{y}_2.\hat{\mathbf{R}})(\mathbf{z}_2.\hat{\mathbf{R}})] \\ & + \varrho_4 \tfrac{1}{2}[5((\mathbf{x}_1.\hat{\mathbf{R}})^4 + (\mathbf{y}_1.\hat{\mathbf{R}})^4 + (\mathbf{z}_1.\hat{\mathbf{R}})^4 \\ & + (\mathbf{x}_2.\hat{\mathbf{R}})^4 + (\mathbf{y}_2.\hat{\mathbf{R}})^4 + (\mathbf{z}_2.\hat{\mathbf{R}})^4) - 6].\end{aligned}$$

(The axes system is defined by the cube which contains the molecule with an atom in the positive quadrant.) This potential was then adapted for $CH_3$ and $CH_2$ groups by adjusting the dispersion coefficient according to the number of hydrogen atoms using the ratio of the long-range $R^{-6}$ coefficients implicit in the atom–atom model. The repulsive potential could remain unchanged, as the extra hydrogen atoms lie along C–C bonds and so their repulsive effects will not be sampled in any simulation. The resulting anisotropic carbon site–site potential predicted the static crystal structures of pentane, hexane and octane with the same accuracy as the original atom–atom

potential, but in a third to a quarter of the computer time. Since the displacement of the hydrogen atom sites is an *ad hoc* method of modelling the anisotropy in the alkane atom–atom potential [50], the more flexible anisotropic carbon type of potential could also have the advantage of greater accuracy if determined carefully against a wide range of experimental data.

This device for reducing the number of interaction sites, while still modelling the repulsion of the hydrogen atoms, becomes increasingly efficient with the number of sites removed, and so should be particularly attractive for calculations on biological molecules. Monte Carlo calculations on benzene using a six-site anisotropic potential (§6) required only a third of the computer time needed for a 12-site isotropic atom–atom potential [51], and the reduction in the number of sites in this example is smaller than that which would be involved for many larger organic molecules. Naturally, the savings in computer time are also dependent on the details of the implementation, and the type of calculation; for example, Monte Carlo calculations require only the potential, whereas molecular dynamics programs also evaluate the forces and torques. However, it is clear that the anisotropic site–site model is computationally competitive for realistic simulations.

## 6. APPLICATIONS TO ORGANIC MOLECULES

The use of anisotropic site–site potentials for organic molecules is attractive because the anisotropic functions can be used to describe important non-spherical features such as lone pairs and $\pi$ electrons, and also to reduce the number of sites involved by representing methyl groups etc. by a single site. Most model potentials for organic molecules are made up of isotropic atom–atom potentials and it is generally assumed that these potentials will be transferable to the same atomic species in other molecules. The systematic nature of organic chemistry shows that the molecular charge distributions are made up of recognizable, transferable functional groups, and the intermolecular potential arising from a particular atom or functional group will be as transferable as the associated charge distribution. Hence, the transferable potential approach to modelling organic molecules has a reasonable foundation, but the use of isotropic atom–atom potentials as the basic building block is more questionable.

The need for anisotropy in the repulsive potential around some heteroatoms will not be apparent from a limited set of crystal structure data, if it samples the repulsive wall between the atoms for only a small range of geometries. In this case the crystal structure may be modelled satisfactorily with an isotropic potential for the atom appropriate to the sampled geometry. However, if the atom is marked by non-spherical, the inadequacy of the isotropic repulsion model will become apparent when it is used to calculate properties sensitive to a close intermolecular contact in another geometry. A good example of this is an analysis of the three polymorphic forms of *p*-dichlorobenzene [52], which clearly showed the need for anisotropy in the Cl interaction potential.

Thus, an anisotropic repulsive potential for a non-spherical atom will be far more accurately transferable to the same atom in other molecules, provided the valence electron distribution is similar, than any isotropic model. Many of the problems that have been experienced in trying to transfer non-bonded potential parameter sets for a given atom, such as nitrogen [53], between organic molecules may be attributed to either the non-sphericity of the atom or changes in the type of bonding. Indeed, some extended parameter sets, such as the molecular mechanics program MM2 [54], do crudely model these effects by having different parameter sets for different

hybridizations of the atom, and some lone pair interaction–site parameters. Although repulsion–dispersion parameters for an atom have sometimes been successfully transferred despite the differences in the atomic charge density being sufficient to require a different electrostatic model [48], the accuracy of this assumption must be limited because all the contributions to the potential are determined by the nature of the charge density. Hence, using the charge distribution of the molecules to develop anisotropic site–site potentials should provide a new generation of more accurate, transferable potentials for organic molecules.

A six-site anisotropic potential scheme has been developed for the azabenzene molecules [55], which are derived by substituting N atoms for CH groups in a benzene ring. This substitution has a major effect on the intermolecular potential, and the six molecules adopt very different crystal structures. The DMAs of the azabenzenes [29] were simplified to provide the electrostatic model, which comprised point charges to model the short-range inductive effect in the CN bond (§3), except for benzene where the dominant electrostatic effect was represented by distributed quadrupole moments. Anisotropic CH···CH, CH···N and N···N repulsion–dispersion potentials were developed by fitting various functional forms to the crystal structures of benzene, pyrazine, pyrimidine and *s*-tetrazine, using the static crystal structure analysis program WMIN [56]. The form of anisotropy in the repulsive potentials required to model these crystal structures satisfactorily could be rationalized as representing the effects of the CH bond and nitrogen lone pair density. These potentials also gave satisfactory predictions of the crystal structures of *s*-triazine and pyridine, showing that the potential scheme was transferable.

A parallel study of the azabenzene interactions, using an isotropic site–site potential [20], found that it was necessary to include extra sites to model the effects of the lone pair density, resulting in a 12-site model. Thus, the lone pair density plays an important role in determining the diverse crystal structures of the azabenzenes and so must be modelled, either by extra isotropic sites or anisotropic functions, for even such simple applications. Since the crystal structures sample the potential at relatively few orientations, these potentials have passed only a preliminary test, so it is noteworthy that the six-site potential has more flexibility for improvement using more testing experimental data.

This six-site potential for benzene has recently been improved [51], as it was found inadequate for the modelling the high pressure monoclinic phase. Monte Carlo simulations of the orthorhombic phase suggested that the original potential was too attractive in the plane parallel sandwich geometry. This fault was remedied by increasing the quadrupole moment on each carbon to a sixth of the total quadrupole moment, thus absorbing the effects of the omitted contributions in the DMA. The potential was reparameterized by fitting to both the high pressure monoclinic and the low temperature orthorhombic crystal structures. The resulting potential was then used in constant pressure and temperature Monte Carlo simulations of the orthorhombic, monoclinic and liquid phases of benzene. In such Monte Carlo simulations the size and shape of the simulation cell is allowed to vary (*c.f.* the new molecular dynamics method §1), and so this provides a stringent test of the potential.

The new six-site model gave a satisfactory account of the orthorhombic phase at 218 K and 0.7 kbar, the monoclinic phase at 294 K and 25 kbar and the liquid at 300 K and 1 kbar. The simulation showed the experimentally observed reorientations of the molecules in the orthorhombic phase. In contrast, Williams 12-site isotropic "atom–atom" model [48] gave somewhat less satisfactory simulations of these phases, and

did not predict any reorientation, suggesting that the model may overestimate the anisotropy of the potential around the hydrogen atoms. This would be consistent with the empirical observation that the effective van der Waals shape of a hydrogen protrudes less when bonded to an $sp^2$ carbon than when bonded to an $sp^3$ carbon [57]. Further improvements in the benzene potential will require more work on the anisotropy of the CH group, particularly the anisotropy of the dispersion.

## 7. CONCLUSIONS AND FUTURE DEVELOPMENTS

The work described in this article shows that the assumption of an isotropic atom–atom potential will often be inadequate for simulating molecular behaviour in condensed phases or predicting the structures of van der Waals complexes. It also points a way forward, through the use of an anisotropic site–site approach, to developing more realistic model potentials.

The anisotropic site–site approach has the flexibility to model the intermolecular potentials of small molecules very accurately, and also to provide a computationally efficient framework for modelling the potentials of organic molecules. In particular, an anisotropic atom–atom potential, which models the effect of non-spherical features in the valence electron distribution, can be more confidently transferred to other molecules where it has a similar charge density, than any crude spherical approximation.

However, as indicated in §1, there are considerable difficulties in quantifying intermolecular potentials for polyatomics using experimental data, and these problems will be enhanced by the use of more complex functional forms requiring the determination of more parameters. If we discard the assumption that the intermolecular potential can be modelled as if a molecule is a superposition of spherical charge distributions, we will need both firmer theoretical guidance on the appropriate form of the model potential (particularly the appropriate form of anisotropy), and have to use *ab initio* data to determine as many parameters as possible. We already have a method of quantifying the electrostatic interactions within such model potentials, through the distributed multipole analysis of the molecular wavefunction (§3).

One of the most pressing requirements is for a theoretically justified method of deriving anisotropic site–site dispersion models. Since this is a long-range term in the potential, it should be possible to quantify anisotropic atom–atom dispersion coefficients from an analysis of the wavefunctions of the isolated molecules (c.f. the distributed multipole analysis for the electrostatic terms, §3). The distributed polarizability analysis of Stone [58] provides an improved method of calculating induced multipole moments and induction energies, and may provide a starting point for the development of distributed dispersion models.

Since crystal structure analysis is a limited method of determining even the form of anisotropy in the repulsion potential, we also require a better method of determining the anisotropy in the site–site repulsion potential. The qualitative links between empirically deduced repulsion anisotropies and the non-spherical features in the molecular charge distributions (§4) suggest that *ab initio* methods may provide the key to this problem. However, empirically fitted repulsive potentials have the debatable advantage of being partially able to absorb various errors, including the changes in the long-range electrostatic and dispersion effects when the molecular charge clouds start to overlap. Thus, a completely *ab initio* based model potential will require

suitable damping functions for the long-range forces. There has been some progress in developing *ab initio* methods to determine such functions for atoms and HF [59].

Hence, there is still a lot of work to be done before we can routinely derive model potentials for polyatomics that can be used with confidence in molecular simulations. However, a prerequisite for success is the development of model potentials that have the flexibility to be able to model the actual pair potential. Simple model potentials may often prove adequate for calculating a small range of properties, as there is considerable scope for the cancellation of errors in empirical potentials. However, we cannot expect such potentials to be reliable for other applications, particularly if the molecule contains atoms with non-spherical charge distributions. Thus, if a model potential is found inadequate for a simulation study, it will often be more effective to alter the form of the model potential according to the molecular charge distribution, than to tinker with the parameters within an inadequate functional form.

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