The Crystal as a Supramolecular Entity

Perspectives in Supramolecular Chemistry

Volume 2

Edited by Gautam R. Desiraju
University of Hyderabad, Hyderabad, India

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Library of Congress Cataloging-in-Publication Data

The crystal as a supramolecular entity / edited by Gautam R. Desiraju.
p. cm.—(Perspectives in supramolecular chemistry : v. 2)
Includes bibliographical references and index.
ISBN 0-471-95015-7 (alk. paper)
1. Molecular crystals. I. Desiraju, G. R. (Gautam R.)
II. Series.
QD921.C755 1995 95-19756
548—dc20 CIP

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0 471 950157

Typeset in 10/12pt Times by Dobbie Typesetting Limited, Tavistock, Devon
Printed and bound by Antony Rowe Ltd. Eastbourne

This book is printed on acid-free paper responsibly manufactured from sustainable forestation,
for which at least two trees are planted for each one used for paper production.

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Preface

The term 'supramolecular' signifies that which is beyond the molecule, and supramolecular concepts have consequently had the greatest influence in organic chemistry where the molecule is paramount. Supramolecular chemistry has gained in importance as it represents a point of departure from classical organic chemistry which, since the time of Wöhler, has continuously emphasized that all physical and chemical properties of substances are derivable from and are delimited by their molecular structures. Supramolecular ideas have much relevance to modern organic chemistry, and it is difficult to conceive of the recent advances in bio-organic chemistry, catalysis and transport phenomena, chemistry at interfaces and organic materials chemistry relying solely on molecule-based thought.

This kaleidoscope of contemporary research interests reveals that another distinctive feature of supramolecular chemistry is its ability to unite areas with seemingly widely differing perceptions. In keeping with such a feature, structural chemists and crystallographers have had little difficulty in recognizing a molecular crystal as the ultimate example of a supermolecule. Consequently, supramolecular chemistry today encompasses the study of molecular crystals with all the applications and ramifications that such study implies in the fields of solid-state chemistry, crystal engineering and materials science. This then is the theme of this volume. Crystals constitute one end of the supramolecular continuum and may be viewed as 'hard' supermolecules in contrast to the 'softer' supramolecular aggregates which exist in solution.

The historical molecular bias of organic chemistry necessitates the reiteration that supermolecules are not just collections of molecules and that their structure and characteristic properties are distinct from the aggregate properties of their molecular constituents. Such a statement is, however, hardly necessary in inorganic crystal chemistry where structures have traditionally been viewed in terms of networks and connectivities and where the very definition of molecularity is excitingly different. And yet, these 'organic' and 'inorganic' viewpoints are only parts of the whole, and another manifestation of the synthesizing aspect of supramolecular chemistry is its ability to bridge organic and inorganic structural chemistry with the result that it will soon probably be difficult to distinguish between organic, inorganic and organometallic viewpoints in solid-state supramolecular chemistry.

The initial motivation behind supramolecular chemistry was to design chemical systems which would mimic biological processes, drawing inspiration, as it were, from nature itelf, for the living cell is a wonderful example of a highly ordered supramolecular species embodying a close relationship between structure, information and function. The crystallography of biological macromolecules has been explored in great detail since the 1930s, and if an organic (small-molecule) crystal is the ultimate supermolecule, a biomolecular crystal is the complete supermolecule, for in it the relationship between structure and function is so much more clearly apparent. Whether it be supersecondary structures in a protein or supramolecular synthons in a small-molecule crystal, however, the motivation behind such identification and classification is the same—to improve our relatively poor present understanding of supramolecular algorithms, i.e. the protocols which connect molecular and supramolecular structure, the operational aspects, as it were, of molecular recognition.

Many of the prerequisites for such an improved understanding have been discussed in this volume. Central to the issue is the nature of weak intermolecular forces, the supramolecular glue, as it were. Surprisingly, this is incompletely known even for the ubiquitous forces; hydrogen bonding, herringbone, $\pi\cdots\pi$ and ionic interactions. Another key element in supramolecular engineering is the ability to dissect and insulate different interaction types, or alternatively the ability to exploit the interference between different interaction types in the design strategy. Again, is it possible to distinguish clearly between a chemical bond and an intermolecular interaction? Even as supramolecular chemistry has sought to demarcate between what is within and without the molecule, it has demonstrated as deficient the classification of forces as 'bonded' and 'nonbonded'. The weakest covalent bonds are indeed feebler than the strongest intermolecular interactions such as those between some metal atoms in organometallic crystals, interactions which confound attempts at distinguishing between molecules and supermolecules. The efficiency of computational methods in the development of supramolecular algorithms is another open question. So, whether it be crystal engineering of an organic zeolite or a frequency doubler for materials science applications or the prediction of the tertiary fold of a protein, the emphasis is on the collective properties of molecules mediated by intermolecular interactions.

This book, which is intended to clarify our perception of a crystal as a supramolecular entity, consists of six chapters which illustrate the diversity and scope of structural supramolecular chemistry. Neither the selection of topics nor the treatment within the individual chapters is exhaustive, and this is entirely intended. In a fast-moving subject such as this, it was felt that it would be more important that the reader obtain an accurate and critical appraisal of important developments in the field rather than a comprehensive coverage of the literature. Such an ethos, it was felt, would also more accurately justify the appearance of this volume in a series entitled *Perspectives in Supramolecular Chemistry*. The chapters convey, in this sense, the respective authors' points of view, and it is hoped that such a presentation will stimulate further discussion, debate and, of course, new work.

I would like to thank the authors for their cooperation, the other series editors for their helpful suggestions and Professor J.-M. Lehn for his encouragement. I am most grateful to the staff at John Wiley & Sons Ltd for their assistance and to Dr C. B. Aakeröy, Queen's University, Belfast, who prepared the cover illustration.

Gautam R. Desiraju
Hyderabad
March 1995

Chapter 1

Thoughts on Crystals as Supermolecules

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1. CRYSTALS VIEWED AS SUPERMOLECULES

The crystal is, in a sense, the supermolecule *par excellence*: a lump of matter, of macroscopic dimensions, millions of molecules long, held together in a periodic arrangement by just the same kind of noncovalent bonding interactions as are responsible for molecular recognition and complexation at all levels. Indeed, the crystallization process itself is an impressive display of supramolecular self-assembly, involving specific molecular recognition at an amazing level of precision. Long-range periodicity is a product of directionally specific short-range interactions, nothing more. Crystals are ordered supramolecular systems.

1.1 Polymorphism

Polymorphism, the existence of a given compound in more than one crystal form, is widespread. If a crystal is a supermolecule, then polymorphic modifications are superisomers and polymorphism is a kind of superisomerism; thus, diamond, graphite and the fullerenes are an extreme example of a family of superisomers. Even with less extreme examples, polymorphs may differ markedly in colour, hardness, solubility, density and other physical properties. As a general rule, the polymorph stable at 0 K, i.e. the one with the lowest potential energy, has the smallest volume. It may be displaced by another polymorph with a higher potential energy if the latter has a larger heat capacity and hence a larger entropy increase as the temperature is raised. Free energy

The Crystal as a Supramolecular Entity. Edited by G. R. Desiraju
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differences between polymorphs are usually quite small, a matter of a few hundred calories per mole, and have different temperature dependences, so that over quite a small range of temperature, and particularly between room temperature and the melting point of the crystals, one polymorph or another can be the thermodynamically stable form. A metastable form can persist for years (e.g. diamond!) or it can undergo spontaneous transformation to the stable form — a solid–solid phase transformation or, in supramolecular terms, an isomerization reaction.

1.2 Cooperative and Noncooperative Processes

Even if crystals are supermolecules, there are obviously important differences between phase transformations in solids and isomerization reactions in solution or the gas phase. One difference is that in a reversible chemical reaction there is at any temperature an equilibrium mixture of reactants and products whereas in a crystal the transformation, once it is triggered on either side of the transition temperature, usually goes practically to completion. In other words, either there is no reaction or one isomer is transformed completely into the other. Secondly, there is the difference in the temperature dependence of the reaction rate. The rate constant of a 'normal' chemical reaction increases smoothly with temperature. With first-order phase transformations (those involving a discontinuous change in free enthalpy or entropy or unit cell parameters), on warming through the thermodynamic transition temperature (where the free energies of the two polymorphs are equal) nothing much happens on the low-temperature side, but once this temperature is passed the transformation rate suddenly increases and the reaction goes rapidly to completion. On cooling from above to below the transition temperature, the reverse transformation may occur or it may not, depending on various factors that influence the kinetics of the transformation. High-temperature crystal modifications can often be kept indefinitely at temperatures far below the thermodynamic transition point. Second-order phase transformations (those involving a more gradual change in thermodynamic properties and unit cell parameters) are usually associated with a change from a more ordered low-temperature phase to a more disordered high-temperature phase. Here the process takes place within a temperature range of a few degrees around the transition temperature, reversibly.

These differences between the 'normal' chemical reaction and the crystal transformation result from the importance of cooperativity in the crystal but not in the liquid or gaseous state. In a 'normal' chemical reaction, molecules react more or less independently of one another; what happens to one molecule has little effect on what happens to its neighbours. In a phase transformation, cooperativity is the essence. Within a crystal, every displacement of a molecule from its equilibrium conformation, position, and orientation is immediately communicated to its immediate neighbours and thence to more distant neighbours and so on, so that molecular motions are coupled in a set of lattice vibrations that extend through the entire crystal. In a liquid, on the other hand, although motions among neighbouring molecules are coupled, there is no long-range correlation between molecular positions or orientations; there are only local effects. It is this difference that is responsible for the different kinds of temperature dependence between normal reactions and the highly cooperative ones that are typical of phase transitions. In general, polymorphic transitions are associated with changes in molecular packing arrangements but there are often radical changes in molecular conformation and hydrogen-bonding patterns as well.

From physics books one might get the impression that as far as phase transitions are concerned there are no problems left. This is very far from the truth. It may be true that no *fundamental* problems are left, but it is also true that practically nothing is understood about the actual mechanisms of solid–solid phase transitions in molecular crystals. It is likely that defects in the ordered crystal structure play a vital role. Indeed, in the absence of defects, the solid–solid transition may be completely inhibited; crystals may be held at temperatures well above their thermodynamic range of stability almost indefinitely. On warming, instead of transforming to the thermodynamically stable form they simply undergo melting at their fusion temperature [1]. For phase transformations in molecular solids there is essentially no theory worth speaking of at the molecular level, only a few broad thermodynamic generalizations and *ad hoc* explanations; we understand hardly anything.

1.3 Self-Recognition of Molecules

One other apparent difference between molecular interactions in crystals and in other chemical and supramolecular systems turns out on closer scrutiny to be nugatory. In chemical recognition processes, including supramolecular and biomolecular ones, we are concerned mainly with interactions among chemically different molecules, and not so much with interactions among identical (or enantiomeric) molecules. With crystals it is usually the other way round. Although some crystals—co-crystals or 'molecular compounds'—are built from more than one kind of molecule, these are the exceptions; most crystals are built from identical (or enantiomeric) copies of the same molecule*.

---

*From the point of view of the phase rule, a crystalline racemate, built from enantiomeric molecules, should be regarded as a co-crystal if the interconversion rate of the enantiomers is slow compared with the time-scale of the crystallization, melting or solution processes. The liquid phase in equilibrium with the crystalline one then has to be described as a two-component (melt) or three-component (solution) system, whereas the pure enantiomer yields a one-component (melt) or two-component (solution) system.

This problem, or rather a closely related one, was discussed by Pauling and Delbrück [2] in their critique of Jordan's views on 'special' forces between identical or nearly identical molecules or parts of molecules. In discussing molecular interactions, they wrote:

> . . . in order to achieve the maximum stability, the two molecules must have complementary surfaces, like die and coin, and also a complementary distribution of active groups. The case might occur in which the two complementary structures happen to be identical; however, in this case also the *stability of the complex between two molecules would be due to their complementariness rather than their identity*[†]

Thus, even when all the molecules are identical (or enantiomeric), an A-part of one molecule can interact with a D-part of a second, and the A-part of the second can interact in exactly the same manner with the D-part of a third, and so on. Indeed, several ways of describing such mutually complementary interactions are commonly encountered (e.g. locks in keys, bumps in hollows, interactions between opposite charges or favourably oriented dipoles, donor–acceptor interactions, acid–base types of interaction involved in hydrogen bonding, etc). The important thing is that they are local effects with strongly directional properties.

If the geometrical aspects of these interactions are preserved from molecule to molecule, one comes naturally to periodicity—to translational symmetry relationships among the molecular units. There are only a limited number of ways in which these relationships can be achieved. In general, identical parts of different molecules avoid one another, which is why space groups containing rotation axes and mirror planes are infrequent compared with those that contain screw axes or glide planes. The contrast is striking. Among the 130 000 or so known crystal structures of organic compounds, only a few % occur in space groups that contain rotation axes or mirror planes, and the overwhelming majority of these crystal structures involve molecules that themselves contain the symmetry elements in question [3]. It is very uncommon

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From this point of view, in the slow-conversion limit the two solid enantiomers and the crystalline racemate would have to be classed as three different compounds (stereoisomers in this case). In the fast-conversion limit, they would be three polymorphic modifications of the same compound.

[†] Emil Fischer's 'lock-and-key' analogy is just 100 years old [E. Fischer, *Ber. Dtsch. Chem. Ges.*, **27**, 2985 (1894)], but the basic idea of complementariness as a factor in the formation of stable associations goes back to much earlier times. It was expressed more than 2000 years ago by Lucretius in his *De Rerum Natura*:

> Things whose textures have such a mutual correspondence, that cavities fit solids, the cavities of the first the solids of the second, the cavities of the second the solids of the first, form the closest union.

(translated by H. A. J. Munro, in *The Stoic and Epicurean Philosophers* (ed. W. J. Oates), Random House, New York, 1940).

for molecules in a crystal structure to be related by rotation axes or mirror planes.

Once the importance of molecular recognition in self-assembly processes such as crystallization is established, one comes to the possibility of influencing these processes by the introduction of mistakes in molecular recognition. This can be achieved by the addition of small amounts of 'tailor-made auxiliaries' to the solution in which the crystallization process is taking place. 'Tailor-made auxiliaries' consist of molecules that simulate the genuine crystal substrate molecules but differ from them in some crucial respect; thus, for example, aspartic acid for aparagine, ω-aminocaproic acid for lysine, D-serine for L-serine, etc. The two molecules are so similar that the guests may be incorporated on a growing crystal face of the host but then reveal themselves as impostors when the next layer of molecules is added, thus inhibiting growth normal to the face and changing the normal crystal habit. The method has been exploited to great effect in studies of crystal nucleation and growth, in the determination of the absolute configuration of chiral additive molecules and of chiral polar crystals, in the lowering of crystal symmetry, leading to alteration of physical properties, and in other applications*.

2. CRYSTAL STRUCTURES

Apart from minor details, the static aspects of crystal structures are relatively well understood. That is to say, there are no fundamental problems, only problems of complexity. Even though there is no rigorous way to do this, the potential energy of a crystal can be factorized into component parts and attributed to various kinds of interaction: electrostatic interactions, hydrogen bonds, donor–acceptor interactions, steric repulsions, van der Waals attractions, and so on. Several sets of more or less elaborate atom–atom interactions are in use (see Section 3), and computer programs are available to estimate their net contributions to the potential energy of the crystal structure — the packing energy. Most potential functions in general use have been parametrized to reproduce room-temperature crystal structures at least and sublimation enthalpies at best, but the calculated packing energies are not accurate to better than a few kilojoules per mole or so. Moreover, they do not

---

*The work summarized in this paragraph has been described in many papers and review articles by a team of crystallographers and chemists from the structural chemistry group at the Weizmann Institute of Science from 1985 onwards. See especially L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, M. Lahav and L. Leiserowitz, in *Progress in Stereochemistry*, Vol. 16 (eds E. L. Eliel, S. H. Wilen and N. L. Allinger), Wiley-Interscience, New York, 1986, p. 1 and L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil, L. J. W. Shimon, M. Lahav and L. Leiserowitz, *Angew. Chem., Int. Ed. Engl.*, **24**, 466 (1985).

include any allowance for the entropic contribution to the free energy and hence they cannot be used for predicting the ranges of relative stability of polymorphs.

We can usually reassure ourselves that an observed structure corresponds, or at least is quite close, to a local minimum in the packing energy as calculated with the help of atom–atom potential functions. Thus, once we know the crystal structure or structures adopted by a given molecule, we can try to analyse the factors that contribute to the stability of these observed molecular arrangements. Once the unit cell dimensions are given, i.e. once the space available to the molecules is fixed, the most important factor in determining the details of the molecular packing is usually minimization of the intermolecular repulsions (the attractive forces have already played their part in bringing the molecules from infinite separation into mutual contact). Nevertheless, given one crystal structure we are generally unable to make reliable predictions about the structures of possible polymorphs or about the packing arrangements that structurally related molecules might adopt, except perhaps for trivial variations.

Given only the molecular structure of a compound, the problem of predicting its crystal structure (or crystal structures) is still essentially unsolved despite considerable contemporary interest and effort in the problem. (See Perlstein [4] for a progress report.) Indeed, for molecules with several degrees of conformational freedom the problem may well turn out to be insoluble, at least with present-day methods. At any rate, it is a challenge that must be, and is being, taken up.

2.1 Simple Models of Intermolecular Interactions

In spite of the formidable and unsolved problems involved in predicting crystal structures, even those of quite simple compounds, it seems hard to resist the temptation to try to *explain* known crystal structures in terms of simple models, i.e. models that ignore much of the complexity and concentrate on only one or two of the factors that are involved. As an extreme example, it might be asserted that the cubic face-centred rocksalt structure is a result of the electrostatic attraction between the Na cations and the Cl anions, both having spherical symmetry. It is true that a spherical cation at the centre of a regular octahedron of anions is attracted equally to all six neighbours, but it is also equally repelled by all six. In fact, this arrangement corresponds not to a minimum in the electrostatic energy but to a local maximum; any slight displacement of the cation from its central position lowers the electrostatic energy but it raises the repulsion energy by a greater amount. The important point is that the equilibrium structure corresponds to a *balance* between attractive and repulsive forces; to concentrate on the attractive forces alone, or on only one of them, can be very misleading. This applies not only to crystals but to supramolecular complexes in general.

While on the topic of repulsive forces, it may be worth remarking here that the recent use of 'clathrate compound' as a more or less synonymous expression for 'inclusion compound' [5] does not do justice to the distinction that Powell wished to make when he introduced the phrase in the first place in 1948. Powell had studied the crystal structures of inclusion compounds formed by various small molecules with quinol and had established that these molecules were enclosed in cavities with the β-quinol framework. He recognized that while the formation of most molecular compounds was due to mutual attraction of the components, the β-quinol inclusion compounds were different; they were based mainly on repulsion. Let Powell speak for himself [6]:

> A molecule to be enclosed must be in the right place when the cage is closing. . . . For an enclosed molecule to leave its enclosure it must overcome the attraction between itself and the cage, but even if it were possible for there to be no attraction, escape will be prevented by another process for some types of cage and enclosed molecule. When this molecule approaches a possible hole of exit its outward passage will be opposed by the repulsive forces that arise when any two atoms approach closely. . . . If the molecules forming the cage are subject to strong mutual attraction they will not be pushed apart readily, and if the holes of exit are sufficiently small the enclosed molecules will therefore be repelled inwards. . . .
>
> There may thus arise a structural combination of two substances which remain associated not through strong attraction between them but because strong mutual binding of the molecules of one sort only makes possible the enclosure of the other. It is suggested that the general character of this type of combination should be indicated by the description 'clathrate' compound—'clathratus', enclosed or protected by cross bars of a grating.

This seems as clear as it could be. Perhaps one should avoid referring to clathrate inclusion compounds as 'host–guest' compounds. After all, guests are usually free to leave, they are not prisoners.

2.2 The Benzene Crystal Structure; A Simple Example

One of the favourite crystal structures that seem to call for a simple explanation is that of benzene, a simple, highly symmetrical molecule which crystallizes at normal pressure in the orthorhombic space group *Pbca* with four molecules in the unit cell (benzene I). Results of several crystal structure analyses have been described in the literature, and we shall refer here mainly to those of the latest and most accurate study, that of perdeuterobenzene by low-temperature neutron diffraction [7]. The unit cell dimensions are $a=7.360$ (7.398) Å, $b=9.375$ (9.435) Å and $c=6.703$ (6.778) Å at 15 K (and 123 K, the latter values in parentheses), and the four molecules are located at the crystallographic centres of symmetry at the origin of the cell and at the

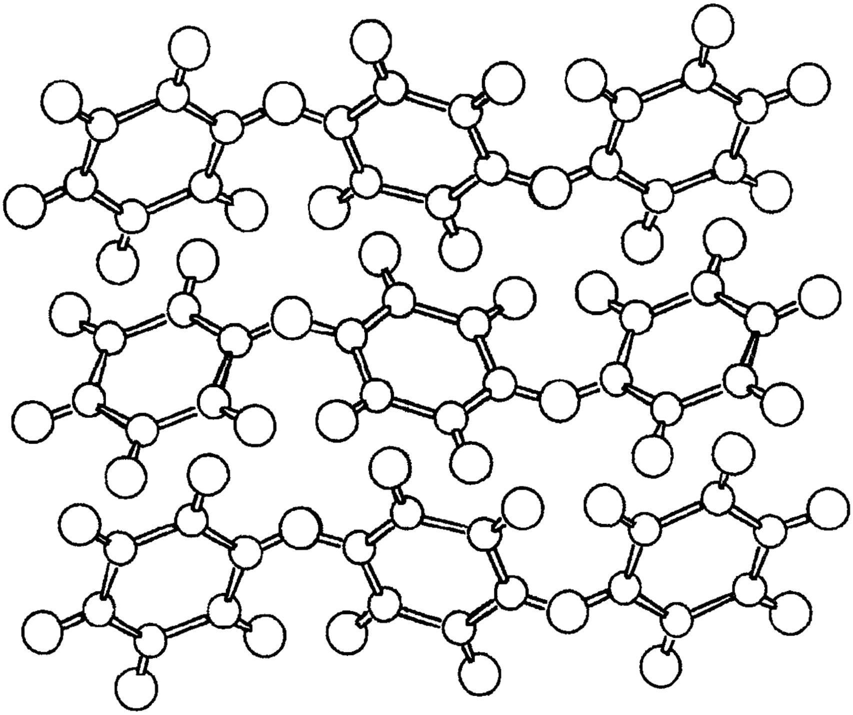

Figure 1 Crystal structure of benzene (benzene I) viewed down the *c*-axis

midpoints of the faces, i.e. at 0,0,0, 1/2,1/2,0, 1/2,0,1/2 and 0,1/2,1/2. Each molecule is surrounded by 12 others, the intercentre distances being 4.98 Å (1/2,0,1/2), 5.76 Å (0,1/2,1/2) and 5.96 Å (1/2,1/2,0). A picture of the structure is shown in Figure 1.

Benzene vapour contains a few % of dimer, and electric deflection measurements have shown that this dimer has an electric dipole moment [8, 9]. The most likely model was taken as one in which the two planes are mutually perpendicular, a so-called T-shaped arrangement 'as observed in crystalline benzene nearest-neighbor pairs' [8]. It was stressed [8] that the observed polarity of the dimer merely identifies its structure as that of an asymmetric top and that virtually all asymmetric top structures behave similarly enough to qualify for compatibility with the experimental result. In other words, the description of the dimer structure as a T-shaped structure was intended merely as a rather coarse characterization. In particular, it was clearly not intended to imply that the experimental data called for a C_{2v}-symmetric dimer with a C–H bond of one benzene molecule pointing towards the centre of the other, involving 'a kind of hydrogen bond to the π-face of a neighbouring aromatic ring', as has been invoked as a dominating factor in the packing of aromatic rings in condensed systems [10]. In any case, this particular orientation of neighbouring benzene rings is not to be found in the crystal structure of benzene itself. As we shall see, the dominating feature of the benzene crystal structure is not so much the attraction of C–H bonds for π-clouds but rather the coulombic attraction between hydrogen atoms and carbon atoms of neighouring molecules. But even if the arrangement with a C–H bond pointing to a ring centre may not correspond to optimal attraction, it could well be the one of local minimal repulsion. This could account for its occurrence in host–guest complexes where a benzene ring is tightly enclosed in the more or less rigid cavity of a host molecule.

In recent analyses of the benzene structure, Williams and Xiao [11] and Klebe and Diederich [12] have considered the pairwise interactions between a central molecule and one at each of the three face centres (Figure 2). (Note that the diagrams in this figure do not represent benzene dimers but nearest-neighbour interactions in infinite chains of molecules. Each molecular centre corresponds to a crystallographic centre of symmetry.) The shortest centre-to-centre distance (4.98 Å to the molecule at 1/2,0,1/2)* involves a nearly perpendicular pair of molecules (interplanar angle 87.6°) such that 'two adjacent CH-bonds of the first molecule point towards the core of the neighbouring benzene molecule, and a shift of the centre of the first from the normal centred on the second molecule is observed so that one hydrogen of the first is located above the centre of the second molecule' [12] (but note that the corresponding C–H bond direction does not point towards the ring centre). The other two pairwise interactions have longer centre-to-centre distances, i.e. 5.76 Å (0,1/2,1/2) and 5.96 Å (1/2,1/2,0); the longest one again involves a nearly perpendicular pair of molecules (interplanar angle 85.1°) but with a larger offset (Figure 2, centre), and the intermediate one involves rings inclined to one another by 29.4°, again with 'two CH-bonds approximately oriented toward the core of the neighbouring benzene ring'. None of these pairs has a geometry that corresponds either to a C_{2v}-symmetric perpendicular plane model dimer or to the optimized dimer, as calculated by Williams and Xiao [11], in which the orientation of the two benzene rings is intermediate between parallel and perpendicular. As these authors point out [11]:

> The structure and energy of a molecular dimer abstracted from its crystal is not expected to be optimum for the isolated gas dimer. The presence of several nearest-neighbor molecules and of long-range intermolecular energy leads one to

---

*The distances and angles given in these analyses [11, 12] differ slightly from those given here because they are based on an earlier structure analysis of C_6H_6 [G. E. Bacon, N. A. Curry and S. A. Wilson, *Proc. R. Soc. London, Ser. A*, **279**, 98 (1964)], not the later one of C_6D_6 described elsewhere [7].

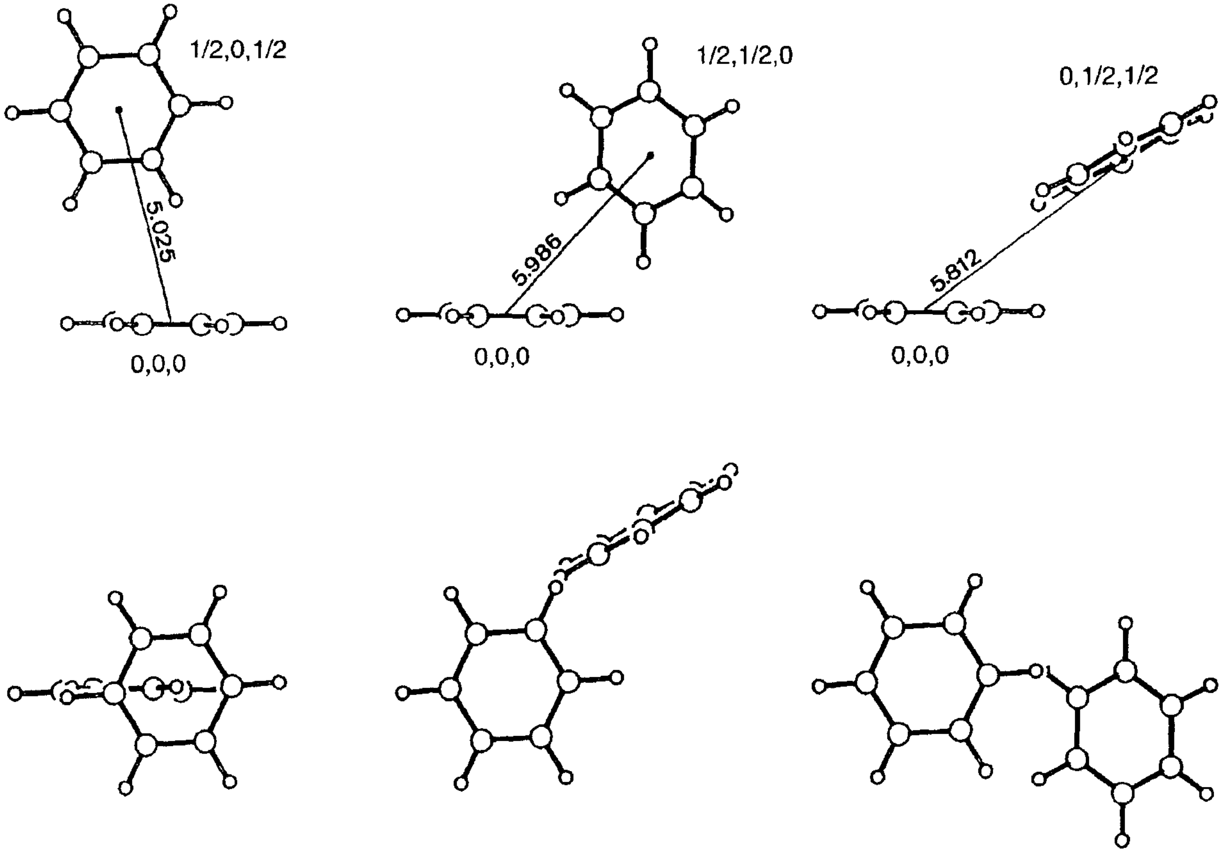
1/2,0,1/2
5.025
0,0,0
1/2,1/2,0
5.986
0,0,0
0,1/2,1/2
5.812
0,0,0

Figure 2 Two orthogonal views (upper and lower rows) of the basic nearest-neighbour motifs (distances in ångstroms) in crystalline benzene (reproduced with permission from Klebe and Diederich [12])

anticipate that these dimers will be different from optimum gas dimers, perhaps even radically.

Thus, while such dimers or other supramolecular assemblies extracted out of observed crystal structures may well be useful in host–guest chemistry in suggesting models for the design of hosts for specific aromatic guest molecules, they should not necessarily be regarded as reliable indicators of the optimal geometry of such assemblies.

Another simple model that has recently been invoked in explaining the benzene crystal structure is based on the interaction between electric quadrupole moments [13]. The benzene molecule has a quadrupole moment of $-29 \times 10^{-40}\,\mathrm{C\,m^2}$ [14], and the negative value can be interpreted in terms of excess negative charge above and below the plane of the ring, and excess positive charge in the plane. The pattern shown in Figure 3, the periodic repetition of the perpendicular T-shaped arrangement mentioned above, has been proposed [13] as the energetically most favourable arrangement of an assemblage of identical quadrupoles.

The quadrupole interaction model for crystalline benzene can be criticized on several grounds and should not be taken too seriously. In the first place, although the charge distribution described above may be compatible with the observed quadrupole moment, it is in no way required by it. For example, the quadrupole moment is just as compatible with a charge distribution in the plane of the ring, with about $-0.15e$ on each of the six carbon atoms and $+0.15e$ on each of the hydrogens. Secondly, the pattern shown in Figure 3 is only two-dimensional and cannot be applied without reservations to a three-dimensional periodic pattern. For example, the crystal structure of carbon dioxide, which can be regarded as the prototype of a quadrupolar molecule, does not follow the pattern shown in Figure 3. The linear CO_2 molecule crystallizes in the cubic space group $Pa\bar{3}$, the four molecules in the unit cell being oriented along the body diagonals (threefold axes) [15]. Thus, each negatively charged oxygen atom does not interact with a single positively charged carbon centre (as would be suggested by Figure 3), but is equidistant from three such centres (Figure 4).

Finally, if the benzene crystal structure were indeed determined by interactions among quadrupoles, one might expect to find essentially the same crystal structure for hexafluorobenzene, a molecule that has the same hexagonal shape, nearly the same size and nearly the same quadrupole moment as benzene but with the opposite sign — the reversal of sign makes no difference to the quadrupole–quadrupole interactions. However, the C_6F_6 structure ($P2_1/n, Z = 6$)[16] is different from that of benzene. Whereas all molecules in the benzene structure are crystallographically equivalent, the C_6F_6 structure contains two types of molecules in crystallographically different environments. One set of molecules (say A) occupy crystallographic centres of symmetry, while the other set (B) occupy general positions (Figure 5). It is interesting that

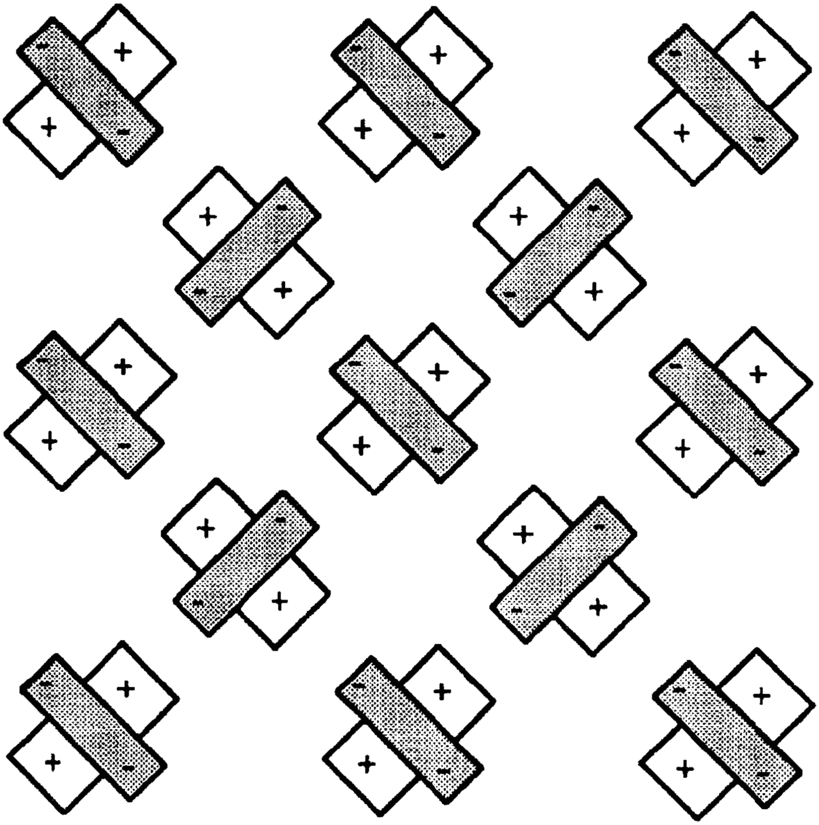

Figure 3 Schematic representation of a regular periodic arrangement of like quadrupolar molecules

two opposite fluorine atoms of the A-molecules point nearly at the centres of the B-molecules (the six C···F distances are roughly equal, ranging from 3.35 to 3.50 Å). This is similar to the T-shaped arrangement that was invoked earlier for benzene–benzene interactions, only here the interplanar angle is about 60° and it is the negatively charged end of the bond dipole that interacts with the π-cloud! Most likely, this arrangement corresponds to a local repulsion minimum—the fluorine atom sits in the 'hole' in the π-cloud. In any case, from the simple quadrupole interaction model, there seems no reason why two such geometrically similar molecules as C_6H_6 and C_6F_6 should adopt such different crystal structures when they have the same quadrupole moment.

A more fundamental objection to the quadrupole interaction model for benzene derives from elementary physics. The electric field or potential at a distance r from a source can be expressed as a multipole expansion, but the

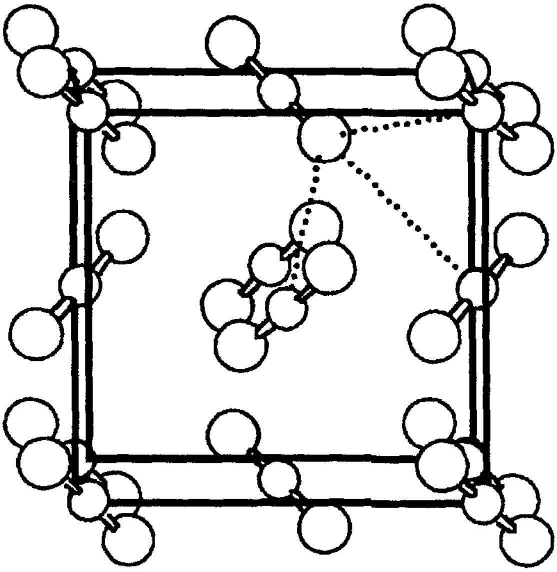

Figure 4 Crystal structure of carbon dioxide (example of a cylindrical quadrupolar molecule in space group *Pa*$\bar{3}$). The molecular centres form a face-centred cubic array, with the oxygen atoms on the body diagonals of the cube. Each oxygen atom is therefore equidistant (3.14 Å) from the carbon atoms of three other molecules (dotted lines)

expansion is only valid when *r* is large compared with the size of the source itself. This requirement is satisfied to some extent for the carbon dioxide structure, where the shortest intermolecular contact distances are about 3.1 Å, in any case larger than the longest intramolecular distance of about 2.3 Å. But it is not satisfied for the benzene crystal structure, where the shortest contact distances between molecules in the tightly juxtaposed array are smaller than the dimensions of the benzene molecules themselves.

The same objection can be raised against the notion that molecular dipole moments are important in determining molecular packing in crystals; in particular, that large molecular dipole moments are an important factor leading to centrosymmetry in crystals. Experimental evidence against this idea, if it were needed, has been provided by a recent study [17], which shows that there is no correlation between the mutual orientation of molecular pairs in crystals and the magnitudes of the molecular dipole moments. For very small molecules, e.g. diatomic ones, it is another matter; here the dipoles can be regarded in good approximation as point dipoles, and similarly for interactions between local bond dipoles.

To calculate the electric field or potential due to a molecule at distances that are not large compared with the molecular dimensions, it is necessary to use the

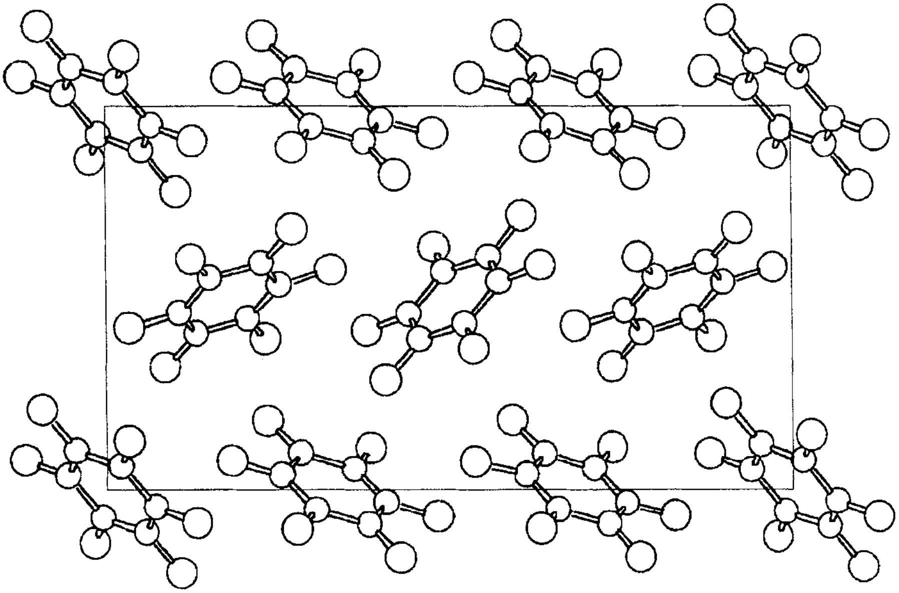

Figure 5 Crystal structure of hexafluorobenzene viewed along the *b*-axis. Note the two types of molecules: the ones at the corners and the centre of the pattern (at crystallographic centres of symmetry) and the others (in general positions)

molecular charge distribution itself, or, for practical purposes, at least a reasonable approximation to this based on local point charges. Indeed, although the C–H bonds of benzene are not usually believed to be highly polarized, the most careful available studies, such as those of Williams and Xiao [11] and Shi and Bartell [18], indicate that the observed crystal structures of benzene and other aromatic hydrocarbons cannot be reproduced in a consistent fashion without introducing local charge–charge interactions. Placing equal and opposite charges on the carbon and hydrogen atoms of benzene makes the C···H coulombic terms attractive, all other atom–atom interactions repulsive. The benzene crystal structure is heavily determined by this pattern of atom–atom interactions.

The orthorhombic benzene I crystal structure can be altered with not too much deformation into a hypothetical cubic close-packed structure in the same space group as that described above for carbon dioxide. The cubic benzene structure with the same volume as that of benzene I and with all three axes equal (space group $Pa\bar{3}$) would have $a = 7.73$ Å, intercentre distance 5.47 Å. In this structure the molecules would occupy sites with $\bar{3}$ (S_6) crystallographic symmetry and the benzene rings would be perfect hexagons (although not necessarily planar). In the observed orthorhombic structure the rings show merely $\bar{1}$ (C_i) crystallographic symmetry, although the deviations from hexagonal symmetry are minimal*. Close packing has long been invoked as an important factor in determining the crystal structures of organic molecules [19], so one may well ask: why does benzene choose a structure that is slightly deformed from this ideally close-packed one? The answer is that there are specific attractions among bits of neighbouring molecules in the crystal that cannot be optimized in the cubic structure, which has only two degrees of freedom: the unit cell dimension and the rotation angle of the benzene molecule in its own plane. In the cubic structure, this plane is required to be perpendicular to one of the body diagonals of the cube, and hence the angle between the ring planes of different molecules is fixed by symmetry at 70° 32′ (the supplement of the tetrahedral angle). By deviating from cubic symmetry, the structure gains degrees of freedom that allow it to lower its potential energy. However, the energy difference between the observed structure and the cubic one is probably quite small, of the order of a few kilojoules per mole only†. For the carbon dioxide crystal structure in $Pa\bar{3}$, with only one degree of freedom (the unit cell dimension), the potential energy is apparently not lowered by deviating from cubic symmetry, at least not at normal pressure. However, it has recently been shown [20] that at very high pressure, CO_2 undergoes a phase transformation to an orthorhombic structure in which the mutual orientation of the molecules is no longer restricted by crystal symmetry.

Benzene also undergoes a pressure-induced phase transformation to a structure of lower symmetry. In addition to the orthorhombic structure discussed so far (benzene I), there is also a monoclinic high-pressure form, benzene II, with unit cell dimensions (294 K, 25 kbar) $a = 5.417$ Å, $b = 5.376$ Å, $c = 7.532$ Å and $\beta = 110°$; the space group is $P2_1/c$ with two centrosymmetric molecules in the unit cell [21], as shown in Figure 6. The molecular volume is about 7% less than that of benzene I at the same temperature (at around 0.7 kbar pressure) and about 10% less than that of benzene I at 0 K and normal pressure (extrapolated value). If the monoclinic *a*-axis and *c*-axis are interchanged to alter the space group to $P2_1/a$, the space group in which the crystal structures of naphthalene and anthracene are usually described, comparison of unit cell dimensions suggests that the three crystal structures must be closely related (Table 1).

The naphthalene and anthracene values are taken from low-temperature X-ray analyses [22] to compensate as far as possible for the contraction in volume of benzene II due to the high pressure required for its formation. As the molecular size increases, there is only a relatively small increase in the *a*-axis

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*In fact, according to the results of the accurate low-temperature neutron diffraction analyses [7], they are less than 0.001 Å for C–C distances and about 0.002 Å for C–D distances; the deuterium atoms deviate from the mean plane of the carbon atoms by about 0.01 Å to give a slight deformation in the direction of a chair conformation.

†According to a rough force field calculation kindly made by Dr Gerhard Klebe in response to a query from the author.

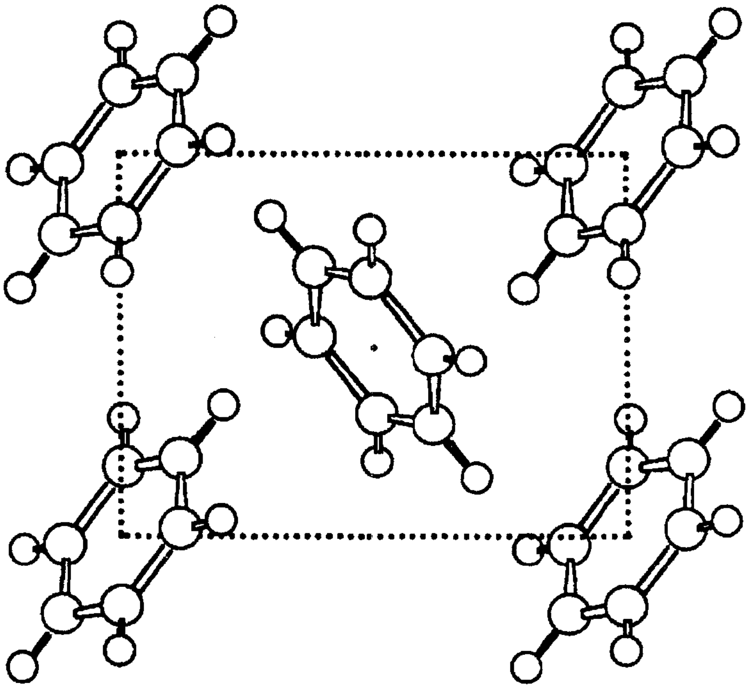

Figure 6 Crystal structure of the high-pressure modification of benzene (benzene II) viewed in projection down the *a*-axis (in the $P2_1/c$ orientation)

Table 1

	a (Å)	*b* (Å)	*c* (Å)	*β* (°)
Benzene II (294 K, 25 kbar)	7.532	5.376	5.417	110
Naphthalene (92 K, 1 bar)	8.108	5.940	8.647	124.4
Anthracene (94 K, 1 bar)	8.414	5.990	11.095	125.3

and *b*-axis, the main extension being in the length of the *c*-axis, by about 3.2–3.4 Å for each additional ring. Indeed, the three crystal structures are very similar. No polymorphs of naphthalene or anthracene are known so far, but possible structures for orthorhombic modifications have been proposed [23].

In contrast to the orthorhombic benzene I structure in which the molecules adopt an approximately cubic close-packed arrangement, the molecular arrangement in benzene II is more like hexagonal close packing: in other words, this crystal contains definite layers of molecules (in the projection plane of Figure 6, perpendicular to the crystal *c*-axis in the $P2_1/c$ orientation). One can discern the same tendency in the naphthalene and anthracene structures, although the distance between the layers is now larger because of the increase in molecular size. When the benzene I structure is compressed and the interatomic distances between molecules are contracted, the repulsion energy increases faster than the attraction energy decreases, i.e. the net energy increases (to balance the work done in compressing the crystal). Hall and Williams [24] have shown that in order to model this change by atom–atom potential calculations, opposite charges of at least $0.09e$ have to be assigned to the carbon and hydrogen atoms. (To fit the experimental value of the quadrupole moment of benzene, the atomic charges should be about $0.15e$, with the inner carbons negative, the hydrogens positive.)

At the same time, it has to be remembered that molecules in condensed phases should not be regarded as systems of rigid, fixed charges. Molecules are polarizable, which means that the local charge distribution is influenced by other charges in the vicinity, i.e. by the presence of neighbouring molecules. There is therefore no fundamental, rigorous way of partitioning the total interaction energy between molecules into separate contributions (dispersion terms, van der Waals energy, coulombic terms, etc.), as has already been mentioned in Section 2. In particular, although the molecular charge density distribution and its associated potential are well-defined quantities that are available from calculation and from experiment, at least in principle, atomic charges are not observables and can be defined in different ways, such as Mulliken atom charges [25], potential-derived charges [26], Hirshfeld charges according to his stockholder recipe [27] and Bader charges [28].

There is no unique or generally accepted answer because of the lack of agreement about what constitutes an atom in a molecule or in a condensed phase. When the outer electron orbitals overlap, how should the boundaries enclosing individual atoms be defined? Nevertheless, whatever the detailed physical interpretation, it seems to be necessary to introduce coulombic interactions into the force field that expresses the short-range attractions of the carbon and hydrogen atoms. As the long-range coulombic effects are relatively unimportant because of extensive cancellations and dielectric polarization, it has been suggested that in atom–atom potential calculations little is lost and much is gained by replacing the r^{-1} dependence of the electrostatic potential energy by an r^{-2} dependence adjusted to yield the correct coulombic forces at molecular contact distances and with the term truncated at 5 Å [18].

More generally, as far as the planar condensed aromatic hydrocarbons are concerned, their crystal structures seem to be determined by a competition between two main types of interaction [29]: a core–edge interaction, involving C···H attractions and producing a herringbone (HB) pattern; and a core–core interaction, leading to interplanar stacking. Their relative importance depends on the ratio of the size of the molecular perimeter (HB promoting) to the molecular area (stack promoting). To model the core–edge interactions in terms of atom–atom potentials, opposite charges on the carbons and hydrogens must be introduced. Models that do not possess this feature fail to reproduce this characteristic feature of the packing of aromatic hydrocarbons. For example, a model introduced by Hunter and Sanders [30] puts a charge of $+1e$ at each carbon nucleus and two compensating charges of $-0.5e$ at 0.47 Å above and below the plane of the π-system. This charge distribution is compatible with the quadrupole moment of benzene and is claimed to explain the strong geometrical requirements for interactions between aromatic molecules, but it does not reproduce the crystal structures of benzene or of other aromatic hydrocarbons.

3. FORCE FIELDS; ATOM–ATOM POTENTIALS

Visit a chemistry or biochemistry laboratory nowadays and you are likely to find a good number of researchers peering at the screen of a computer monitor instead of busying themselves with experiments with actual materials. Ask what they are doing and you are likely to be informed that they are trying to predict by calculation the outcome of possible experiments or at least obtain some guidance as to which experiments are likely to be worthwhile and which a waste of time. Among the most popular types of such calculation are those that fall into the general class of molecular mechanics calculations. Given an atomic arrangement compatible with a molecular (or supramolecular) structure, this type of calculation will adjust the relative atomic positions in directions corresponding to a lowering of the potential energy until a local energy minimum is reached. More elaborate versions may be able to sample regions of the parameter space and find not just a single energy minimum but several. Almost all such types of calculation are based on a summation of interaction energies between pairs of atoms — atom–atom potentials.

The use of atom–atom potentials in molecular mechanics calculations on strained molecules goes back to the late 1940s and early 1950s [31–34]. The idea is that the geometrical structure of a molecule is described by some set of ideal bond distances, bond angles and torsion angles. Deviations from these ideal values may occur, but only at the cost of an increase in potential energy, as estimated by some assumed force field, usually a fairly simple one, including mainly harmonic terms and neglecting cross-terms among the variables. In addition, it was found necessary to introduce non-bonded interactions as perturbations on the hypothetical, unstrained molecular structure. The sum of the deformation energies and of the non-bonded interactions is the strain energy, which is a function of the relative atomic positions. These are varied until an energy minimum is found. The ideal values of the structural parameters and the functions describing the energy cost of deviations from these ideal values were initially based mainly on empirical information about the structures of simple molecules then available, but they are now based on a miscellany of structural, thermochemical and spectroscopic information. Many programs itemize the separate contributions to the total strain energy, i.e. from bond-stretching energy, angle-bending energy, torsional strain, non-bonded repulsion, etc., but the itemized values should not be taken too seriously. The individual terms in the energy expansion are strongly coupled, which means that as one bond angle, say, is changed from its assumed equilbrium value it may become more or less easy to deform another bond distance or angle, but the cross-terms that express such couplings are often inadequate or even absent in the construction of the force field. As computers become cheaper, more powerful and more generally available, molecular mechanics calculations are being increasingly backed by quantum mechanical calculations, at least for simple molecules, and by molecular dynamics calculations for more complex systems.

The connection between molecular mechanics and crystal structures came about in the attempt to quantify the non-bonded interactions. These were first taken over from intermolecular interaction potentials of rare-gas-type molecules. They start from the premise, contained in the van der Waals equation of state for real gases, that atoms are not localized at points, i.e. not at their respective nuclei. They occupy a volume of space and can be assigned, at least as a first step, more or less definite radii, by custom called van der Waals radii, which were initially estimated for many types of atom mainly from packing radii in crystals*. Mutual approach of non-bonded atoms to distances less than the sum of these radii leads to strong repulsive forces. The empirical atom–atom potentials that were introduced to describe the balance between atom–atom attractions and repulsions were assumed to be characteristic of the atom types and independent of the molecules they are embedded in. They were assumed to hold equally for interactions between non-bonded atoms in

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*These van der Waals radii are only distantly related to the constant b in the van der Waals equation of state $(p+a/v^2)\ (V-b)=RT$, and the great Dutch chemist would undoubtedly have been surprised to know that his name was to be associated with them. Indeed, it is difficult to trace how the term established itself in the everyday language of structural chemistry. One likely source is Pauling's influential text *The Nature of the Chemical Bond*. In the section entitled 'Van der Waals and Nonbonded Radii of Atoms', Pauling wrote:

> In a crystal of the substance (chlorine) the molecules are attracted together by their van der Waals interactions and assume equilibrium positions at which the attractive forces are balanced by the characteristic repulsive forces between atoms, resulting from interpenetration of their electron shells. Let us call one-half of the equilibrium internuclear distance between two chlorine atoms in such van der Waals contact, corresponding to the relative positions of two molecules, the van der Waals radius of chlorine.

Pauling's table of van der Waals radii of atoms still stands as a set of convenient rule-of-thumb values.