

CRYSTAL PACKING

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1. Introduction

We all know by everyday experience that matter has many different states of aggregation. Chemists also know that matter is made of atoms, ions and molecules, and that the macroscopic properties of any object depend on the size, shape and energies of these microscopic constituents.

One mole of gaseous substance occupies about 24 liters at room temperature, while the volume of the same amount of substance in the liquid or solid state is a few tens to a few hundreds cubic centimeters. It follows that the molecules¹ are much, much closer to each other in a liquid or in a solid than in a gas. An easy calculation shows that in condensed phases the average volume per molecule is about one and a half times the volume of the molecule itself. Molecules are tightly packed in space, and therefore the compressibility of condensed media is very small. You can sit on a rock simply because its atoms and molecules are so close to each other that they can't give way under external pressure.

A gas will diffuse very quickly out of an open bottle, while a solid can usually be left in open air almost indefinitely without apparent change in size and shape (there are exceptions, like mothballs). Besides repelling each other at short distances, molecules in a solid are reluctant to leave their neighbors, which means that some sort of attraction is holding them together. Temperature has a much more dramatic effect on all this than pressure: ordinary liquids boil when mildly heated, and even solid rock melts and vaporizes in volcanic depths.

Through simple reasoning on simple evidence, we are led to the following conclusions: upon cooling or with increasing pressure, molecules stick together and form liquid and solid bodies, where the distance between them is of the same order of magnitude as the molecular dimensions; and a steady repulsion arises if they are forced into closer contact. The reverse occurs upon heating or lowering the external pressure.

While a layman may be more than satisfied at this point, a scientist must ask him- or herself at least two further questions: 1) what is the nature and magnitude of the forces

holding molecules together, and 2) what is the geometrical arrangement of molecules at close contact. Restricting the scope, as we do in this pamphlet, to crystalline solids, these questions define the subject of crystal packing. Since crystals are endowed by the beautiful gift of order and symmetry, the spatial part is not trivial. Packing forces and crystal symmetry determine the chemical and physical properties of crystalline materials.

2. Thermodynamics

Now put yourself in the place of a molecule within a pure and perfect crystal, being heated by an external source. At some sharply defined temperature, a bell rings, you must leave your neighbours, and the complicated architecture of the crystal collapses to a liquid. Textbook thermodynamics says that melting occurs because the entropy gain in your system by spatial randomization of the molecules has overcome the enthalpy loss due to breaking the crystal packing forces:

$$T[S(\text{liquid}) - S(\text{solid})] > H(\text{liquid}) - H(\text{solid})$$

$$G(\text{liquid}) < G(\text{solid})$$

This rule suffers no exceptions when the temperature is rising. By the same token, on cooling the melt, at the very same temperature the bell should ring again, and molecules should click back into the very same crystalline form. The entropy decrease due to the ordering of molecules within the system is overcompensated by the thermal randomization of the surroundings, due to the release of the heat of fusion; the entropy of the universe increases.

But liquids that behave in this way on cooling are the exception rather than the rule; in spite of the second principle of thermodynamics, crystallization usually occurs at lower temperatures (supercooling). This can only mean that a crystal is more easily destroyed than it is formed. Similarly, it is usually much easier to dissolve a perfect crystal in a solvent than to grow back a good crystal from the resulting solution. The

nucleation and growth of a crystal are under kinetic, rather than thermodynamic, control.

3. The forces

A molecule consists of a collection of positively charged atomic nuclei surrounded by an electron cloud. Even if it has no net charge, such an object can hardly be considered as neutral. Its electrostatic potential is a superposition of the fields of all nuclei and electrons. An approaching charge can alter, by its own electrostatic field, the electron distribution in a molecule; this phenomenon is called polarization.

The attractive forces holding molecules together are a consequence of molecular electrostatic potentials. For purely ionic crystals, one can just use Coulomb's law with integer charges; for organic molecules, it takes a more complicated expression, involving an integration over continuous electron densities. Alternatively, the charge distribution can be represented by a series expansion using multipoles, and the interaction energy can be calculated as a function of multipole moments.

Different atoms have different electronegativities. Larger charge separations within the molecule — in the jargon of the trade, more polar molecules — build up stronger intermolecular forces. Ionic crystals are very hard and stable, while naphthalene or camphor (two common ingredients of mothballs) sublime rather easily. These non-polar hydrocarbon molecules must rely on mutual polarization to produce attraction; the resulting forces are feeble, and are called dispersion or van der Waals forces; they are usually described by empirical formulas. In this way, even argon does form a solid, at very low temperatures.

Ubiquitous in crystals is the hydrogen bond, a polar interaction which is the most effective mean of recognition and attraction between molecules; so effective, that molecules with donor and acceptor groups will form hydrogen bonds without exception. There is no case (at least, to this author's knowledge) where a molecule that can form hydrogen bonds doesn't do so in the crystal.

The repulsion at short intermolecular distance arises from a quantum mechanical effect. According to Pauli's principle, electrons with the same quantum numbers, no matter if belonging to different molecules, cannot occupy the same region of space. Thus, Pauli "forces" — although they are not forces in the sense of newtonian mechanics — steer electrons to mutual avoidance.

Table 1 collects the simple potentials so far mentioned. Direct but non-specific measures of the strength of crystal forces are the melting temperature and the sublimation enthalpy.

4. Crystal symmetry

Intermolecular attraction brings molecules together, but there is no a priori implication of order and symmetry. Glasses, where molecules are oriented at random, are some-

Table 1. Formulae for potential energies in crystals

Electrostatic (ions or point charges):

$$E = \sum_{i,j} (q_i q_j) / R_{ij}$$

Electrostatic (molecules A and B with electron distributions σ_A and σ_B):

$$E = \iint \sigma_A(r_1) \sigma_B(r_2) |r_2 - r_1|^{-1} dr_1 dr_2$$

Dispersion-repulsion (A, B, C, D, m, ..., Q are empirical parameters; R_{ij} is the distance between two sites — usually, atomic nuclei — on different molecules):

$$E = \sum_{i,j} A \exp(-BR_{ij}) - CR_{ij}^{-6} + DR_{ij}^{-m} + \dots + QR_{ij}^{-1}$$

Hydrogen bond: empirical potentials involving local charges, local dipoles, etc. (there is little agreement in the literature).

times as stable as crystals, where molecules are arranged in an ordered fashion. The ordering of irregularly shaped, electrically charged molecules does however imply anisotropy; for mechanical properties, it results in preferential cleavage planes, while the consequences of optical, electrical and magnetic anisotropy lead to a variety of technological applications of crystalline materials.

But what is the link between order, symmetry and crystal stability?

Crystal symmetry² has two facets. On one side, in a milestone mathematical development, it was demonstrated that the possible combinations of symmetry elements (inversion center, rotation axes, mirror planes) give rise to no less and no more than 230 independent three-dimensional space groups. After the advent of X-ray crystallography, space group symmetry was used to determine systematic extinctions and to help in the calculation of structure factors and Fourier syntheses.

The other side of crystal symmetry has to do with the crystal structure, as resulting from mutual recognition of molecules to form a stable solid. This is a fascinating and essentially chemical subject, that requires an evaluation and a comparison of the attractive forces at work in the crystal. Space group symmetry is needed here to construct a geometrical model of the crystal packing, and comes into play in judging relative stabilities.

It should be clear that the necessary combinations of symmetry elements in space bears no immediate relationship to crystal chemistry. The fact that 230 space groups exist does not mean that molecules can freely choose among them when packing in a crystal. Far from it, there are rather strict packing conditions that must be met, and this can be accomplished only by a limited number of combinations of very few symmetry elements; for organic compounds, these are the inversion center (*I*), the twofold screw axis (*S*) and the glide plane (*G*). Some space groups are mathematically legitimate, but chemically impossible, and the crystal structures of organic compounds so far determined belong to a rather restricted number of space groups³ (Table 2).

Table 2. Space group frequencies for organic compounds (from reference 3d).

Rank	Group	Total no. of crystals	Molecules in general position	Point-group symmetry
1	$P2_1/c$	9056	8032 (89%)	$\bar{1}$
2	$P2_12_12_1$	4415	- (-)	none
3	$P\bar{1}$	3285	2779 (85%)	$\bar{1}$
4	$P2_1$	2477	- (-)	none
5	$C2/c$	1371	802 (58%)	$2, \bar{1}$
6	$Pbca$	1180	1064 (90%)	$\bar{1}$
7	$Pna2_1$	445	- (-)	none
8	$P1$	370	- (-)	none
9	$C2$	275	225 (82%)	2
10	$Pnma$	266	33 (12%)	$m, \bar{1}$
12	$Pbcn$	205	94 (46%)	$\bar{1}, 2$
14	$P2_1/m$	127	40 (31%)	$\bar{1}, m$
16	$P2_12_12$	92	46 (50%)	2
17	$Fdd2$	88	51 (58%)	2

When charge is evenly distributed in a molecule, and there is no possibility of forming hydrogen bonds, no special anchoring points exist. Every region of the molecule has nearly the same potential for intermolecular attraction, and hence it is reasonable to expect that each molecule be surrounded by as many neighbours as possible, forming as many contacts as possible. Empty space is a waste, and molecules will try to interlock and to find good space-filling arrangements. This close packing idea appeared very early in its primitive form⁴, but was consciously put forward by Kitaigorodski⁵.

Order and symmetry now come to the foreground, since for an array of identical objects a periodic, ordered and symmetrical structure is a necessary (although not sufficient) condition for an efficient close-packing. When special interactions (like hydrogen bonds) are present, the close-packing requirement may be a little less stringent (Figure 1), but it

turns out that all stable crystals have a packing coefficient⁶ between 0.65 and 0.80.

5. Symmetry elements

In a crystal, some symmetry elements can be classified as intramolecular, meaning that they are also point group elements and relate in fact different parts of the same molecule. The symmetry elements acting as true crystal packing operators may be called intermolecular, being those who relate different molecules in the crystal. This classification implies that molecules be distinguishable in crystals (see note (1)).

The simplest intuitive way of viewing a symmetry element is as an operator that reproduces in space one or more identical copies of a given object, according to a well defined

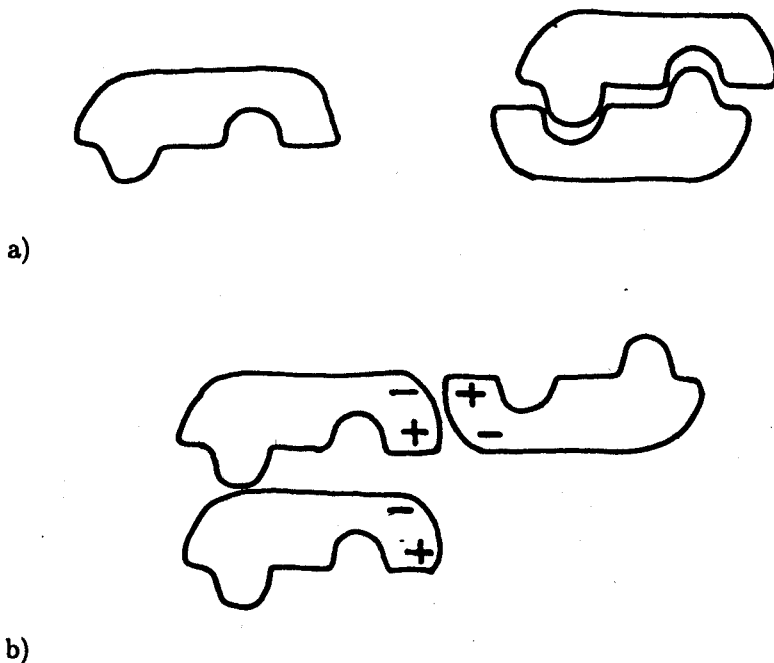


Figure 1. a) A molecule without strongly polar sites chooses to close-pack in the crystal. b) If other attractors are present, the close-packing requirement may be less compelling.

convention (Figure 2). The spatial relationship between the parent and the reproduced molecules is strict, so a moment's pondering will convince the reader that some operators are more effective than others towards close-packing. For objects of irregular shape, mirror planes and twofold axes produce bump-to-bump confrontation, while inversion centers,

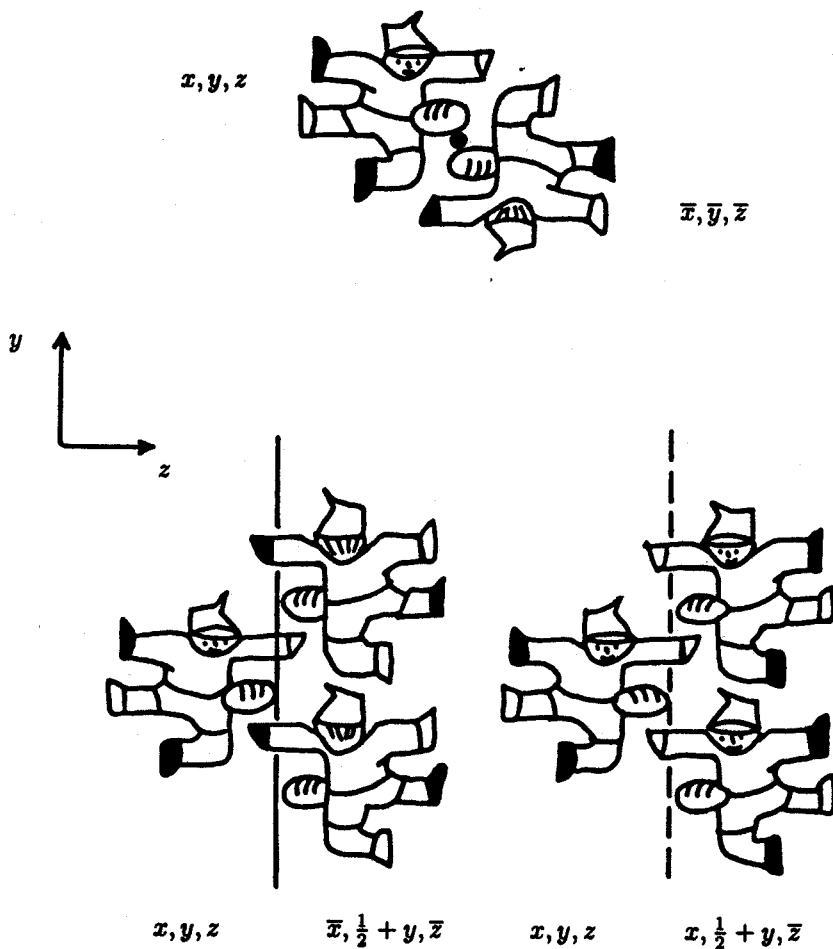


Figure 2. Sketches of the effect of symmetry elements; top, center of symmetry, left, twofold screw axis, right, glide plane. These last two elements give rise to infinite strings in the y direction.

screw axes and glide planes favor bump-to-hollow, more close-packed arrangements (Figure 3).

One must not forget that pure translation (T) is always present in a crystal. Except when infinite strings or layers are present, it is an intrinsically intermolecular operator, whose role in close-packing is probably intermediate (Figure 4); space group $P1$ is the eighth most populated one for organic substances.

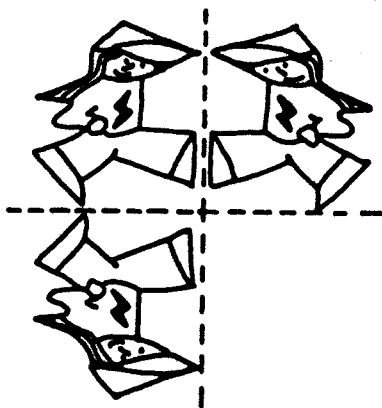


Figure 3. A mirror plane (perpendicular to the page, with trace along the dotted line) cannot produce close-packing. Translation along some direction is required.



Figure 4. A two-dimensional pattern obtained by pure translation; not so bad for interlocking and close-packing. For a complete set of two-dimensional drawings in all the 17 plane groups, see A. Gavezzotti, *Atti Accad. Naz. Lincei*, Ser. VIII, Vol. XIII, p. 107 (1976); photocopies available from the author upon request.

The clearest proof of the leading role of I , S and G in close packing comes from a statistical analysis of the space group frequencies in organic compounds, care being taken to distinguish between inter- and intramolecular symmetry elements. Table 2 shows that mirror planes and twofold axes appear in organic crystals most often as intramolecular operators: thus $C2/c$ is a favourite for molecules with twofold axes, $Pnma$ for molecules with mirror symmetry, and for these space groups the percentage of structures with molecules in general position is very low. $C2$ is an apparent exception; in fact, the combination of centering and twofold axis results in a twofold screw axis (the symmetry operation $\frac{1}{2}-x, \frac{1}{2}+y, -z$). Viewing the issue from the other end, Table 3 shows that a pairwise combination of I , S and G produces rows, layers or full structures in all the most populated space groups for organics. A student who cares to work out in detail the results in this Table will understand all the basic principles of geometrical crystallography and crystal symmetry.

A similar statistic, with a recognition of point-group operators, is not available for inorganic compounds, but a similar trend would probably be found. These compounds frequently contain highly symmetrical (tetrahedral, triangular, square-planar) ions or groups, which carry over their symmetry to the crystal. This causes a spread of the space group frequencies towards the tetragonal, hexagonal or cubic systems (a no-man's land for organics); no space group has more than 10% of the structures for inorganic compounds (Table 4).

One is never too careful when generalizing on such topics; crystal packing is a subtle, elusive subject. To give just an example of its intricacies, when dealing with the importance of symmetry to crystal packing one should consider that a symmetry element is relevant only when it relates close-neighbour molecules. Wilson (3b) has pointed out that, in some space groups, some elements may be silent, or "encumbered"; they appear as products of other elements, but are prevented, by their location in space, from acting between first-neighbour molecules. The relative importance of symmetry operators in the most populated space groups has been quantified by packing energy calculations⁷.

Table 3. Combinations of the most common symmetry elements in organic crystals.

Note: 2, twofold axis; M, mirror plane; G, glide plane; S, twofold screw axis; I, inversion center; T, translation; CE, centering. The labels near to each space group symbol are as follows: C, cluster; R, row; L, layer; 3D, full three-dimensional structure. When several possibilities are given for a combination, they depend on the relative orientation of the two elements.

	2	M	G	S	I
2				$P2_12_12$ L	$[P2/m$ C $]P2/c$ R
M					$[P2_1/m$ R $]P2/m$ C
G				$[P2_1/c$ L $]Pca2_1$ L $]Pna2_1$ 3D	$[P2_1/c$ L $]P2/c$ R
S			$[P2_1/c$ L $]Pca2_1$ L $]Pna2_1$ 3D	$[P2_12_12_13D$ L $]P2_12_12$ L	$[P2_1/m$ R $]P2_1/c$
I		$[P2/m$ C $]P2_1/m$ R	$P2/m$ C	$P2_1/c$ L	$P2_1/c$ L
CE	$C2$ L	Cm L	Cc L	L	

Another reminder: the choice of a space group is to some extent arbitrary, and one might even argue that for example in some cases the presence or absence of a center of symmetry is a questionable matter. This may be true for all symmetry elements; a glide plane can be almost there, and its assignment can be a matter of sensitivity in the apparatus for the detection of weak reflections (where should be the borderline between a "very weak" and an "extinct" reflection can even

Table 4. Space group frequencies for inorganic crystals (from reference (3e)).

Rank	Group	Number of crystals	% of total
1	<i>Pnma</i>	2863	8.3
2	<i>P2₁/c</i>	2827	8.2
3	<i>Fm$\bar{3}$m</i>	1532	4.4
4	<i>P$\bar{1}$</i>	1508	4.4
5	<i>C2/c</i>	1326	3.8
6	<i>P6₃/mmc</i>	1254	3.6
7	<i>C2/m</i>	1180	3.4
8	<i>I4/mmm</i>	1176	3.4
9	<i>Fd$\bar{3}$m</i>	1050	3.0
10	<i>R$\bar{3}$m</i>	858	2.5

be a matter of personal taste). In this respect, the resolution of single-crystal X-ray diffraction experiments is much higher than actually needed, and the presence of a semi- or pseudo-symmetry element, violated because of minor molecular details, has the same chemical meaning as that of a fully observed symmetry element.

What to say, then, of crystals with more than one molecule in the asymmetric unit? Many are presumably just cases of accidental overlooking of a symmetry element in the crystal structure determination and refinement, and many more do have pseudo-symmetry elements relating the molecules in the asymmetric unit (see the remarks in the former paragraph). The conformations of the independent molecules are usually quite similar⁸. While the overall frequency of such structures is about 8% for organics (3c), they seem to be unevenly distributed among chemical classes. For example, for monofunctional alcohols the frequency rises to 50%; a possible interpretation is in terms of hydrogen-bonded dimers and oligomers which are already present in the liquid state, and are so strongly bound that they are transferred intact to the crystal.

The case is similar for molecules which must pick up solvent molecules to crystallize in the form of solvates, or which can form inclusion compounds with a variety of guest molecules. The reasons for the appearance of these phenomena, and their control, are presently beyond reach [but see reference (9)].

6. Crystal structure descriptors

Simple but useful crystal structure descriptors are the density, the melting point and the packing coefficient; mention of the first is mandatory for papers in *Acta Crystallographica*, but unfortunately mention of the other two is not.

The intermolecular geometry is another Cinderella in crystallographic papers. Clearly, a long list of intermolecular interatomic distances is not generally useful or significant, but, for hydrogen-bonded crystals, the crucial $X \cdots X$ or $H \cdots X$ contact distances are usually sufficient. As a general rule, the description of intermolecular geometry requires the use of macro-coordinates, like the distances between molecular centers of mass or the angles between mean molecular planes in different molecules or fragments. It can be said that the crystal structure of naphthalene can be described by just two parameters — the angle between the molecular planes of glide-related molecules and the distance between their centers of mass, which contain most if not all of the chemical information on the properties of the crystalline material. It is also unfortunate that such macrogeometry is very seldom highlighted in crystallographic papers, and has to be painstakingly recalculated from the atomic coordinates.

A crystal model suitable for computer use can be built very simply, using the crystal coordinates for a reference molecule (RM) and the space group matrices and vectors, as given in the *International Tables for X-ray Crystallography*. In this respect, finding in the primary literature a set of atomic coordinates representing a completely connected molecular unit, as near as possible to the origin of the crystallographic reference system, with a reduced cell and in a standard space group, helps in saving a substantial amount of time and mistakes (let this be said as an encouragement to

experimental X-ray crystallographers to help their theoretician colleagues).

The required algebra is as follows. Calling \mathbf{x}_0 the original atomic fractional coordinates of the RM, \mathbf{P}_i and \mathbf{t}_i a space group matrix and (column) translation vector, the atomic coordinates in a given surrounding molecule (SM) are given by:

$$\mathbf{x}_i = \mathbf{P}_i \mathbf{x}_0 + \mathbf{t}_i$$

From this expression the coordinates of all atoms in the crystal model can be calculated, remembering that translation vectors whose components are an arbitrary combination of integer unit cell translations can always be added to the \mathbf{t}_i vectors.

Symmetry elements can be associated with a matrix-vector pair [although not all matrix-vector pairs can be associated with a symmetry element; see reference (10)]. Thus:

$$\mathbf{P} = \begin{pmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} \mathbf{t} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \text{ inversion center at the origin}$$

$$\mathbf{P} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \mathbf{t} = \begin{pmatrix} 0 \\ 0 \\ \frac{1}{2} \end{pmatrix} \text{ a glide plane with translation along } z$$

$$\mathbf{P} = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} \mathbf{t} = \begin{pmatrix} 0 \\ \frac{1}{2} \\ 0 \end{pmatrix} \text{ a screw axis along } y$$

but note that:

$$\mathbf{P} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} \mathbf{t} = \begin{pmatrix} 0 \\ \frac{1}{2} \\ 0 \end{pmatrix} \text{ a twofold axis at } \frac{1}{4} \text{ on } y$$

A most important crystal property that can be calculated by this model is the packing energy. For an ionic crystal, if the coordinates and charges of all ions in the crystal model are known, the interionic distances and hence the coulombic energy can be calculated. In organic crystals with purely dispersive-repulsive forces, the packing energy can be approximated by empirical formulas:

$$PE = \frac{1}{2} \sum \sum E(R_{ij})$$

$$E(R_{ij}) = A \exp(-B \cdot R_{ij}) - CR_{ij}^{-6}$$

where R_{ij} is an intermolecular interatomic distance, and A, B and C are empirical parameters.

7. Polymorphism: thermodynamics versus kinetics

It was said earlier in this pamphlet that crystal nucleation and growth are quite often under kinetic control. The final product, the (single) crystal, may result from less stable but faster growing nuclei; the transformation to the thermodynamically stable phase is forbidden by an energy barrier, because the forces holding together the metastable phase have to be overcome, so that molecules can rearrange into the stable crystalline form. In some favourable (and almost exceptional) cases, the spatial rearrangement is so simple that a highly cooperative single crystal to single crystal transformation can occur.

The natural outcome of all this is polymorphism, or the ability of a given compound to crystallize in different forms. Thermodynamics holds that only one form is the stable one at a given temperature and pressure, but, not surprisingly, kinetics sometimes allows many coexisting phases¹¹. A typical enthalpy difference between polymorphs for an organic compound is 4–8 kJ/mole, which, for transition temperatures of the order of 300 K, implies entropy differences of the order of 10–20 J K⁻¹ mole⁻¹ ($\Delta G = 0 = \Delta H - T\Delta S$). These figures are now at the borderline of the accuracy of both detection apparatus and theoretical methods¹².

8. Chirality

Space groups that do not contain inversion centers or mirror planes are chiral. Solutions or melts of chiral molecules, containing only one optical isomer, must crystallize in a chiral space group; this is the case for many natural products whose crystal structures appear in the Cambridge Structural Database, that have been isolated in optically pure form from plants or animals. Since natural compounds are chemically and biologically interesting, their crystal structures are determined more frequently, and this artificially increases the frequency of occurrence of chiral space groups.

It sometimes happens that a racemic solution or melt produces chiral crystals, in which only one optical isomer at a time appears; in these cases, a spontaneous resolution has been achieved, and this phenomenon is often quoted as one of the possible sources of optical resolution in the biological world. The reasons for such a selectivity, undoubtedly brought about by crystal packing requirements, is part of the mystery that shrouds the formation of crystalline solids. A comparative study of the crystal packing of pure compounds and of their racemates has been carried out¹³; no clear sign of a more compact crystal packing has been found for racemates.

It is difficult, if not impossible, to ascertain the frequency of this resolution by crystallization, because the chemical history of the sample and the optical status of the starting materials for crystal formation and growth are seldom or never mentioned by the authors of crystallographic papers. A source of potentially extremely useful chemical information is thus lost.

9. Experiments

X-ray and neutron diffraction give a detailed picture of crystal packing. It is difficult to find, in all natural sciences, a more undisputable experimental result, than that of well performed single-crystal diffraction work. The information is however mainly static, although skillful elaborations may provide a tinge of dynamics to the picture.

Crystal dynamics may be probed by infra-red spectroscopy, for the frequencies of lattice vibrations. Hole-burning spectroscopy can address single impurity molecules in a crystalline environment, and so potentially probe the packing environment. NMR spectroscopy can be used to detect molecular motions and large-amplitude rearrangements, ESR spectroscopy to study the fate of organic radicals produced after a chemical reaction in a crystal.

All measurements of mechanical, electrical, optical, or magnetic properties of crystals are in principle relevant to the study of molecular packing. These experiments are seldom performed by chemists, being beyond the border with the realm of solid-state physics. The relationship between these properties and the crystal structure is strict, but not known in a systematic way.

One most important experiment for the science of crystal packing is a humble one, that is performed every day in every chemical laboratory, but whose results are seldom recorded and almost never published: crystallization from solution. This is a small step for any single chemist, but a systematic analysis of the relationship between molecular structure and ease of crystallization from many solvents and in many temperature conditions would be but a giant leap for the chemical sciences.

10. Concluding remarks, and a suggestion

Crystal packing is a fascinating, and at the same time such a complicated phenomenon. The physics of the interaction between molecules is relatively simple, but the rules that determine the ways in which these forces can be satisfied are complex and still obscure. For this reason, crystal packing prediction and control are still far away goals: there are simply too many spatial possibilities with very nearly the same free energy.

The principles of crystal packing are still largely unknown. No one has a unique and general answer even to the most fundamental question: why some substances do crystallize, and others do not? Is there any trend in molecular

size, shape, stoichiometry, conformation, polarity, that accounts for the crystallization ability? And then, more detail; for example, for nonlinear optics applications, it is important to grow non-centrosymmetric crystals, but no one knows why and when a molecule will adopt an inversion center in forming its crystal structure.

The problem is being tackled, however. On one side, we have the Cambridge Database, with an enormous potential for intermolecular information, which can be studied by statistics; and the first law of cryptography states that any code can be cracked, given enough text. On the other side, a number of theoretical techniques can be used; for example, if a reliable intermolecular potential function is available, the packing energies of different crystal structures for the same compound can be calculated and compared¹⁴; eventually, a full molecular dynamics simulation may become possible.

In our times, scientific breakthroughs are fostered by large numbers of small, most often unconscious, contributions. The accumulation of basic data plays a key role. But the problem is to look at the right things.

The age of intramolecular structural chemistry is declining for small molecules. There is very little that can be added to the average intramolecular geometrical data collected¹⁵ by use of the Cambridge Structural Database; anything at variance with these well established averages is most probably wrong. Long experience has shown that discussing electronic effects in terms of molecular geometry alone is a tricky business. So, if you are an X-ray diffractionist, instead of looking at your molecule, try looking at your crystal. There is plenty to be discovered, at a low cost and with perfectly high confidence, by looking at what molecules do when they interact with each other, and single-crystal X-ray diffraction is still the best technique to this purpose.

References and notes

- (1) From now on, the term "molecule" denotes a molecule proper, or any other chemical entity recognizable also in the gas phase (a helium atom, an Na^+ or SO_4^{2-} ion, an $\text{Fe}_2(\text{CO})_9$ complex). In general,

it can be said that a molecule is a distinguishable entity when the forces acting within it are much stronger than the forces acting on it in the crystal. Difficulties arise with infinite strings or layers; diamond and NaCl crystals are examples of three-dimensionally infinite systems where the term "molecule" is meaningless. Also, whenever "organic" compounds are mentioned in the text, one should read "organic and organometallic" compounds.

- (2) The term "crystal symmetry" refers to microscopic relationships between molecules or parts of molecules, and not to macroscopic morphology.
- (3)
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- (6) The packing coefficient is the ratio of volume occupied by molecules in the cell to the volume of the cell. Molecular volumes can be calculated in a number of ways; the simplest ones are in reference 5, in A. Bondi, *J. Phys. Chem.* **68**, 441 (1964), and in A. Gavezzotti, *J. Am. Chem. Soc.* **105**, 5220 (1983).
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- (11) J.A.R.P. Sarma and J.D. Dunitz, *Acta Cryst.* B46, 784 (1990).
- (12) A. Gavezzotti, *Acc. Chem. Res.* 27, 309 (1994); A. Gavezzotti and G. Filippini, *J. Am. Chem. Soc.* 117, 12299 (1995)
- (13) C.P. Brock, W.B. Schweizer and J.D. Dunitz, *J. Am. Chem. Soc.* 113, 9811 (1991).
- (14) A. Gavezzotti, *Acta Cryst.* B52, 201 (1996).
- (15) F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J. Chem. Soc. Perkin II*, S1, (1987).

Suggestions for further reading:

- (a) Two fundamental books on condensed phases are those by A. Bondi, *Physical Properties of Molecular Crystals, Liquids and Glasses*, Wiley, New York (1968), and A.R. Ubbelohde, *The Molten State of Matter*, Wiley, Chichester (1978). They probably have long been out of print, but must be still available in your chemistry library.
- (b) The works of A.I. Kitaigorodski, a pioneer in the field of crystal packing studies, are collected in two main books: i) the one quoted here as reference 5; ii) A.I. Kitaigorodski, *Molecular Crystals and Molecules*, Academic Press, New York (1973).
- (c) A similar role is played for inorganic structures by the multi-author book: *Structure and Bonding in Crystals*, edited by M. O'Keeffe and A. Navrotski, Academic Press, New York (1981).
- (d) A compendium of the theory of the structure and of the optical, electrical and properties of organic materials is in J.D. Wright, *Molecular Crystals*, Cambridge University Press, Cambridge, (1987). For an emphasis on optoelectronics, see J. Simon,

P. Bassoul and S. Norvez, *New J. Chem.* **13**, 13 (1989), and also P.J. Fagan and M.D. Ward, *Scient. Amer.* July 1992, p. 48.

- (e) If you want to read an amusing and stimulating book, and learn about molecular orbitals for periodic systems into the bargain: R. Hoffmann, *Solids and Surfaces, a Chemist's View of Bonding in Extended Structures*, VCH, New York (1988).
- (f) The most comprehensive review to date on methods for the investigation of the geometrical and energetic properties of crystal packing is the book by G.R. Desiraju, *Crystal Engineering, the Design of Organic Solids*, Elsevier, Amsterdam (1989).
- (g) A quick reference monograph on the nature of intermolecular forces is M. Rigby, E.B. Smith, W.A. Wakeham, G.C. Maitland, *The Forces between Molecules*, Clarendon Press, Oxford (1986). As an example of a more technical paper, on the derivation of site charges to describe the electron density of organic molecules in crystal packing problems, see: D.E. Williams, Net Atomic Charge and Multipole Models for the ab initio Molecular Electric Potential, in *Reviews in Computational Chemistry*, Vol. 2, edited by K.B. Lipkowitz and D.B. Boyd, VCH, New York (1991).

The empirical fitting of potential functions for organic crystals, and their use in lattice statics and dynamics, has been reviewed by A.J. Pertsin and A.I. Kitaigorodski, *The Atom-Atom Potential Method*, Springer-Verlag, Berlin (1987).

- (h) Studies of hydrogen bonding have been reviewed and analyzed in many books and monographs; a classic one is: G.C. Pimentel and A.L. McClellan, *The Hydrogen Bond*, Freeman & Co., (1960); a very recent one is by G.A. Jeffrey and W. Saenger, *Hydrogen Bonding in Biological Structures*, Springer-Verlag, Berlin (1991).

For a recent approach to the classification of hydrogen bonding with explicit reference to crystal packing, using graph set theory, see M.C. Etter, *Acc.Chem. Res.* **23**, 120, 1990.

- (i) A collection of over 1000 heats of sublimation for organic com-

pounds has been given by J.S. Chickos, in *Molecular Structure and Energetics*, edited by J.F. Liebman and A. Greenberg, VCH, New York (1987). Such compilations may seem uninspiring, but quantitative measurements are the only sound basis of quantitative understanding.

- (j) For molecular dynamics and reactivity in the solid state, see: M. Simonetta and A. Gavezzotti, *Chem Rev.* **82**, 1 (1982); J.M. McBride, B.E. Segmuller, M.D. Hollingsworth, D.E. Mills, B.A. Weber, *Science* **234**, 830 (1986); G.R. Desiraju (Editor), *Organic Solid State Chemistry*, Elsevier, Amsterdam (1987); J. Scheffer, N. Turro and V. Ramamurthy (Guest Editors), *Tetrahedron* **43**, 1197 (1987), (Symposia-in-Print no. 29); D. Braga, *Chem. Rev.* **92**, 633 (1992).
- (k) A study of the chemical consequences of crystal symmetry is in D.Y. Curtin and I.C. Paul, *Chem. Rev.* **81**, 525 (1981).
- (l) On NMR spectroscopy, see C.A. Fyfe, *Solid State NMR for Chemists*, CFC Press, Guelph, Ontario 1983.