CRYSTAL STRUCTURES OF DRUGS: ADVANCES IN DETERMINATION, PREDICTION AND ENGINEERING

Sharmistha Datta and David J. W. Grant

Most marketed pharmaceuticals consist of molecular crystals. The arrangement of the molecules in a crystal determines its physical properties and, in certain cases, its chemical properties, and so greatly influences the processing and formulation of solid pharmaceuticals, as well as key drug properties such as dissolution rate and stability. A thorough understanding of the relationships between physical structures and the properties of pharmaceutical solids is therefore important in selecting the most suitable form of an active pharmaceutical ingredient for development into a drug product. In this article, we review the different crystal forms of pharmaceuticals, the challenges that they present and recent advances in crystal structure determination. We then discuss computational approaches for predicting crystal properties. Finally, we review the analysis of crystal structures in furthering crystal engineering to design novel pharmaceutical compounds with desired physical and mechanical properties.

Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, Minnesota 55455-0343, USA.
Correspondence to D.J.W.G.
e-mail: grant001@umn.edu
doi:10.1038/nrd1280

Pharmaceutical solids can be classified as either crystalline solids, which have regular arrangements of molecules that repeat in three dimensions, or amorphous solids, which lack the long-range order present in crystals[1]. These differences in the long-range periodicity of the molecules result in the substantially different physical and chemical properties of crystals and amorphous solids[2,3]. Although amorphous solids often have desirable pharmaceutical properties — such as faster dissolution rates — than their crystalline counterparts, they are not marketed as widely as the crystalline forms because of their lower chemical stability and their innate tendency to crystallize. Most marketed pharmaceuticals therefore consist of molecular crystals[4].

The arrangement of the molecules in a crystal determines its physical properties and, in certain cases, its chemical properties[5]. The physicochemical properties of the solid drug can affect its performance. The shape and particle size of the solid drug can influence pharmaceutical operations, such as filtration, washing, drying, milling, mixing, tableting, dissolution, recrystallization of a suspension and lyophilization[2,6]. Several pharmaceutical crystals — for example, theophylline[7], chlorpropamide[8], carbamazepine[9,10], phenobarbital[11], lactose[12], chlorpromazine hydrochloride[13], uricosuric agent FR76505 (REF. 14) and pentamidine isethionate[15] — are known to undergo a variety of PHASE TRANSFORMATIONS during their processing and formulation[16,17]. These phase transformations can affect the stability of the product and, in some cases, even the bioavailability of the drug[18]. An understanding of the relationship between the solid-state properties and the crystal structure of the likely phases might be utilized for optimizing operational and formulation strategies and in designing suitable stability protocols to avoid later problems[19–23]. The characterization and understanding of the crystal properties is also important for quality control and regulatory purposes[24].

Pharmaceutical crystals can exist as single molecular entities or as MOLECULAR ADDUCTS[5]. As single molecular entities, organic solids can show polymorphism, which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice[25]. BOX 1 lists the differences that can

Box 1 | **Polymorph property differences**

Packing properties
- Molar volume and density
- Refractive index, optical properties
- Conductivity, electrical and thermal
- Hygroscopicity

Thermodynamic properties
- Melting and sublimation temperatures
- Internal energy
- Enthalpy
- Heat capacity
- Entropy
- Free energy and chemical potential
- Thermodynamic activity
- Vapour pressure
- Solubility

Spectroscopic properties
- Electronic transitions, ultraviolet-visible spectra
- Vibrational transitions, infrared and Raman spectra
- Rotational transitions
- Nuclear magnetic resonance chemical shifts

Kinetic properties
- Dissolution rate
- Rates of solid state reactions
- Stability

Surface properties
- Surface free energy
- Interfacial tensions
- Habit

Mechanical properties
- Hardness
- Tensile strength
- Compactibility, tabletability
- Handling, flow and blending

PHASE TRANFORMATION
The transformation of a solid from one physical form to another. Phase transformation can involve the transformation of a single component into one or more components, and can result from changes in physical conditions, as in pharmaceutical processing. Examples of phase transformation include polymorphic transitions, crystallization of amorphous solids, and solid-state solvation and desolvation.

MOLECULAR ADDUCT
A crystal is termed a molecular adduct when its lattice consists of more than one chemical component.

SOLVATE
A solid phase that contains solvent molecules, in addition to molecules of the major component, in the crystal lattice.

HYDRATE
A solid phase that contains water molecules, in addition to molecules of the major component, in the crystal lattice.

HYDROGEN BOND
An attractive interaction between two electronegative atoms through a hydrogen bridge. The hydrogen bond is partly electrostatic and partly covalent in nature, with limited orbital overlap between the participating atoms. Of the two electronegative atoms, one is the proton donor and the other is a proton acceptor. When present within the same molecule, a hydrogen bond is termed intramolecular. When present between two molecules, a hydrogen bond is termed intermolecular.

SLIP SYSTEM
The term slip refers to the translational motion of lattice planes relative to each other. Such planes are termed slip planes. A family of slip planes, together with the slip direction, is termed a slip system.

be shown by different polymorphs[19], many of which might be important in drug performance. A recent case that exemplifies the importance of polymorphism in pharmaceuticals is highlighted in BOX 2.

Molecular adducts include SOLVATES and HYDRATES, which can be stoichiometric or nonstoichiometric in nature[26]. Clathrates are a special type of molecular adduct in which the guest molecules occupy, fully or partially, cages in the crystal lattice of the host[27,28] without specifically interacting with the host molecules. Solvates and hydrates generally demonstrate different solubilities and consequently different intrinsic dissolution rates (dissolution rates per unit surface area) than their unsolvated counterparts[29]. Moreover, the stability profiles of hydrates and solvates at various temperatures and at different vapour pressures of water or organic solvents differ from those of the unsolvated crystal form[30]. These differences can influence formulation, processing and stability under various storage conditions of the drug compound, as well as the pharmaceutical product.

Pharmaceutical salts can exist in any of the above solid forms. However, the presence of ions strongly influences the physicochemical properties of the crystals, including solubility, dissolution rate, stability and hygroscopicity[31–34]. Recently, interest in the physical properties and crystal structures of chiral drugs has also grown[35,36]. It is well recognized that the pharmacological, toxicological, pharmacodynamic and pharmacokinetic properties can differ markedly between the opposite enantiomers and the racemates of a chiral drug[37,38]. The molecular environments in each of these solids are unique and impart different physicochemical properties to the crystals[39].

The structure of a crystal also affects its mechanical properties and thereby its processability. For example, Agbada and York[40] showed that the monohydrate of theophylline possesses higher mechanical strength than anhydrous theophylline, by virtue of the greater number of intermolecular HYDROGEN BONDS in its crystal structure. The weaker mechanical strength of the anhydrate makes it more brittle than the monohydrate. Similarly, Sun and Grant[41] showed that the presence of water molecules in the crystal structure of 4-hydroxybenzoic acid facilitates plastic deformation as compared with that of 4-hydroxybenzoic acid anhydrate. Bandopadhyay and Grant[42] showed that knowledge of the crystal structure and the SLIP SYSTEMS can be used to model the tableting and compaction behaviour of molecular crystals, such as the anhydrate and dihydrate forms of L-lysine hydrochloride. Furthermore, comparing the crystal structures of two polymorphs of sulfamerazine (FIG. 1), Sun and Grant[43] showed that polymorph I, which has well-defined slip planes, gives greater plasticity, compressibility and tabletability than polymorph II, which has no discernible slip planes.

In summary, an understanding of the crystalline state leads to an understanding of the drug properties, which is crucial for many of the activities of the pharmaceutical industry. In this article, we review the different crystal forms of pharmaceuticals, the challenges that they present and recent advances in crystal structure determination. We emphasize the computational approaches for predicting crystal properties, and also review the analysis of crystal structures in furthering crystal engineering to design novel pharmaceutical compounds with desired physical and mechanical properties.

Crystalline state: fundamental concepts

Crystal systems. Crystals, following the discussion above, consist of minimal building blocks, each of which contains all the structural features and symmetry elements, and which is repeated regularly in three-dimensional space. The minimal building block is termed the unit cell[44] (FIG. 2), and contains at least one molecule. Symmetry considerations show 230 unique arrangements of points in space, termed space groups. These 230 space groups describe all the possible ways in

Box 2 | Importance of pharmaceutical polymorphism: ritonavir

Ritonavir (Norvir; Abbott) is a drug for treating patients infected with human immunodeficiency virus-1 (HIV-1) that acts by inhibiting the HIV-1 protease[185]. When it was first discovered in late 1992, ritonavir crystallized as Form I. Other crystal forms of ritonavir were not discovered at that time. A New Drug Application for ritonavir was filed in 1995 and ritonavir was launched on to the market in 1996. The drug was formulated as soft gelatin capsules and as oral solutions. Early in 1998, some lots of ritonavir capsules failed the dissolution test. Investigation of this phenomenon revealed that a new crystal form of ritonavir precipitated from the formulation. The new crystal form, named Form II, is less soluble than Form I, and is therefore thermodynamically more stable. The lower solubility of Form II as compared with that of Form I resulted in the precipitation of the drug and also decreased the dissolution rate of the marketed formulations. Within days–weeks, the new form, Form II, was produced in all the production lines, resulting in the failure of the established formulation. To investigate whether any significant changes had been made to the bulk manufacturing process of ritonavir, a team of scientists who had been exposed to Form II in the United States visited the facility manufacturing ritonavir in Italy. Until then, Form II had not been detected in the bulk drug lots in the Italian sites. However, soon after this visit, significant amounts of Form II appeared in the bulk drug manufactured in Italy, perhaps as a result of accidental seeding with Form II. The adverse effect of the decreased dissolution rate on the bioavailability of ritonavir led to withdrawal of the extant formulated products. Eventually, after considerable effort and expense, a new formulation of ritonavir was developed, submitted to the FDA, approved and launched onto the market[186].

which identical objects can be arranged in an infinite lattice[45]. Certain space groups are seen frequently, whereas other space groups have never been found in crystals[46]. According to the Cambridge Structural Database (CSD), ~76% of all organic and organometallic compounds crystallize in only five space groups — $P2_1/c$, $P2_12_12_1$, $P\bar{1}$, $P2_1$ and $C2/c$ — and ~90% of all organic and organometallic crystal structures belong to the 17 most common space groups[47].

Forces responsible for crystal packing. The packing energy of a crystal, termed the lattice energy, is the summation of a large number of relatively weak intermolecular interactions (0.5–2 kJ per mol), relatively strong intermolecular interactions (~30 kJ per mol), and especially strong intramolecular and interionic interactions (~150 kJ per mol)[48]. Although the intramolecular interactions bond the atoms in the molecule, the intermolecular forces minimize the energy of the molecules in the crystal and are primarily responsible for the formation of organic crystals[49]. The intermolecular forces, which can be attractive or repulsive in nature, consist of non-bonded (sometimes termed non-covalent) interactions, such as van der Waals forces and hydrogen bonds[50–52], and ionic and electrostatic interactions. Hydrogen bonds and van der Waals interactions, both of which are attractive interactions, are the major intermolecular forces in most pharmaceutical crystals[53–56]. However, if the molecule is polar and charged, ion–ion contributions can significantly affect the overall crystal packing energy[57].

ENANTIOTROPE
The members of a pair of polymorphs are termed enantiotropes when their mutual transition temperature is less than the melting point of either polymorph. Each enantiotrope has its own temperature range of stability.

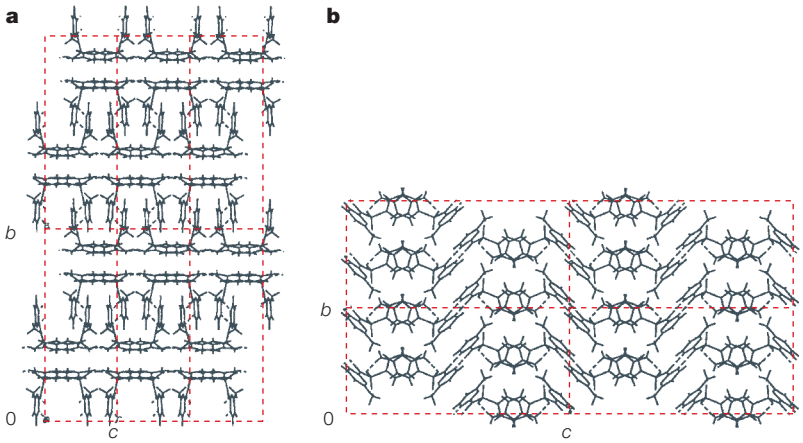


Figure 1 | **Influence of crystal structure on properties of polymorphs.** The crystal structures of sulfamerazine polymorphs looking into the *a* axis. **a** | Polymorph I, in which the slip planes are parallel to the *ac* plane of the unit cell. **b** | Polymorph II, in which no slip plane is observed. The hydrogen bonds are indicated by dotted lines between molecules[168]. Reproduced, with permission, from REF. 43 © (2001) Kluwer Academic Press.

Crystalline states. Crystalline solids can exist as polymorphs, hydrates or solvates, or combinations thereof. According to the corresponding thermodynamic relationships, polymorphs can be classified as either ENANTIOTROPES or MONOTROPES, depending on whether or not one form can transform reversibly to another[58–66]. Organic molecules are capable of forming different crystal lattices through two different mechanisms. One mechanism, termed packing polymorphism or orientational polymorphism, represents instances in which molecules that are conformationally relatively rigid can be assembled into different three-dimensional structures through different intermolecular juxtapositions. The other mechanism, termed conformational polymorphism, arises when a flexible molecule bends into different conformations, which subsequently can be packed into alternative crystal structures. The structural aspects associated with polymorphs have been reviewed recently, as have the analogous features of solvates and hydrate systems[16].

Approximately one-third of active pharmaceutical substances are capable of forming crystalline hydrates[67]. The water molecule, because of its small size, can often fill structural voids and, because of its ability to participate in multidirectional hydrogen bonding, is also capable of linking to most drug molecules to form new crystal structures. On the basis of the location of water in their structures, crystalline hydrates can be classified into three categories[68,69]: ISOLATED SITE HYDRATES (for example, cephadrine dihydrate[70]); ION-ASSOCIATED HYDRATES (for example, dihydrate and trihydrate of disodium adenosine 5′-triphosphate[16,71]); and CHANNEL HYDRATES (for example, theophylline monohydrate[72]), which can be further classified into two subcategories, the EXPANDED CHANNEL or nonstoichiometric hydrates (for example, cromolyn sodium[73–75]) and the PLANAR HYDRATES (for example, nedocromil zinc[76]). On account of the multiple roles of water, some hydrates can comprise more than one category; for example, the nedocromil bivalent metal salt hydrates[77]. The mere presence of water in a system is not sufficient for hydrate formation. The molecular (and crystal) structure, the activity of water in the crystallization medium and the temperature determine whether a given hydrate structure will form[78].

MONOTROPE
The members of a pair of polymorphs are termed monotropes when they have no mutual transition temperature. One monotrope is always more stable than the other polymorph under all conditions in which the solid state can exist.

ISOLATED SITE HYDRATE
In an isolated site hydrate, the water molecules in the crystal lattice of the hydrate are isolated from direct contact with other water molecules by intervening molecules of the major component.

ION-ASSOCIATED HYDRATE
In an ion-associated hydrate, the water molecules in the crystal lattice of the hydrate are coordinated to certain ions (often metal ions).

CHANNEL HYDRATE
In a channel hydrate, the water molecules present in the crystal lattice of the hydrate lie next to other water molecules of adjoining unit cells, forming channels through the crystals along a direction in the lattice.

EXPANDED CHANNEL HYDRATE
An expanded channel hydrate can take up water into the channels when exposed to relatively high humidity and can release water from the channels when exposed to relatively low humidity. The crystal lattice can expand or contract as hydration or dehydration proceeds, changing the dimensions of the unit cell.

PLANAR HYDRATE
A planar hydrate is a channel hydrate in which water molecules are localized in a plane, corresponding to two-dimensional order.

SOLID SOLUTION
A solid solution can be substitutional or interstitial. A substitutional solid solution is a homogeneous crystalline phase in which some of the constituent molecules are substituted by foreign molecules that possess sufficient similarity that the lattice dimensions are changed only slightly. In an interstitial solid solution, the foreign molecules are inserted into interstitial positions, such that the lattice dimensions are changed only slightly.

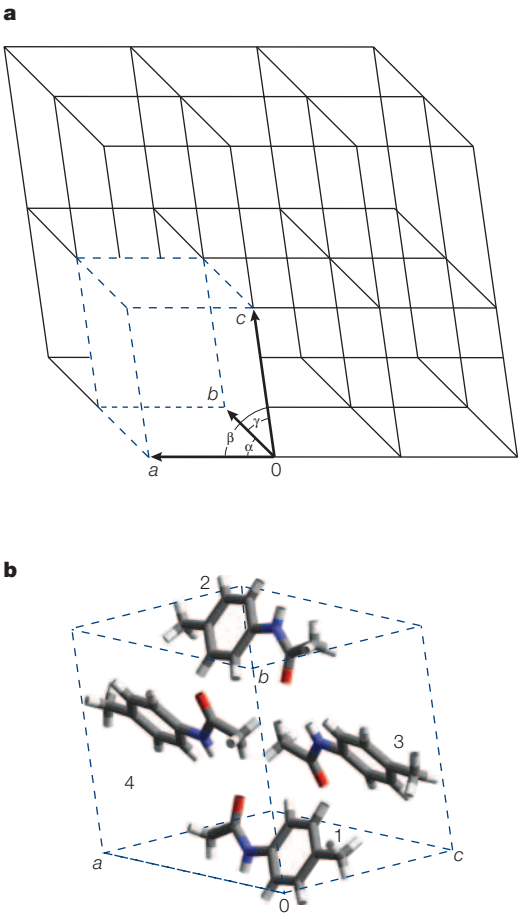


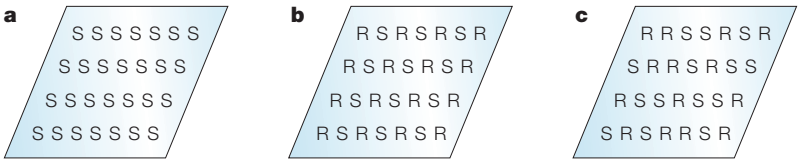
Figure 2 | **Fundamentals of crystal structure. a** | Crystals consist of minimal building blocks, termed unit cells, each of which contains all the structural features and symmetry elements and is repeated regularly in three-dimensional space. The dimensions of the unit cell are characterized by six quantities; three axial lengths (*a, b, c*) and three interaxial angles (α, β, γ). Each unit cell contains at least one molecule and can be classified by one of the seven three-dimensional coordinate systems, which are the seven primitive crystal systems. Each of these crystal systems has one or more symmetry elements that describe the internal symmetry of the unit cell. The different symmetry elements comprise rotation, mirror, screw, glide, and rotation-inversion operations. There are 32 possible unique combinations of the different crystallographic symmetry elements, each defined by a point group. Bravais discovered that some crystal lattices are more complex but still conform to the seven crystal systems. In these so-called nonprimitive lattices, each lattice point and every symmetry element in the primitive lattice are reproduced with a corresponding offset. In total, there are 14 Bravais lattices consisting of seven primitive and seven nonprimitive lattices. The combination of 32 point groups with 14 Bravais lattices leads to 230 unique arrangements of points in space, termed space groups. **b** | The features and symmetry elements of space group $P2_1/c$ (in which pharmaceuticals often crystallize) is exemplified with the unit cell of 4-methylacetanilide (CSD Refcode ACTOLD01), which contains two independent symmetry elements: (i) rotary inversion (about the centre of the unit cell), and (ii) screw symmetry (with rotation parallel to *b*-axis and translation along *c*-axis). The molecular pair (1, 2) and (3, 4) are related by symmetry of rotary inversion. The molecular pair (1, 3), (1, 4), (2, 4) and (3, 4) are related by the screw symmetry.

More than half of all marketed drug molecules contain one or more chiral centres. No matter whether a racemate or an enantiomer is chosen for administration, the physical properties of the chiral drug must be thoroughly characterized during the development of the drug to provide a safe, efficacious and stable pharmaceutical formulation[28,79,80]. Most chiral drugs are marketed as racemates. Three known types of racemates — racemic conglomerate, racemic compound and pseudoracemate — are shown schematically in FIG. 3 (REF. 81). Because of the strict spatial requirements for formation of SOLID SOLUTIONS, pseudoracemates are rare racemic species. Racemic compounds and pseudoracemates comprise heterochiral crystals. The differences in properties between the two enantiomers in a conglomerate and a racemic compound arise from the different interactions between the homochiral or heterochiral molecules and from their different packing arrangements in the crystal structures. These differences in crystal structures lead to different physical properties and/or biological activities of racemic conglomerates and racemic compounds. The elements of inverse symmetry present in the achiral space groups of the racemates contribute to close packing, leading to greater stability of the racemic compound compared with that of homochiral mixtures or conglomerates[82].

Polymorphism and solid-state solvation are common among chiral drugs. Polymorphism can be shown by individual enantiomers (for example, carvoxime[82] and nitrendipine[83]) as well as by racemates (for example, mandelic acid[84]). The existence of polymorphism of a chiral drug will not only affect its pharmaceutically relevant properties, but can also result in interconversion between the different types of racemates, as shown by nicotine derivatives[85] and sodium ibuprofen[86].

Certain chiral drugs can form solvates. In chiral systems, the racemic compound and the enantiomer undergo different degrees of solvation under given conditions. For example, enantiomeric histidine hydrochloride forms a monohydrate when crystallized from water, whereas racemic histidine hydrochloride forms a dihydrate[87]. Diastereomeric pairs also form solvates with different degrees of solvation that can affect their individual solubilities.

The non-superimposibility of a chiral molecule on its mirror image is reflected in the crystal structure[88]. Although chirality does not imply a total lack of symmetry (asymmetry), the existence of chirality in a crystal does require the absence of an IMPROPER ROTATION ELEMENT. Consequently, the overall crystal structure of an enantiomer must be dissymmetric. Enantiomers can therefore crystallize in only 66 of the 230 space groups. A survey of 430 cases of enantiomers[89] revealed that enantiomers crystallize preferentially in certain selected space groups: 67% in the $P2_12_12_1$ space group, 27% in the $P2_1$ space group, 1% in the $C2$ space group, and 5% in some of the other 63 space groups. Racemic compounds, on the other hand, can crystallize in any one of the 164 achiral space groups. However, a study of 792 cases of racemic compounds revealed



Homochiral or enantiomorphic crystal (same chirality)

Heterochiral or racemic crystal (paired enantiomers)

Solid solution (randomly arranged enantiomers)

Figure 3 | **Types of racemate.** Schematic representation of the molecular arrangements in the following three types of racemic species. **a** | Racemic conglomerate (Type I) is a 1:1 physical mixture of homochiral crystals of the enantiomers, for example, asparagine or sodium ibuprofen. **b** | Racemic compound (Type II) is a homogeneous solid phase with the two enantiomers present in equal amounts in each unit cell of the crystal lattice, for example, ibuprofen free acid or ephedrine free base. **c** | Pseudoracemate (Type III) is a homogeneous solid solution containing equimolar amounts of the opposite enantiomers more or less unordered in the crystal, for example, camphor[77]. Reproduced, with permission, from REF. 82 © (1981) John Wiley.

that 56% crystallized in the $P2_1/c$ space group, 15% in the $C2/c$ space group and 13% in the $P\bar{1}$ space group, whereas 16% crystallized in some of the other 161 achiral space groups[89].

Crystal structure determination

Crystallization techniques. Determination of the crystal structure by conventional single-crystal X-ray diffractometry (SCXRD) requires crystals of suitable size and quality[90,91]. In general, the minimum dimension along each axis of the crystal should exceed 0.05 mm, unless a heavy atom (atomic number >17) is present in the constituent molecules. However, with the advancement of SYNCHROTRON and neutron scattering techniques, the minimum crystal size required has considerably decreased. The crystal should also possess uniform internal structure. Special procedures are often used to prepare satisfactory crystals[92]. These techniques include slow cooling of saturated solutions, slow diffusion of a non-solvent liquid or vapour into a saturated solution, diffusion of reacting solutions and the use of seed crystals to obtain larger crystals[92–95]. A variety of methods can be used for preparing polymorphs of drugs, such as crystallization from different solvents at different temperatures, crystallization from supercritical fluids, addition of non-solvents, pH adjustment, sublimation and crystallization from the MELT[94]. Furthermore, various combinations of the above techniques are used in a systematic manner to rapidly screen polymorphs, solvates and salt forms, to establish which are most suitable for further development and scale-up. In recent years, polymorphs have also been intentionally crystallized by EPITAXIAL GROWTH[96] and CAPILLARY CRYSTALLIZATION[97]. Zaccaro *et al.* have shown that the exposure of a supersaturated solution to light from a laser can result in the nucleation of hitherto unknown polymorphs[98]. The crystals obtained, even if not suitable for single-crystal studies, can be used as seeds for the growth of larger crystals[99]. However, in many cases, it is difficult to obtain the desired compound as a single crystal of sufficient size and quality. The material might be available only as a polycrystalline powder. Further, solving the crystal structure of certain types of substance might be beyond the capability of SCXRD, even when performing microcrystal diffraction with a synchrotron radiation source. Substances that undergo rapid transformation under conditions of SCXRD, such as metastable polymorphic forms, solvates and hydrates, might be highly flawed crystals. Twinned crystals have two different orientations of the lattice in an apparently single crystal, making their structural solution difficult[100,101]. In spite of these various drawbacks, structure solution by SCXRD is the most reliable technique for crystal structure determination.

Single-crystal X-ray diffractometry. If a satisfactory crystal is available, the crystal structure is determined by SCXRD, which is the most unambiguous way of solving crystal structures[90]. Crystals diffract X-rays in a pattern that is unique to the respective crystals and depends on their internal structure, and so X-ray diffraction can be used to determine crystal structure (BOX 3)[102–104]. The structure solution, which essentially provides the atomic positions of all the atoms in their regular, repeating positions in the crystal, is determined from the intensities and phases of the diffracted X-rays. The intensities can be determined directly from the diffraction pattern. However, the phases cannot be determined unambiguously, a limitation that is termed the phase problem (see below)[90,104].

To solve the crystal structure, the unit-cell type and the space group are first identified by acquiring a few diffraction frames and then comparing the observed pattern for missing diffraction intensities (called SYSTEMATIC ABSENCES)[105]. Knowledge of the space group can simplify the analysis of the diffraction pattern and can reveal the important symmetry element(s) within the unit cell[106]. Next, the phase problem is solved using one of the several available complex and elaborate methods; that is, the PATTERSON METHOD, ISOMORPHOUS REPLACEMENT METHOD or the direct method[106]. The direct method is normally used to determine the crystal structures of organic compounds, including drugs, and is described very briefly in BOX 4 (REFS 107,108).

Computational techniques. When the determination of a crystal structure using SCXRD is difficult because of the nonavailability of suitable single crystals, computational techniques can be utilized to predict crystal structures.

Several predictive techniques have now been developed, as described below, and the programs are being refined to generate more reliable results[109–111]. The accuracy of a predicted structure can be initially assessed by visual comparison with the experimentally determined structure. The similarity between the predicted and the experimental structure can also be judged qualitatively by comparing their space groups and can be quantified by measuring the differences between their corresponding lattice parameters, crystal structure densities and root mean square deviations for the molecular conformation and crystal packing[112,113]. Usually, a predicted structure is considered to be successful if the lattice parameters differ by less than ±5%, the molecular positions by less than ±1% and the molecular orientations by less than ±5° (REF. 113). Most methods

IMPROPER ROTATION ELEMENT
A 360°/*n* rotation about an *n*-fold axis of improper rotation, followed by a reflection through a mirror plane perpendicular to the rotation axis.

SYNCHROTRON
An electron accelerator that uses synchronized magnetic fields. When the high-speed electrons are directed to collide with an appropriate target, high-energy X-ray radiation or ultraviolet radiation is produced.

MELT
When a solid is heated beyond its melting temperature, it fuses (melts) to produce a liquid that can be termed a melt.

EPITAXIAL GROWTH
The growth of one crystal on the surface of another crystal (the substrate), on which the growth of the deposited crystal is oriented by the lattice structure of the substrate.

CAPILLARY CRYSTALLIZATION
A specific crystallization technique in which the crystals nucleate and grow inside a capillary as a result of slow solvent evaporation.

SYSTEMATIC ABSENCES
The systematic absence of specific groups of reflections in a diffraction pattern of a crystal indicates the presence of certain symmetry elements and enables the crystallographic space group of the crystal lattice to be defined.

Box 3 | Fundamentals of X-ray crystallography

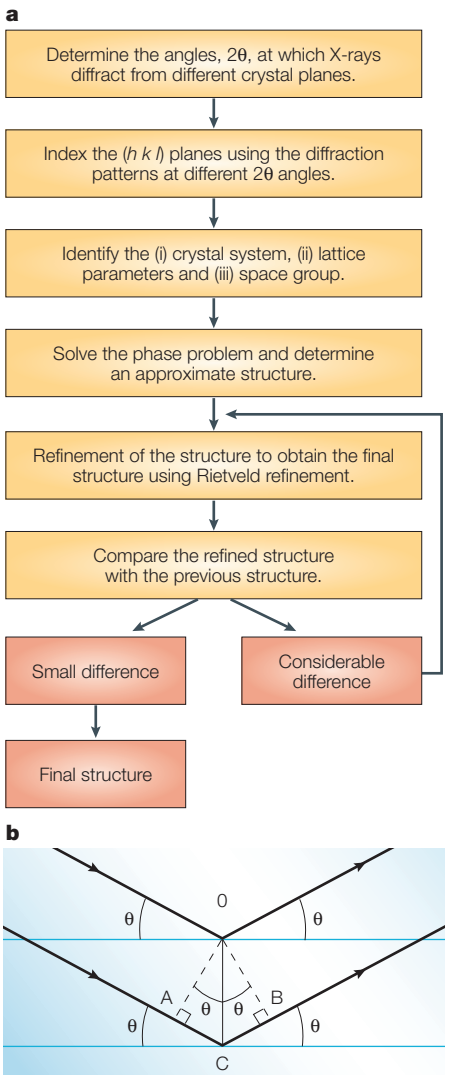
The diffraction of X-rays by crystals was discovered by M. von Laue in 1912 (see part **a** for steps in determining crystal structure from X-ray diffraction patterns and part **b** for diffraction of X-rays by the planes in a crystal). He showed that the phenomenon could be described in terms of diffraction from a three-dimensional grating[102]. However, W. L. Bragg was the first to exploit the similarity of diffraction to ordinary reflection. He deduced a simple equation, now known as the Bragg equation — $n\lambda = 2d\sin\theta$ — in which d is the distance between the crystal planes, θ is the angle of diffraction of the X-rays, λ is the wavelength of the X-rays and n is an integer[103,104]. The intensity of diffracted electromagnetic radiation is maximized when the path difference between the incident and the diffracted beam is an integral multiple, n, of the wavelength of the radiation, λ. When X-rays diffract from a given crystal plane ($h\,k\,l$), the intensity is maximized at a particular angle of incidence when the path difference of the radiation is equal to twice the distance, d, between the ($h\,k\,l$) planes multiplied by the sine of the angle of incidence of the X-ray beam. So, for monochromatic X-rays impinging on a single crystal, diffraction by each of the various planes ($h\,k\,l$) will be observed only for certain values of the angle of incidence, θ.

Using the principles of the Bragg equation, the crystal structure is determined by following a series of discrete steps[104]:

- Indexing the diffraction pattern and determination of the crystal system and lattice parameters.
- Identification of the space group.
- Conversion of the experimentally determined intensities into an image of the atoms in the unit cell, by performing a three-dimensional Fourier summation equation 1:

$$\rho(x, y, z) = \frac{1}{V}\sum_{h}\sum_{k}\sum_{l} F_{hkl} e^{-2\pi(hx + ky + lz)} \qquad (1)$$

where ρ is the electron density at point (x, y, z), V is the volume of the unit cell, and F_{hkl} is the structure factor for each plane of the corresponding Miller index ($h\,k\,l$). The structure factor depends on both the intensity and the phase of the diffracted radiation (which requires solution of the phase problem; see main text and BOX 4).



PATTERSON METHOD
The Patterson method employs the relatively large electron diffraction resulting from the presence of heavy atoms (atomic number >17) to determine the crystal structures of inorganic and organic compounds.

ISOMORPHOUS REPLACEMENT METHOD
In the isomorphous replacement method, a heavy atom is introduced into the crystal lattice without disrupting the original crystal structure. The new crystal obtained is known as the derivative crystal. The aim of isomorphous replacement is to obtain the structure of the original crystal by constructing a map (that is, a Patterson map) of the difference in electron density between the diffraction pattern of the derivative crystal and that of the heavy atom. This method is used to determine the crystal structures of proteins.

for solving crystal structures use a partial or full Rietveld analysis for the final refinement of the structure, which is discussed in detail in BOX 5.

Ab initio *crystal structure prediction.* The ability to predict the crystal structure from the molecular structure of a compound is the ultimate goal in crystal structure prediction. Although the structures of many small molecules (organic, organometallic and inorganic) have been solved successfully by this technique, it is still not widespread because of the complexity of the task[113–116].

The *ab initio* method consists of calculating lattice energies of molecular crystals followed by ranking of these structures according to their structural stabilities, thereby using purely energetic criteria for predictions[117–119]. When no previous information is available, such as unit-cell dimensions, it is recommended to search the seven most probable space groups; that is, $P2_1/c$, $P2_12_12_1$, $P2_1$, $P\bar{1}$, $C2/c$, $Pbca$ and $Pnma$[120]. The probable number of molecules in the unit cell can be estimated from the unit-cell volume, if available, or from the true density of the material. The lattice energies of the crystals are calculated using force fields, which assign parametric potentials to various atoms in their different hybridization states. The potentials of each of the atoms can be calculated from first principles when the molecule consists of fewer than 50 atoms[121]. Because typical organic molecules consist of more than 50 atoms, it is difficult to calculate real potentials for each of the atoms in these molecules using current technology. As a result, parametric expressions are used[122]. A short description of the definition and the various force fields in current use is given in ONLINE TABLE S1. The derivation of the necessary parameters can use several experimental quantities to improve the fit, such as heats of sublimation and melting, and lattice vibrations and intermolecular distances that have previously been reported for related crystal structures. If the molecules in the crystal structure show conformational

Box 4 | Direct method for structure determination from single crystals

The direct method attempts to derive relationships among the phases of different reflections[107]. These relationships predict the phases of other reflections and also provide a probability that the phase is correct. The phases are used to map the electron densities in space defined by the crystal. In some cases, several electron-density maps must be calculated and inspected until a chemically reasonable structure is recognized. Once rough atomic positions are determined from electron-density maps, the structure is refined by least-squares minimization of the difference between the calculated intensities and the observed intensities. When this refinement process converges, accurate atomic positions and atomic displacement parameters, known as temperature factors, are obtained. The resulting atomic positions can then be used to construct images of the molecule and/or contents of the unit cell. Hence, the crystal structure is determined[108].

flexibility, the complexity of finding adequate parameters increases greatly[123]. The effect of internal vibrations and kinetic energies can be incorporated into the calculation by introducing suitable corrections. Once suitable parameters have been obtained and the interacting atom types are identified, the interacting atom–atom potentials are added in lattice summations, to produce the total lattice energy[124].

It should be stressed that when predicting crystal structures using energetics, the differences between the lattice energies of the probable structures seldom exceed 20 kJ per mol, which is usually less than 5% of the total lattice energy[125]. For this reason, it is most important that the selected force field be as accurate and as robust as possible. Any source of inaccuracy in the energy function, corresponding to an error of a few kJ per mol in the lattice energy, can lead to inaccurate prediction.

However, the lattice energy is not the only factor that influences the crystal structure. The kinetics of crystallization are an important factor in influencing not only the size and morphology of the crystals but also the structure of the crystals that crystallize. Recent advances in the field of *ab initio* crystal structure prediction have incorporated the kinetic factor during crystallization into the overall prediction process[126]. Information from factors such as space group symmetry, relative crystal stability and the physicochemical properties of phase transitions has also been utilized to arrive at more plausible crystal structures[127].

Ab initio crystal structure prediction requires the determination of the correct molecular conformation of the constituent molecules. Although for a rigid molecule this step poses no problem, for a conformationally flexible molecule, or for a molecule exhibiting TAUTOMERISM, the process can be more complicated[128,129]. A full systematic search might be required in such cases, which can involve an iterative search using lattice energy and other structural information, such as the X-ray diffraction profile of the crystal. It might also be instructive to make use of the observed conformational preferences by examining the conformations found in similar molecules in the CSD, which is a storehouse of more than 250,000 organic and organometallic crystal structures consisting of small molecules[129–131].

TAUTOMERISM
An equilibrium, usually under ambient conditions, of two isomers of a compound.

The method of *ab initio* crystal structure prediction has been used to predict the crystal structure of many small organic molecules, such as methanol, propanol, benzene, terephthalic acid, and pharmaceutically relevant molecules, such as estrone and theophylline[114,116,132,133]. The trial crystal structure for anhydrous theophylline derived by a systematic search elucidated two different crystal structures, which were indistinguishable in terms of lattice energy calculated using the isotropic atom–atom approximation, and fitting of the X-ray diffraction pattern to experimental data. More sophisticated analysis of the lattice energy hypersurfaces, using a distributed multipole-based intermolecular potential, was able to distinguish between the stability of the two structures. The most stable predicted structure resembles the experimentally obtained polymorph of anhydrous theophylline[120]. In another study, Dong *et al.* reported that the crystal structure of neotame anhydrate polymorph G, determined by simulation, closely resembles the experimental crystal structure only when the correct conformation of the neotame molecule is selected beforehand[134]. The crystal structure of 3-hydroxy-4-methyl-2(3H)-thiazolethione was determined experimentally using a synchrotron radiation source. In this case, powder X-ray diffraction data and *ab initio* crystal structure prediction were utilized to compare the predicted crystal structures with the experimentally determined structures. The *ab initio* method was successful when an initial pseudo-centrosymmetric subunit constructed via O-H···S hydrogen bonds was specified[115].

Simulated annealing and energy minimization. Methods of predicting crystal structures that rely on minimization of the lattice energy are based on the assumption that the structure with the least lattice energy is the most plausible. This simple model has two inherent weaknesses: the omission of the entropy term, which contributes to the free-energy and explicit dynamic effects; and the local minimum problem, which is explained below[126]. The simulated annealing algorithm developed by Kirkpatrick *et al.* in 1983 has been utilized to overcome this problem[109]. In this method, the temperature of the physical system is elevated, which permits the system to attain a range of higher energy states. The subsequent gradual reduction in temperature shifts the equilibrium until low energy states dominate. This method introduces the possibility of accepting energy-increasing moves or 'uphill' moves in the minimization of a given function and therefore prevents the system from becoming trapped in a local minimum. The relative probabilities of existence of two states at a given temperature are represented by Boltzmann statistics. A criterion of acceptance of structures generated by simulated annealing is developed on the basis of the statistics of the Boltzmann distribution. A variety of schemes for governing the annealing of the system have been developed. For example, the effective heat capacity can be monitored to detect the onset of melting and

freezing. Alternatively, the rate of cooling applied to the system can be determined by monitoring the jumps, termed the Metropolis moves, in the simulated annealing step. Predictive capabilities of crystal structures have been strengthened by the use of this technique[135]. Gdanitz *et al.* used the simulated annealing technique to predict the crystal structures of hexamethylbenzene and ethene, and the accuracies of the predicted structures were better than 0.02Å and 0.1Å, respectively, when compared with the optimized experimental structure[136]. The simulated annealing technique is now used in conjunction with other methods for improved predictions.

Powder X-ray diffractometry (PXRD). It is sometimes difficult to obtain single crystals of sufficient size and purity for SCXRD, such that only powders, which are actually polycrystalline forms, are available. If the sample is available in powder form and is of high purity, then the solution of the crystal structure can be attempted using the powder X-ray diffraction pattern[111,137]. Because the diffraction pattern is collected on a sample of crystallites of random orientation, structure solution by the powder method circumvents the problem of small size and twinning of the crystals[138].

Crystal structure determination from PXRD patterns can, however, be complicated by a variety of factors.

Box 5 | Rietveld method for refinement

The information required for a full Rietveld analysis are the unit-cell parameters, the experimental or the observed diffraction intensities (such as powder X-ray diffractometry (PXRD) profile parameters), the calculated diffraction intensities (from any predictive methodologies) and the background contribution. In the classical Rietveld method, the weighted sum of square difference between the observed and calculated reflected X-ray intensity, *y*, is minimized. Refinement is usually performed in sets of two to five cycles at a time. The progress of the refinement is monitored by the profile fit and the nature of the parameter shifts. The fit of the calculated pattern to the observed data can be presented quantitatively in terms of agreement indices or *R* values[187]. The weighted-profile *R* value, R_{wp}, is defined as shown in equation 2:

$$R_{wp} = \left\{ \sum_i w_i [y_{iobs} - y_{icalc}]^2 / \sum_i w_i [y_{iobs}]^2 \right\}^{1/2} \quad (2)$$

where y_{iobs} is the observed intensity at step *i*, y_{icalc} the calculated intensity and w_i the weighting factor. The expression in the numerator is the value that is minimized during a Rietveld refinement. In order to evaluate the goodness of fit of the peaks, an R_{wp} value for which the background contribution has been eliminated should also be calculated.

Ideally, the final R_{wp} should approach the statistically expected *R* value, R_{exp}, as defined in equation 3:

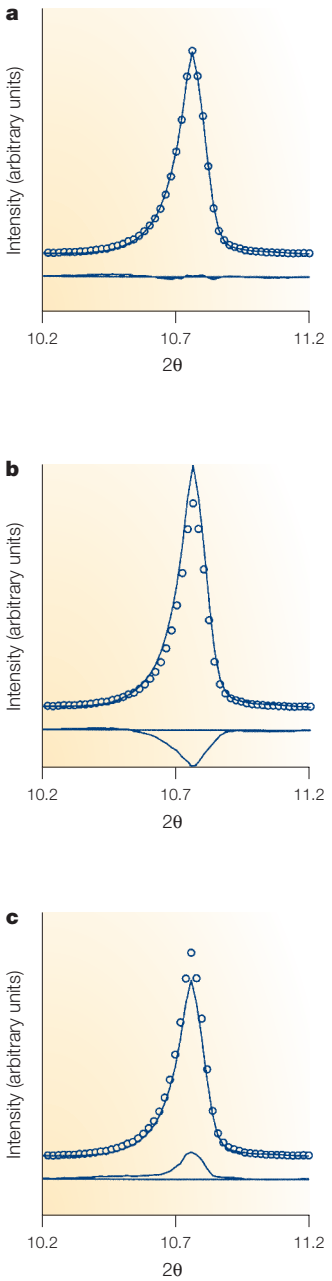
$$R_{exp} = \left\{ [(N-P)/\sum_i^N w_i y^2_{iobs}] \right\}^{1/2} \quad (3)$$

where *N* is the number of observations, *P* is the number of parameters and R_{exp} reflects the quality of the data. The ratio R_{wp}: R_{exp} is termed the goodness of fit and is represented as χ^2 (REF. 188).

The difference profile plot, which is the difference between the observed and calculated intensities, is the visual way to check the profile fit. It should be emphasized that profile plots are much more informative than *R* values, because they can indicate whether a high *R* value is due to a profile parameter problem or to a total deficiency in the structural model as shown in the figure.

Quantitative phase analysis by means of the Rietveld method is now an especially important ancillary procedure to refine crystal structures[189]. The Rietveld method has also been applied to improve the crystal structure prediction from PXRD patterns[190,191]. The main drawback of the conventional powder method for determining crystal structures is that the patterns grossly overlap, thereby preventing maximum utilization of the experimental information. The Rietveld method was developed to separate effectively these overlapping data, thereby allowing accurate determination of the structure.

The figure shows the observed (circles), calculated (line) and difference (bottom) profiles for a good fit of a peak (**a**), a calculated intensity that is too high (**b**) and a calculated intensity that is too low (**c**). The characteristic difference profile for intensity is either positive or negative and is concentrated at the centre of the peak[188]. Reproduced, with permission, from REF. 188 © (1999) International Union of Crystallography.



For powder diffraction patterns, the reflections from different crystal planes are averaged over directions and projected onto a single variable, the diffraction angle 2θ. This averaging makes the reconstruction of the underlying crystal structure much more difficult than for single-crystal diffraction patterns[139]. Space group determination using powders is more ambiguous than with single-crystal diffraction. This problem arises because the regions in the pattern, which should be free of peaks because of the systematic absences, are often overlaid with peaks of other reflections. Also, poor quality PXRD patterns, obtained from solid samples of poor crystallinity or solid samples with considerable amorphous content, preclude their successful indexing. When the crystals have a strongly anisotropic morphology, such as flat plates or long needles, then the crystallites tend to align along a certain direction. The nonrandom distribution of crystallite orientation affects the relative intensities of given peaks and hinders the correct solution of the pattern[140]. These problems notwithstanding, crystal structure determination from PXRD data is an important and emerging discipline. To determine the crystal structure from the PXRD pattern, it is essential that the powder diffraction data be collected appropriately. Factors to consider before data collection are the geometry of the diffractometer, the quality of the alignment and calibration of the instrument, the most suitable radiation, the wavelength, appropriate sample preparation and thickness, slit widths and necessary counting time. Here, we outline some of the basic concepts and recent developments. Structure solution from PXRD data falls into two classes: traditional methods and direct-space approaches.

Traditional methods include the Patterson method, direct methods that differ from direct-space approaches, and the method of entropy maximization and likelihood ranking. The traditional approach to crystal structure solution from PXRD data attempts to extract the integrated Bragg intensities of individual reflections directly from the PXRD pattern[141]. Once the integrated intensities are known, an electron-density map is constructed using the same techniques that have been developed for single-crystal diffraction data[142] (for particularly informative papers on pattern decomposition, see REFS 143–146). Variants of this basic idea have been applied successfully to organic systems with up to 31 non-hydrogen atoms. Although traditional techniques for structure solution from PXRD data have been applied successfully in several cases, these techniques have certain intrinsic limitations[126]. For example, peak overlap can create major difficulties in extracting intensities from PXRD patterns, which limits the complexity of structures that can be solved by traditional methods. Because of the above limitation, much recent interest has focused on the development of new methods for solving crystal structures directly from PXRD data. The direct-space approach is such a method that is particularly well suited for molecular crystals.

In direct-space approaches, trial structures are generated in direct space — that is, they are generated independently of the experimental powder diffraction pattern. The suitability of each trial structure is assessed by comparing the powder diffraction pattern calculated for the trial structure and the experimental powder diffraction data[139] via a least-squares fit of the calculated diffraction pattern to the experimental diffraction pattern. The agreement factor for the trial configuration is denoted $R_{wp(trial)}$ and is calculated using equation 4 (REF. 111).

$$R_{wp(trial)} = 100 \times \sqrt{\frac{\sum w_i (y_i - y_{ci})^2}{\sum w_i y_i^2}} \qquad (4)$$

in which y_i is the intensity of the ith observed point in the experimental powder diffraction profile, y_{ci} is the intensity of the corresponding point in the calculated powder diffraction profile from the trial structure, and w_i is a weighted factor for the ith point in the powder diffraction profile. The aim is to find the trial structure with the lowest value of $R_{wp(trial)}$. The process is therefore equivalent to exploring a hypersurface $R_{wp}(\Gamma)$ to find the global minimum, where Γ represents the set of variables that define the structure in direct space. Methods that can be used to locate the global minimum, within strategies for direct-space structure solution, include simulated annealing by the Monte Carlo method[111,147], genetic algorithm techniques[148,149] and techniques employing a systematic search approach using a grid-based search with lattice energy calculations[150].

Most direct-space approaches are stochastic in nature, and so it is recommended that the calculation of the structure solution be repeated several times from different random starting populations.

Monte Carlo method. The Monte Carlo method is a technique for surveying the hypersurface as defined above. In this approach, starting from a random configuration of atoms in the unit cell, each atom is displaced by a random amount in a random direction to generate a trial configuration[151]. The powder diffraction pattern corresponding to the trial configuration is calculated. After a sufficient number of configurations have been generated via the Monte Carlo algorithm, the best configuration — that is, the one that with the lowest $R_{wp(trial)}$ — is considered further[151]. This configuration then provides the structural model for the initial conventional Rietveld refinement calculation. Occasionally, the structures obtained by the Monte Carlo procedure are incomplete and further development through difference Fourier methods might be required. When a complete structural model has been obtained, a full Rietveld refinement calculation is carried out to give the final refined crystal structure.

Bond and Jones successfully predicted the crystal structure of a series of divalent complexes of the cyclic thiohydroxamic acids pyrithione, methylpyrithione and methylthiazolethione with zinc, copper and nickel from PXRD data using a combination of a Monte Carlo procedure, the refinement of cell parameters using the Rietveld method, and energy minimization within the constrained unit cell[111]. ONLINE TABLE S2 compares the

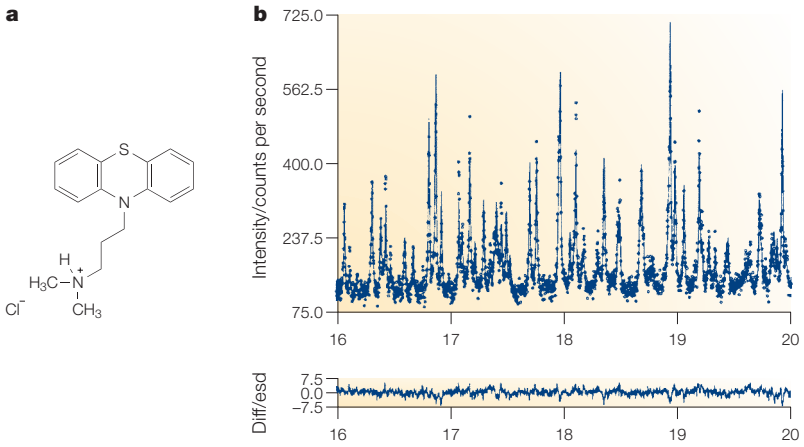


Figure 4 | **Application of the Monte Carlo method in crystal structure solution. a** | The molecular structure of promazine hydrochloride. **b** | The observed powder diffraction data, the calculated powder pattern resulting from the Rietveld refinement of the structure obtained from Monte Carlo simulated annealing of the structure generated from the experimental powder pattern, and the difference shown below[147]. Reproduced, with permission, from REF. 147 © (1998) Royal Society of Chemistry.

single-crystal structures and predicted structures of these compounds. The authors judged the success of each predicted structure by comparing the simulated PXRD patterns of the predicted structure with that of the corresponding experimental structure, in addition to comparing the space group, lattice parameters and lattice energies, as mentioned earlier.

David *et al.* determined the crystal structure of capsaicin, thiothixene and promazine hydrochloride from their powder diffraction data[147]. FIGURE 4 shows the observed powder diffraction data and the calculated powder pattern resulting from the Rietveld refinement of the structure obtained by simulated annealing using the Monte Carlo method of the structure generated from the experimental powder pattern.

Genetic algorithms. In the genetic algorithm (GA) method, a population of trial crystal structures is allowed to evolve and optimize, subject to the rules and operations that govern evolution in biological systems[152,153]. The set, Γ, can be regarded as the genetic code. The initial population of structures is allowed to evolve through subsequent generations by applying the evolutionary operations of mating, mutating and natural selection. Through these operations, a given population is converted to the next generation, and the number of structures remains unchanged. The quality of each structure depends on its value of R_{wp} and fitness is defined as an appropriate function of R_{wp} or by the figure of merit, χ^2, as described in Rietveld analysis (BOX 5).

In the mating procedure, pairs of structures are first selected from the population. The probability of selecting a given structure as a parent is proportional to its fitness. For each pair of parents, two offspring are generated by distributing parts of the genetic codes of the two parents between the two offspring. In the mutating procedure, new values of individual genetic variables are introduced into the population. In the natural selection procedure, only the structures with the lowest R_{wp} are allowed to pass from one generation to the next[152].

Among the recent improvements in the GA technique for crystal structure solution is the implementation of a Lamarckian approach to evolution, rather than the more commonly used Darwinian evolution[154]. In the Lamarckian procedure, each new structure generated by a GA calculation is subjected to local minimization of R_{wp} with respect to the structural variables in the set Γ. Only these minimized structures are used subsequently in the GA calculation. This procedure therefore combines the stochastic and deterministic components within the global minimization strategy.

The analysis of the evolutionary history of a GA structure can provide important insights into the development of the algorithm itself, which can be utilized to improve the quality of prediction, as well as to decrease the time required for the prediction[155]. These analytical methods are the evolutionary progress plot, evolutionary distribution plot and evolutionary trajectory plot.

Another development in crystal structure prediction by GA has been the addition of the energy minimization component into the algorithm to generate the most probable structure. Both the potential energy $E(\Gamma)$ function and the $R_{wp}(\Gamma)$ function are minimized together in an appropriate functional form to define a new hybrid hypersurface $G(\Gamma)$[156]. The hybrid function $G(\Gamma)$ is designed to behave as an energy term, when the value of potential energy, E, is high, and to give increasing importance (ultimately absolute importance) to R_{wp} as lower values of E are approached. This behaviour is achieved by means of a sliding weighting parameter $w(\Gamma)$, which is defined as an appropriate function of E. As the energy of the system increases, the weighting function has greater values, which implies greater significance of $E(\Gamma)$ in determining $G(\Gamma)$. $G(\Gamma)$ therefore guides one property — that is, the $E(\Gamma)$ — to enable another property — that is, the $R(\Gamma)$ — to reach the optimum value. The guiding function can itself be derived by several techniques. FIGURE 5 illustrates the application of the GA method by Harris *et al.* to structure solution of 4-methoxybenzoic acid and formylurea[149].

Maximum entropy algorithm. The maximum entropy (ME) method for solving crystal structures views the unknown crystal structure as consisting of atoms of known chemical identity but with unknown positions, and considers the latter as random, with an initially uniform distribution in the asymmetric unit of the crystal[157]. Structure determination involves the gradual removal of that randomness. The ME algorithm is a deconvolution technique that utilizes Bayesian statistics to generate the most probable structures by comparing the calculated structures with the experimental structures obtained from PXRD. This method purports to generate an electron-density map from the PXRD pattern, which can then be used to solve the structure of the crystal.

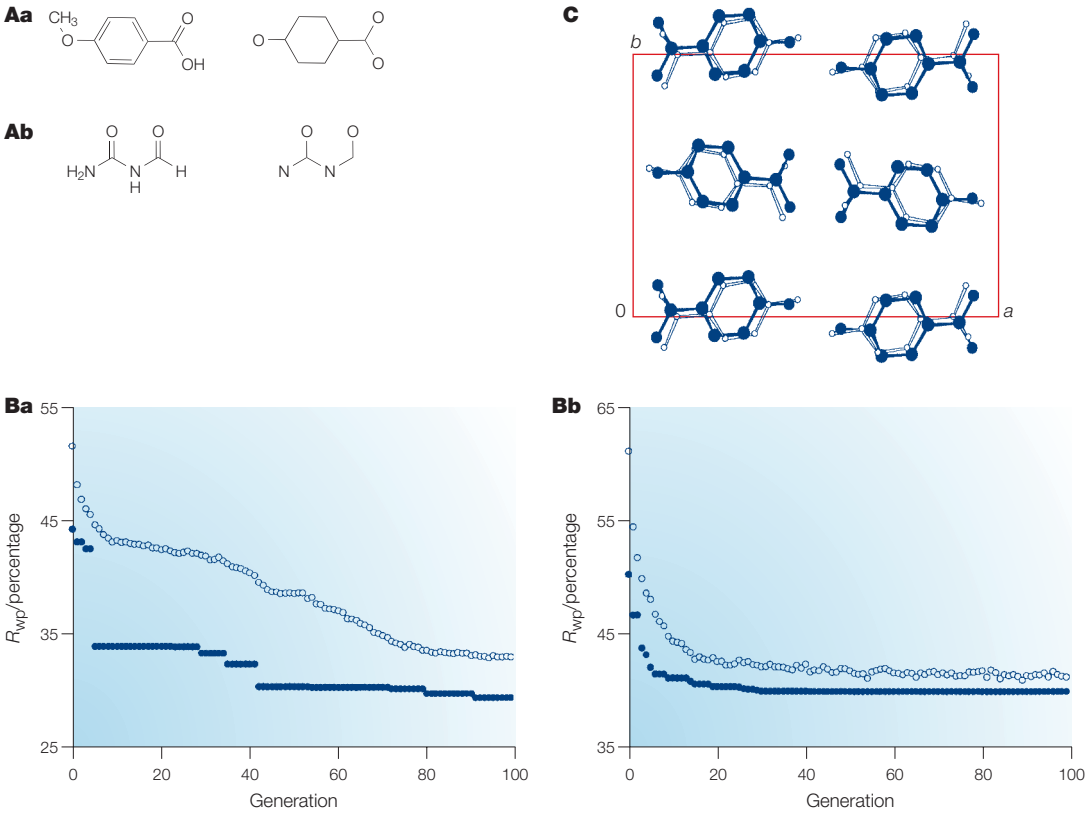


Figure 5 | **Application of the genetic algorithm (GA) method in crystal structure solution. A** | Molecular structures and definitions of the structural fragments used in the GA structure solution calculations for: 4-methoxybenzoic acid (**a**) and formylurea (**b**)[149]. **B** | The evolutionary progress plot for 4-methoxybenzoic acid (**a**) and formylurea (**b**), showing the evolution of R_{min} (filled circles) and R_{ave} (open circles) as a function of generation number[149]. **C** | Comparison between the position of the structural fragment in the best structure solution obtained in the GA calculation for 4-methoxybenzoic acid (open circles) and the position of the corresponding atoms in the known crystal structure (filled circles)[149]. Reproduced from REF. 149 © (1998) International Union of Crystallography.

The crystal structure of perchlorocoronene, $C_{24}Cl_{12}$, was solved by Gilmore *et al.* using the ME method[158]. The Fourier transformation of the reflection data of the compound yielded four phases, which were used as a basis set for further analysis. The electron-density map obtained from the Fourier transformation of the electron microscope image is shown in FIG. 6a. Routine phase extension using ME procedures led to a map in which the diffraction intensities are phased, as shown in FIG. 6b.

Crystal engineering

Nobel laureate Richard Feynman once remarked that if the arrangement of things can be controlled on a small scale, then the possible properties of the material can be modulated to a greater extent and the range of applications to which it can be applied can be greatly enhanced[159]. In accordance with this idea, crystal engineering is defined as the modelling, design, synthesis and application of crystalline solids with predefined and desired aggregation of molecules and ions[160]. The aim of crystal engineering is to design and synthesize crystals in which the arrangement of the constituent molecules is controlled so as to elicit one or more desired functional properties from the crystal. Pepinsky first introduced the concept of crystal engineering in a seminal paper[161], and Schmidt was the first to show the importance of this field to the solid-state photodimerization of olefins[162].

Crystals can be assumed to be *de facto* manifestations of self-recognition and self-organization of molecules by means of intermolecular interactions and packing preferences. The self-assembly of molecules to form crystals confers distinct physical and chemical properties to the crystal as compared with the individual molecules that constitute the crystal. Molecular crystals can therefore be viewed as supermolecules with characteristic physical and chemical properties. An essential requirement in designing crystals is understanding the intermolecular interactions involved in crystal packing, and utilizing such understanding in the design of new solids with desired physical and chemical properties[163]. Though the physical nature of the forces acting between organic molecules in crystals is usually quite well understood, it is still difficult to grasp the complex spatial pattern of such forces[164]. The term supramolecular synthon was developed to define the structural units that result from known or conceivable synthetic operations involving intermolecular interactions among

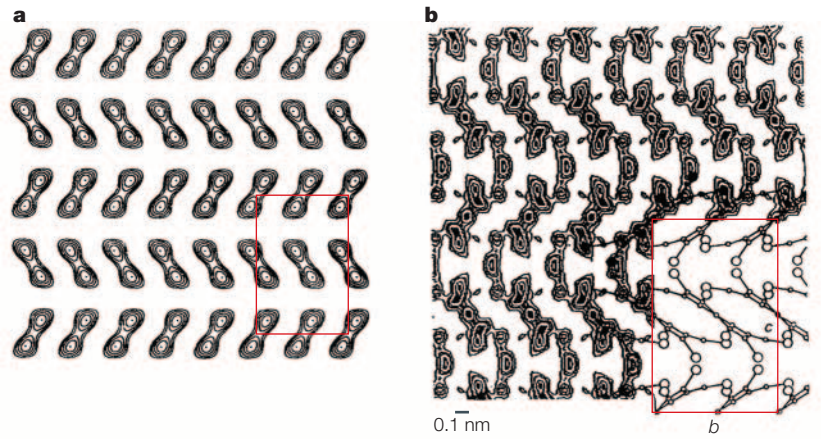


Figure 6 | **Application of the maximum entropy (ME) method to crystal structure solution.** Perchlorocoronene crystal structures are shown. **a** | Projection down the *a* axis of an electrostatic potential map based on four reflections obtained from the Fourier transformation of the electron microscope image. **b** | Electrostatic potential map derived from ME phasing. The refined structure from a single crystal X-ray analysis is superimposed in the bottom right-hand corner[158]. Reproduced, with permission, from REF. 158 © (1993) The Royal Society.

constituent molecules of a crystal which, when extended in three-dimensional space, result in a crystal[165]. The available crystal structures give insight into the varieties of supramolecular synthons that exist. The goal in crystal engineering is to attain collective crystal properties by an adequate choice of the building blocks (molecules) that can be modulated to self-assemble in accordance with suitable synthons to form desired crystals.

The properties of crystalline matter are manifold and diverse. As discussed in the introduction to this review, the crystalline form affects such physical properties as the solubility, stability, dissolution rate, bioavailability and mechanical properties of the solid drug. Using crystal engineering, new phases of pharmaceuticals can be synthesized to improve, and ultimately to optimize, these properties.

The design of binary compounds using complementary molecules is an application of crystal engineering. Pharmaceutical molecules inherently contain molecular recognition sites that bind selectively to biomolecules. These sites have the potential to be used to form supramolecular self-assemblies with desired physicochemical properties. For example, Walsh *et al.* co-crystallized the anti-inflammatory molecules *rac*-ibuprofen and *rac*-flubiprofen (shown in FIG. 7A) with 4,4′-dipyridyl to yield co-crystals with a 2:1 stoichiometry[166]. The co-crystals exhibit heterosynthons formed by the interaction between the drug molecules and 4,4′-dipyridyl, whereas the pure drug components exhibit dimeric homosynthons formed by the interaction between two drug molecules. The co-crystals exhibit physical properties different from those of the parent compounds as a direct result of hydrogen-bonding interactions between the binary components of the crystal.

Similarly, drugs, such as indomethacin, phenobarbital, aspirin and carbamazepine, were co-crystallized with a number of secondary molecules, such as acetone, benzoquinone and 1,2-bis(4-pyridyl)ethylene[167,168]. The physical characteristics of the co-crystals are reported to be considerably different from those of the pure drug molecules[169]. However, the utility of the co-crystal formers in pharmaceutical products is limited by their pharmacological and toxicological properties. Nevertheless, food additives and selected 'generally regarded as safe' compounds have also been used as co-crystal formers. For example, itraconazole, a poorly water-soluble antifungal drug, forms co-crystals with a number of pharmaceutically acceptable acids, such as fumaric acid, succinic acid and L-, D- or DL-tartaric acid, when crystallized from polar aprotic solvents or from mixtures of hydrocarbons and polar aprotic solvents. FIGURE 7B shows that co-crystallization increases the dissolution rate of the drug[170]. This example shows that, with a suitable application of supramolecular chemistry, it should be possible to rationally design co-crystals of compounds with significantly complex molecular structures.

The relationship describing the influence of crystallographic structure on the mechanical properties of crystals and powders is another area in which crystal engineering can be utilized, but which has received little attention so far. In one such study, the YOUNG'S MODULUS of aspirin was estimated from its crystal structure[171]. In another study, Roberts *et al.*[172] showed that the mechanical properties of aspirin, sulphathiazole, carbamazepine and polymorphs of primidone (forms A and B) can be

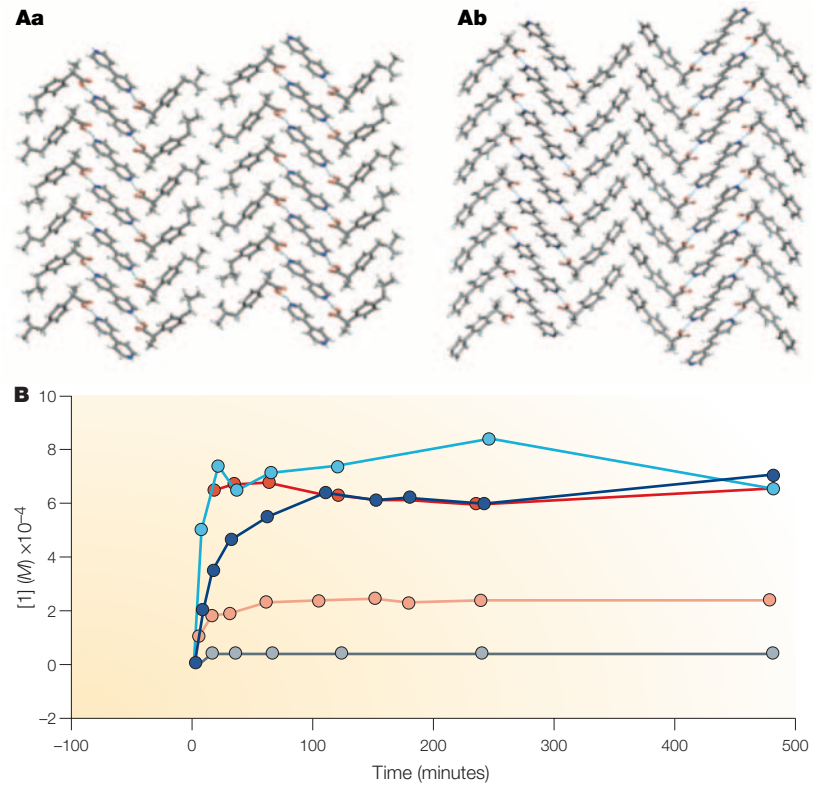


Figure 7 | **Crystal engineering. A** | The 1:2 adducts of 4,4′-dipyridyl with ibuprofen (**a**) and flubiprofen (**b**)[166]. **B** | A comparison of the dissolution profiles of crystalline itraconazole (grey) and co-crystals of itraconazole with succinic acid (orange), L-malic acid (red), L-tartaric acid (dark blue) and SPORANOX BEADS (light blue) in 0.1 M hydrochloric acid at 25°C[170]. Part **A, b** reproduced from REF. 166 © (2003) Royal Society of Chemistry. Part **B** reproduced from REF. 170 © (2003) American Chemical Society.

predicted by applying lattice dynamics to the atom–atom potential model. In this case, the crystal morphology was taken into account when considering the experimental results. Although the mechanical properties of a compound can be predicted from its crystal structure, crystal engineering of pharmaceuticals has not yet resulted in the design of crystals with desired mechanical properties. If a molecular basis for the origins and magnitude of mechanical properties can be developed, then the required controlled modification might be achieved by analysis of the structural and constituent molecular information[173–175]. Then, the knowledge gained might be utilized to design crystals with desired mechanical properties[176].

Afterword

Statistical analysis of structural data in the CSD provides a better understanding of the nature of hydrogen bonds and intermolecular interactions, and facilitates the identification of frequently occurring interaction patterns and supramolecular synthons[177]. With enhanced knowledge of hydrogen-bond synthons in crystals, novel strategies can be designed for the self-assembly of supramolecular architectures from multifunctional molecules. Using the database, the twin phenomena of polymorphism and solid-state solvation (pseudopolymorphism) are being studied by examining the information on molecular conformations and solvent inclusion. The hydrogen-bonding patterns elucidated in small molecules are used as models in structure-based drug design and pharmacophore mapping. So the implications of crystal engineering extend far beyond organic and organometallic crystal design into supramolecular materials, nanotechnology, ligand–protein binding and crystal structure prediction[177].

The field of crystal structure prediction has recently made significant progress. However, certain factors have not yet been considered when predicting crystal structures. These factors include the enthalpy force field issue, intra–intermolecular energy issues, the entropy issue, the temperature issue, kinetic energy issues and the kinetic dynamic issues. Incorporation of these factors into the prediction process is expected to improve the overall results generated[178].

Modelling techniques have also been successful in determining the energetics and location of sorbed molecules within solids, especially in inorganic solids. Their use in studies of organic solids is still at an early stage. Computational techniques are progressively becoming more common for morphology prediction[179]. Simulation techniques are expected to have an expanded role in solving the problems involved in the determination and study of the crystallographic and molecular sites occupied by sorbed molecules on the surfaces of solids or within solids. Other analytical techniques, especially vibrational spectroscopy (for example, infrared spectroscopy and Raman spectroscopy) and nuclear magnetic resonance (NMR) spectroscopy, might complement the results obtained from computational studies. For example, the structure of *N*-(*p*-tolyl)-dodecylsulfonamide was determined from PXRD data and was validated by solid-state NMR spectroscopy[180] (for recent reviews on the application of spectroscopic techniques to the characterization of pharmaceuticals, see REFS 181–184).

We hope this review has highlighted the major advances in crystal structure solution and prediction, as well as the utilization of this information in designing solids with desired physical properties. Increased computational speed and memory will further improve the analytical procedures and the modelling of the crystal structure and energy calculations. Much scope remains for improving the modelling of intermolecular interactions. Such improvements will also enhance the engineering of new crystal forms with novel properties and for novel applications.

SPORANOX BEAD
An amorphous capsule that is used to achieve the required oral bioavailability of extremely water-insoluble drugs, such as itraconazole.

YOUNG'S MODULUS
A measure of a material's elasticity, which is defined as the force per unit cross-section of the material divided by the fractional increase in length that results from the stretching of a standard specimen of the material.

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Acknowledgement
We thank A. Sheth for kindly reviewing the manuscript and for his valuable suggestions.

Competing interest statement
The authors declare that they have no competing financial interests.

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