Crystal Engineering

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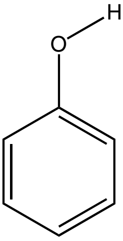
Crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties. It is a subject of great scope and application that has developed by a coming together of thought streams from many other subjects. During the last 30 years, it has attracted the attention and interest of a varied group of scientists, notably crystallographers and chemists. The purpose of this text book is to provide a brief, basic introduction to this fascinating and important subject that has moved from the fringes into the mainstream of chemistry. Crystal engineering is concerned primarily with molecular solids. We need to distinguish these substances from extended solids such as rocksalt, diamond and metal oxides.

The molecular concept is fundamental to chemistry. Our awareness of the *molecule* as an entity in itself originates from the time when organic chemistry became a separate subject. In 1828, Friedrich Wöhler synthesized urea from ammonium cyanate (Chapter 3) in an experiment that was counter intuitive for that time. Gradually, there arose the idea of the molecule, and during much of the 19th century this molecular paradigm became reinforced through the efforts of the legendary German chemists of that time. The molecule is a group of atoms held together with interactions that are so strong that it remains relatively stable under many variations in temperature and pressure. Molecules do not normally revert spontaneously to atoms. A molecule of, say phenol is the form of that chemical substance that exists in the gas, liquid and solid phases of the compound. The thermal energy that is needed to convert solid phenol to a liquid and eventually to a gas is much smaller than the energy that is required to break the strong interactions between the C, H and O atoms that make up the

The molecule is paramount in chemistry. But rather than talk about molecules in themselves, we discuss in this book *assemblies of molecules* and why molecules associate in specific ways. A crystal is a very precise and specific type of molecular assembly. Crystal engineering teaches us how to bring molecules together exactly as we want.

Crystals have been known to mankind since antiquity. This is a photograph of one of the oldest salt pans in the world, still in use, in Aveiro, Portugal.

molecule of phenol. Eventually, the word *bond* was used to describe the very strong intramolecular interactions that hold atoms together in molecules and the work of Linus Pauling during the 1930s, more than anything else, gave chemists a full appreciation of the meaning of the phrase *chemical bond*.



A molecular crystal is a crystal that is made up of molecules. It is the crystalline form of any chemical substance that exists as molecules. Organic acids and bases can form cations and anions respectively. When such ions are present in a crystal, one obtains an organic salt. Such salts are also taken as molecular crystals. Not all compounds exist as molecules. Phenol, naphthalene, $SiCl_4$ and D-glucose do so but NaCl, ReO_3 and Fe_3O_4 do not. Many molecular solids are organic substances. Crystal engineering was therefore mostly synonymous with organic crystals in its initial years. During the last 20 years, however, a large number of very interesting metal–organic compounds, also called *coordination polymers*, which are highly crystalline and also of a molecular nature, have come under the scope of crystal engineering. These substances are described in Chapter 7.

A definition of the term *molecular crystal* was provided in the middle of the previous century by the great Russian physicist Alexander I. Kitaigorodskii, who said that "within a molecular crystal, it is possible to identify groups of atoms such that for every atom in a group, at least one interatomic distance within this group is significantly shorter than the smallest interatomic distance to an atom in another group." Notice that Kitaigorodskii's definition of a molecular crystal is worded in the language of geometry and not in the language of chemistry. He equates a molecule with a "group of atoms" that are defined according to distance criteria. This definition is quite useful and becomes an operational criterion of a molecular crystal. Of course, we know today that it is also possible to define a molecular crystal in chemical terms. If the energies of covalent bonds, the interactions that hold atoms together in molecules, are in the range of 75–125 kcal mol^{-1}, the energies that hold molecules together in molecular crystals are much less, by more than an order of magnitude. In Chapter 2, we will learn about the *intermolecular interactions* that hold molecules together in crystals. The energies of these interactions range between 1 and say, 20 kcal mol^{-1}. At the lower end, these energies are a little greater than the thermal energy, kT, at ambient conditions. So we can take home the idea of the molecular crystal as a collection of molecules, entities that are held internally by rather strong interactions but associated with each other by somewhat weaker interactions.

Why do we study crystal engineering? Molecular crystals have interesting physical and chemical properties that are not associated with other categories of crystalline substances. These properties are connected to, and closely related to, their internal periodic structures. These internal structures are known as *crystal structures* and they are of outstanding importance in crystal engineering. So, there is a need to be able to design particular crystal structures, wherein molecules are assembled in particular ways. A particular crystal structure, in turn, has a particular property that is desired. Crystal engineering therefore consists of many different operations. These include the determination of crystal structures, the understanding or analysis of these and other known crystal structures, the use of this understanding in trying to design a crystal structure of a particular type including hitherto unknown structure types, the actual crystallization experiment, and finally the realization of a pre-desired crystal property. Clearly, many skills are involved in the art and science of crystal engineering. We will now trace the historical background of the several scientific streams of thought that have come together in this new subject.

Zero, One, Two and Three-dimensional Molecules

One can use Kitaigorodskii's definition of a molecular crystal to obtain a useful geometrical concept of molecularity. A conventional molecule, say naphthalene, phenol or methane, is a zero-dimensional object. One finds limits, in all directions, to the molecular structure. Beyond a certain distance there are no more atoms in the molecule, in any direction. There are non-bonding boundaries in all directions. We can say accordingly that the molecularity of naphthalene or methane extends in all three dimensions. If we consider a crystal like $PdCl_2$, we find that there is an infinite linear bridged structure of Pd and Cl atoms. This structure constitutes a one-dimensional object. The molecularity of $PdCl_2$ extends into two dimensions but in the third dimension, which is along the length of the bridged structure, the molecule is extended infinitely. Let us next take graphite. Here the object is a two-dimensional molecule (sheet) and the molecularity extends only in one dimension, namely perpendicular to the sheet. Finally, extended solids like diamond and ZnS are giant three-dimensional molecular objects. Such ideas easily allow for coordination polymers (Chapter 7) to be defined as molecules and bring this large and interesting group of compounds well within the scope of crystal engineering.

1.1 X-ray Crystallography

Following the work of Max von Laué and the Braggs, father and son, and the visualization of a crystal as a periodic array that was capable of diffracting X-rays, the stage was set for the determination of crystal structures of pure chemical compounds. The earliest organic crystal structures to be determined were those of simple, symmetrical molecules like hexachlorobenzene and urotropin. Very early on, in 1921, W. H. Bragg commented that certain structural units like a benzene ring, having a definite size and form, might be retained with little or no change in going from one crystal structure to another. Bragg noted that the unit cell parameters of naphthalene and anthracene were related; two axial lengths were nearly the same while the third was 8.66 Å in naphthalene and 11.16 Å in

anthracene. Accordingly, he concluded that the long axis of the molecules coincided with this third axis and further that the fused benzene ring dimension is approximately 2.50 Å. This is perhaps the earliest correlation between a crystal property and a molecular property, and is of relevance to modern crystal engineering because one of the fundamental questions of crystal engineering is "*Given the molecular structure of a compound, what is its crystal structure?*" The aims and goals of crystal engineering are well summarized in this question because one attempts, in this subject, to design crystal structures by using the molecule as a building block.

John Monteath Robertson (1900–1989).

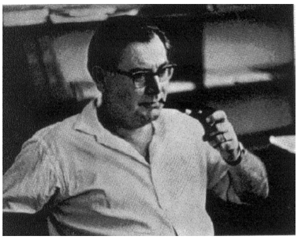
The first systematic answer to this fundamental question, which relates molecular and crystal structure, was given by J. M. Robertson, one of the most illustrious students of W. H. Bragg. Robertson, who worked for many years in the University of Glasgow, carried out a monumental study of the crystal structures of polynuclear aromatic hydrocarbons. This group of compounds includes not only simple compounds like naphthalene, anthracene and phenanthrene but larger and more complex molecules like perylene, coronene, ovalene and dibenzanthracene. These compounds are not only difficult to make and/or isolate but in the 1940s, when Robertson was carrying out many of his investigations, the crystal structure determinations of such compounds were of formidable difficulty. In 1951, Robertson concluded that these hydrocarbons could be classified into two groups. The first, in which the molecular area was small in comparison to the molecular thickness, is populated by hydrogen rich molecules like naphthalene and anthracene. The crystal structures in this group are characterized by short axes of around 5.0 Å; they contain molecules related by a *herringbone packing* of molecules inclined at about 40° to this short axis. The second group, in which the molecular area is large in comparison with the molecular thickness, is represented by carbon rich graphitic structures of coronene and ovalene. This classification is discussed further in Chapter 2. Robertson, in effect, carried out the first systematic experiment in crystal engineering. He identified a series of molecules, made them, determined their crystal structures and established a correlation between molecular structure and crystal structure. He was the first of a series of chemist-crystallographers, scientists who were adept in two rather different disciplines, and who did research in a topic where expertise in both disciplines was essential.

More about X-ray crystallography as a modern technique is given in Section 2.6.1.

1.2 Organic Solid State Chemistry

A coming together of crystallographic and chemical schools of thought, in the context of organic compounds, was seen more definitely during the period 1950–1980. This period saw the introduction of the terms *crystal engineering* and the allied term *crystal chemistry*.

In 1955, at a meeting of the American Physical Society in Mexico City, Ray Pepinsky first used the term *crystal engineering* when he stated that "crystallization of organic ions with metal-containing complex ions of suitable sizes, charges and solubilities results in structures with cells and symmetries determined chiefly by packing of complex ions. These cells and symmetries are to a good extent controllable: hence crystals with advantageous properties can be *engineered*." This definition encompasses the modern scope of crystal engineering as it is being practised 55 years later because it contains all three important elements of the subject: analysis, design and function. When this trio of attributes is taken together, our subject falls well within the scope of *engineering*.



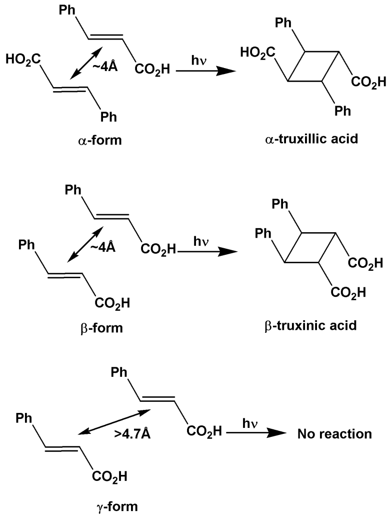
Gerhard Schmidt (1919–1971) is widely credited with the introduction of the term *crystal engineering* into the chemical literature in 1971. However, it is clear that the term was first used by Ray Pepinsky in 1955 in more or less the same context that Schmidt did, and largely in the sense that we use today. Schmidt began his work on the topochemistry of crystalline alkenes in the early 1950s. He only began systematic publication of his results in 1964 in a long series of monumental back to back papers in the *Journal of the Chemical Society*. It is also known that Schmidt and Pepinsky knew each other. Pepinsky's reference to the term *crystal engineering* is traced to just one occurrence in 1955. Schmidt published a voluminous amount of material on the subject. Did they discuss these ideas together?

The chemical slant of crystal engineering can surely be traced to the work of Gerhard M. J. Schmidt and his colleagues in the Weizmann Institute of Science during the period 1950–1970. Schmidt realized the power and significance of X-ray crystallography in organic chemistry. He laid the foundations of a new subject that he called *organic solid state chemistry*. Solution reactivity is largely a molecular property but solid state reactivity in crystals is characteristic of periodic assemblies of molecules. The link between structure and reactivity in the solid state structure was clearly established by Schmidt for a series of photodimerizable alkenes. Taking substituted *trans*-cinnamic acids as examples he studied their 2+2 photocycloaddition reactions to cyclobutanes. He found that for these compounds, the crystalline matrix provides an extraordinary spatial control on the initiation and progress of the solid state reaction. For a start, the cinnamic acids do not undergo dimerization in solution, and even if they do, there are many products and the overall conversion to dimer is low. In the solid state, however, the conversion efficiencies are high and the regiospecificities of the obtained products are clear and decisive. When the crystal contains nearest neighbour molecules in which the reacting double bonds are related by a crystal inversion centre, the cyclobutane that is obtained has inversion symmetry. When the nearest neighbour molecules are related by translation symmetry in the crystal, the product has mirror-symmetry.

Let us illustrate these principles further. Substituted cinnamic acids crystallize in one of three structural types α, β and γ and while the α and β forms react in a 2+2 manner to give cyclobutanes when irradiated in the solid state, the γ forms are photostable. Schmidt assumed that reactivity in the solid state takes place with a minimum of atomic and molecular movement, the *topochemical principle*. Accordingly, the formation of mirror symmetry truxinic acids from the β-cinnamic acids and that of the inversion symmetry truxillic acids from the α-acids becomes intuitively obvious, as is the photostability of the γ-acids.

Because this on-off model for predicting the outcome of a solid state reaction was so successful, attention became directed to the control of the crystal structures themselves. This proved to be much more difficult to do. Simple substitutions on a molecular skeleton usually caused deep-seated changes in the crystal structure. Therefore the concept of crystal engineering came into being. The term was employed by Schmidt to denote rules that could be used to generalize and predict the packing of molecules within crystals. In 1971, just before his death, he stated in a now well known paper in the journal *Pure and Applied Chemistry* that "the systematic development of our subject will be difficult if not impossible until we understand the intermolecular forces responsible for the stability of the crystalline lattice…any rational development of the physics and chemistry of the solid state must be based upon a theory of molecular packing; since the molecules studied are complex, the theory will be empirical for some time yet. Rules are now becoming available in what I would regard as phase three, *the phase of crystal engineering*."

In the 15 or so years that followed the death of Gerhard Schmidt, chemical crystallographers made some efforts aimed at the design of reactive solids. Topochemical 2+2 reactions were designed by scientists in the Weizmann Institute, notably Mendel Cohen, Meir Lahav and Leslie Leiserowitz. A group in



Possibly the first "rule" of crystal engineering was that developed by G. M. J. Schmidt and B. S. Green who found that aromatic molecules that are dichlorosubstituted have a marked tendency to adopt a crystal structure with a short axis of around 4 Å. This is equivalent to the β-structure of cinnamic acid. This empirical "chloro rule" was used to make alkenes that would undergo photodimerization to give mirror symmetry cyclobutane derivatives.

Cambridge, headed by John M. Thomas developed a series of cyclic ketones, namely the 2-benzyl-5-benzylidenecyclopentanones, which showed an interdependence of crystal structure and solid state reactivity. Gerhard Wegner, in Freiburg, showed that the polymerization of crystalline diacetylenes is governed by topochemical rules. Masaki Hasegawa and others showed that the solid state polymerization of 2,5-distyrylpyrazine is very similar to that of the diacetylenes in that there is a close relationship between the crystal structure of the starting monomer and the likelihood of a solid state reaction taking place.

Another type of solid state chemical reactivity was exemplified by the reactions of organic crystals with gases. In the University of Illinois, David Y. Curtin and Iain C. Paul discovered a striking anisotropy in the reactions of ammonia with crystalline benzoic acids. Reaction was fastest on those faces where carboxylic groups emerged and slowest on those where the hydrocarbon fragments were situated. Solid-gas reactions are important in some industrial processes but are difficult to predict, organize and control. Once again, however, a connection was established between internal crystal structure and molecular packing, which are microscopic properties, and bulk chemical reactivity which is a macroscopic property. The fact that such connections do exist makes it important to achieve some measure of control over crystal packing. How does one predict the crystal structure of an organic compound? We come back to the basic question: Given the molecular structure of an organic compound, what is its crystal structure?

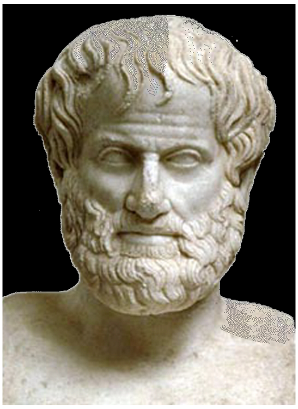
The synthetic chemist is likely to have many opportunities to encounter unusual phenomena by accident during everyday chemical work with crystalline solids and without the proper background will not be prepared to recognize and take advantage of such chance discoveries. There is the further misfortune that those workers in areas where the most dramatic applications…have occurred are, in general, uncomfortable when dealing with structures of complex organic molecules; the result is a serious lack of communication between groups whose interaction should be mutually beneficial.

D. Y. Curtin and I. C. Paul, *Chem. Rev.*, 1981.

Chemist crystallographers in the 1970s and early 1980s were, on the whole, restricting their attention to organic reactions in the solid state. These systems were hard to study. The routine determination of organic crystal structures was not yet quite a reality and methods of studying molecular solid state reactions were not similar to the methods employed in the solid state chemistry of extended inorganic solids. In consequence, this period saw something of a hiatus.

1.3 The Crystal as a Supramolecular Entity

A distinct thought stream, and one which was to ultimately bring crystal engineering into the chemical mainstream was the theme of *supramolecular chemistry*. Chemistry, especially organic chemistry, was a wholly molecule centric subject till around 50 years ago. The molecule was considered to be the ultimate delimiter of all significant properties of a substance. By looking at a molecular structure, the chemist was able to conceive of all the useful and important attributes of a chemical compound. The molecular paradigm of organic chemistry was the inspiration for synthetic chemistry. The philosophy of organic synthesis and the way it grew over the last century is described in Chapter 3. The fact that there are some fundamental properties of a compound, like its melting point, that depend on the structure of groups or assemblies of molecules was either ignored or not considered carefully enough.



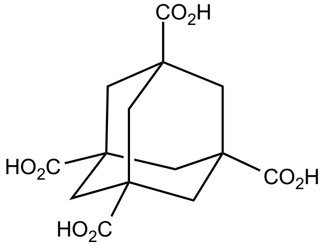
Aristotle is widely credited with introducing holistic thinking into science, although this type of thought was also widely prevalent in ancient India and China, forming the basis of many current Eastern systems of philosophy. Aristotle believed in the predominance of the species rather than the individual members of the species. In the context of supramolecular chemistry, for example, the network is more important than the molecules that constitute it. The whole is greater than the sum of the parts. Holism stands in direct contrast to reductionism which stresses the importance of the individual and the uniqueness of everything. This school of thought was originally propagated by Charles Darwin. According to reductionist thinking a complex phenomenon can be fully understood by dissecting it down to simpler components and understanding their individual behavior. According to reductionist thinking, chemistry is reducible to physics, and physics in turn is reducible to mathematics. Supramolecular chemistry is perhaps the first important thought stream in the history of chemistry that is blatantly non-reductionist in its approach.

The development of supramolecular chemistry is outlined in Section 3.2. In this introductory chapter, it will be sufficient to mention that the first modern stirrings of supramolecular thought occurred in the description of an organic crystal structure as a network by H. M. Powell who, in 1948, discussed the hydroquinone clathrates in this context. A network description of a structure is a holistic description that de-emphasizes the constituents of the network, namely the molecules. Topology and form take precedence over content. A major premise in supramolecular chemistry is that the whole is greater than the sum of its parts. An assembly or collection of molecules has a structure and properties that are more than the sum total of the properties of the individual molecules.

The supramolecular concept successfully draws together organic, inorganic and organometallic chemistry in the context of crystal engineering. This conceptual coming together of disciplines that were traditionally considered to be distinct occurs through the visualization of crystal structures as networks. An organic crystal structure, in other words, a molecular crystal structure, was usually viewed as a collection of molecules and not as a network. Inorganic infinite solids, on the other hand, are more often than not viewed as networks that are made up of atoms or ions (Section 1.4.3). With supramolecular chemistry, an organic crystal may be depicted as a network. One can also look at an inorganic solid as a "molecular crystal". Let us discuss these interpretations further.

In 1988, Otto Ermer, in the University of Cologne, provided a beautiful and, at the time, unique example of a three-dimensional hydrogen bonded network in his description of the hydrogen bonded crystal structure of adamantane-1,3,5,7-tetracarboxylic acid. The structural formula of this acid is shown in the inset. The formation of hydrogen bonds at each of the four tetrahedrally disposed carboxyl groups to other such groups on adjacent molecules leads to a diamondoid lattice (see also Section 3.3.2). This structure is topologically equivalent to the diamond lattice with the C–C bonds replaced by O–H···O hydrogen bonded dimers. This structure deviates considerably from close packing. The open diamondoid network creates a large empty hollow within, but this problem is solved by the *interpenetration* of no less than five such diamondoid networks. Notably, there is no hydrogen bonding between networks. The appearance of this paper in the late 1980s was significant. Clearly the scientific community was ready for supramolecular thinking. The Nobel Prize had just been awarded to Charles J. Pedersen, Donald J. Cram and Jean-Marie Lehn in 1987 for supramolecular chemistry. Chemists were finally willing to consider holistic approaches. The depiction of an organic crystal structure as a network is one such non-reductionist approach.

In the end, *all* organic crystal structures can be viewed at as networks. The chemist emphasizes the linkages between molecules rather than the molecular structure itself. For example, the orthorhombic crystal structure of benzene approximates a face centred cubic packing (FCC), and this is not surprising, given the hydrocarbon nature of the molecule and its discoid shape. The more spherical urotropin forms an accurately body centered cubic (BCC) crystal and there are not many conceptual differences between such structures and those of the metallic elements. All organic crystal structures may be considered as networks with the molecules being the nodes and the non-bonded intermolecular interactions being the node connections (Section 1.4.3). The dissection of an organic crystal structure into one, two or three-dimensional networks would become very important in crystal engineering in the years to come because such an analysis reveals similarities between crystal structures of molecules with widely different molecular structures. This can occur because the node connections in a network can be formed from a wide variety of intermolecular interactions.



Traditionally, organic and inorganic crystal chemistry have proceeded along different lines of thought even though propositions such as the need to fill space most economically and the conflict between close packing and directionality are of universal applicability. In some instances, it is quite useful to seek similarities between organic and inorganic crystal structures. Such analysis is extremely important in the study of coordination polymers (Chapter 7). These similarities are topological in nature with equivalences being found between intermolecular interactions in organic solids and ionic and covalent bonds in extended inorganic solids. Just as an organic structure can be viewed as a network with nodes (molecules) and node connections (interactions), an inorganic crystal structure can be looked upon as a giant molecule using the concepts of molecularity as outlined earlier in this chapter. Diamond and cubic ZnS are indeed giant molecules and there is no difficulty in such visualization. For ionic structures like NaCl and CsCl, a "molecular" visualization is nominally possible if the ions are likened to "atoms" and the ionic bonds to "atom connections". Considering also that covalent bonds and intermolecular interactions form a continuum and that the strongest interactions are stronger than the weakest bonds, it is possible to find an inorganic topological counterpart for many organic structures. The analogy between adamantane-1,3,5,7-tetracarboxylic acid and diamond is described here. Some others are mentioned in the set of problems at the end of this chapter.

1.4 Modern Crystal Engineering

The fundamental laws necessary for the mathematical treatment of a large part of physics and the whole of chemistry are thus completely known, and the difficulty lies only in the fact that application of these laws leads to equations that are too complex to be solved.

This famous statement, which is dismissive of chemistry as a whole, was made by the famous physicist P. A. M. Dirac and could be termed the reductionist's high noon.

A new scientific subject generally emerges when there is a critical mass of thought coupled with advances in instrumentation. The emergence of a new subject is, however, not fully predictable and can be influenced in part by random events. The appearance of a new area is usually triggered by a few critical papers, a small number of individuals, and some opinion-making conferences. In any event, the scientific climate should be such that there is a willingness to accept new ideas. The arrival of modern crystal engineering in the late 1980s and early 1990s arose from a combination of expected and unexpected reasons. Let us first examine how chemistry has been organized as a subject in the past.

1.4.1 *Horizontal and Vertical Divisions of Chemistry*

Wilhelm Ostwald (1853–1932), one of the founding fathers of physical chemistry.

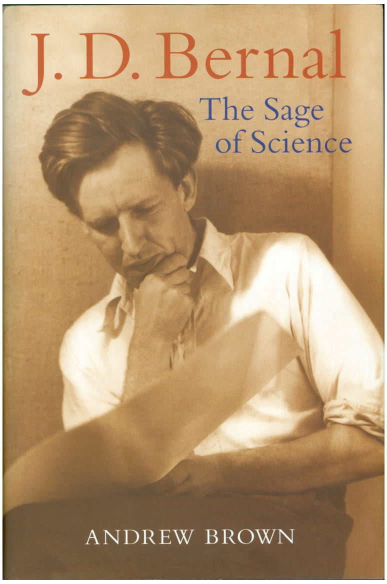
Chemistry was perceived as a distinct subject following John Dalton's atomic theory and its history over the past 200 years represents a consolidation of reductionist thinking, which brought about a division into organic, inorganic and physical streams. Chemistry in the 19th and 20th century was seen as being more or less reducible into physics and finally mathematics. Depending on the importance of quantitative ideas as manifested in the ease of reducibility, these three streams of chemistry came into being. Organic chemistry, the most qualitative and irreducible of the streams, developed as a separate subject after Friedrich Wöhler's urea synthesis in 1828 and was strengthened by the work of Justus Liebig, August Kekulé and others. Physical chemistry became clearly demarcated with Wilhelm Ostwald's contributions in the later part of the 19th century, and underwent something of a metamorphosis after Linus Pauling's work in the 1930s on the chemical bond. This set the stage for the appearance of quantum chemistry, which was always considered to lie within physical chemistry. Inorganic chemistry, the part of chemistry that did not "go away" became greatly focused after Alfred Werner's work on coordination compounds (Chapter 7). In the decades that followed, considerable overlap was found between physical and inorganic chemistry. Solid state chemistry (of inorganic compounds) lies in this intersection. Some chemists consider analytical chemistry to rank along with organic chemistry, inorganic chemistry and physical chemistry as the fourth fundamental pillar of the subject. These are the vertical divisions of chemistry. These divisions do not carry the same significance today, in a research sense, that they did say 50 years ago but they are still very convenient demarcations in a pedagogic sense.

In the last part of the 20th century, several other branches of chemistry came into prominence. These new subjects resisted an easy docketing into one of the three vertically divisible streams of chemistry. Therefore they may be called horizontal divisions. They include medicinal, environmental, theoretical, computational, solid state, pharmaceutical, materials and supramolecular chemistry. These subjects are so interdisciplinary and eclectic that it is scarcely possible, and not even necessary, to try and pigeon hole them into the conventional organic-inorganic-physical classification. Crystal engineering is one of these new horizontal branches of chemistry. It takes ideas from organic, inorganic, physical, computational, supramolecular and solid state chemistry, and surely from X-ray crystallography. Some of these thought streams have been described earlier in this chapter. Others will be discussed in subsequent chapters. The appearance of modern crystal engineering on the scientific scene owed in no small measure to the award of the 1987 Nobel Prize to work in supramolecular chemistry. Crystal engineering is noteworthy in that it represents, like supramolecular chemistry, a departure from reductionist thinking. In this new non-reductionist chemistry, a case is made for the emergence of a new set of properties from the interplay of macrosystems that are not related directly to their component atoms and molecules. The idea of emergence was linked to complex pathways and was used to explain the evolution of complex self-organizing systems, like molecular crystals. By the late-1980s, the time was ripe for the launching of new areas within the chemical sciences. Crystal engineering was one of these new areas.

Not included in Section 1.4.1 is a description of the areas of overlap between chemistry and biology. Biochemistry emerged from chemistry around 1900 with the work of Emil Fischer (1852–1919) but it is not even considered a part of chemistry today. Systems biology is more closely related to modern day supramolecular chemistry and much interdisciplinary work is carried out under the umbrella of chemical biology. Curiously, Fischer is also credited with the first mention of supramolecular ideas in his lock-and-key model for the working of enzymes (Section 3.2). It is surely not a coincidence that the same chemist initiated thinking in both biochemistry and supramolecular chemistry.

1.4.2 *Organic Crystal Engineering*

Several factors were responsible for the evolution of modern crystal engineering in the late 1980s. Notable among them was the fact that it became easy, around then to determine the crystal structures of small organic molecules. This was due to advances both in



Bernal suggested in the 1930s that collections of crystallographic data would be of value.

instrumentation (computer controlled single crystal diffractometers) and computation (Direct Methods for structure solution and programs such as SHELX written by George Sheldrick). The second was the emergence of the Cambridge Structural Database as a research tool of importance. A paper by Olga Kennard, Frank Allen and Robin Taylor in *Accounts of Chemical Research* in 1983 was to have far-reaching importance. The CSD could be used for *data mining* of crystal structure information. It became possible to analyze and identify recurring patterns of molecules in organic crystals. A recurring pattern is more likely to repeat itself in a new crystal structure, and the ground rules of crystal structure prediction thus laid. There was also the increasing perception that if crystal engineering was to live up to its promise of becoming a new and interesting subject, it should outgrow the then-existing emphasis on solid state reactivity. Other properties were of interest too. Fundamental questions were being asked as to the underlying causes for the adoption of crystal structures. Organic crystal structures were not even categorized or classified into types, as had been done for inorganic solids. There were stirrings of new ideas with respect to intermolecular interactions, notably the weaker varieties of hydrogen bonds. A seminal paper in *Acta Crystallographica* by Leslie Leiserowitz, in 1976, on the crystal chemistry of carboxylic acids was an early hint of these new ideas. Could weak hydrogen bonds possibly be important in organic crystal structures?

There is general consensus that many present-day motivations of crystal engineering originated from a book that appeared in 1989, authored by G. R. Desiraju, entitled *Crystal Engineering. The Design of Organic Solids*. Notable in this book are the following points of departure from the then-existing paradigms: (i) Crystal engineering is a subject of wide-ranging applications and its scope extends much beyond the topochemical photoreactivity of organic solids; (ii) Organic crystal structures are predominantly governed by Kitaigorodskii's close packing principles, which invoke geometrical arguments, but the minor deviations from close packing, which owe to chemical factors, are of the greatest importance because they lead to the formation of crystal structures that can be *engineered* in a systematic manner. Directionality, such as it exists in organic crystals, is the handle that permits crystal design; (iii) The collection of machine retrievable data on 70,000 crystal structures that existed at that time (the number is now greater than 525,000) is sufficient to establish trends in crystal packing. Pattern recognition is one of the first steps in crystal engineering strategy; (iv) Directional interactions are anisotropic in nature and they cause deviations from close packing. These interactions need to be manipulated in the crystal design exercise. The most important of these directional interactions is hydrogen bonding, which exists in strong and weak varieties; (v) Other directional interactions are based on halogen and sulfur atom non-bonded contacts in crystals; (vi) The design of crystals that lack an inversion centre was identified as a systematic endeavour in crystal engineering; (vii) Multi-component molecular crystals, the study of which is seen as an activity of the greatest importance in modern crystal engineering, were identified as a distinct sub-group of structures which might be amenable to distinct methods of design; (viii) Polymorphism, the existence of multiple crystal forms for the same molecule, was labeled as a Nemesis of crystal engineering, thwarting the plans of the crystal engineer.

Some of these ideas will be elaborated in this textbook. In Chapter 2, we will discuss close packing and directional intermolecular interactions. In Chapter 5, we will describe polymorphism in all its ramifications and understand why this subject, while still being a Nemesis in terms of its difficulty, has come to be of the greatest practical significance. In Chapter 6, we will examine multi-component crystals and try to understand if they are similar to single component crystals.

A number of important papers and studies quickly followed. A set of three papers co-authored by Desiraju and Angelo Gavezzotti classified the crystal structures of polynuclear aromatic hydrocarbons and identified the molecule → crystal paradigm as a primary concern of crystal engineering. Influential papers by Margaret Etter focussed on hydrogen bonding as a design tool. She termed hydrogen bonds as being both strong and directional and described a method of classifying and labelling hydrogen bond networks; this is detailed in Section 2.6.2.1. In hindsight, it is interesting to observe that both these sets of studies reinterpreted the early works of Robertson: the Desiraju-Gavezzotti papers expanded and quantified his studies of hydrocarbons while Etter did practically the same thing with her work on hydrogen bonding. Such reinterpretation is almost mandatory in an interpretative science, which is what crystal engineering is all about.

Nemesis, the Greek goddess of retribution, symbolizes the spirit of divine vengeance against those who submit to arrogance. There is something of the inevitable in this kind of divine wrath. Implied almost is that there is a modicum of good and bad for all of us. Nemesis is the distributor of fortune in due proportion. Undeserved good fortune would attract her attentions and would not go unpunished. In science too, it is interesting to wonder if such themes actually prevail. The subject of polymorphism in crystal engineering is full of anecdotes (Chapter 5) in which punishment, in the form of a disappearing polymorph or a contentious law suit, has often thwarted the moves of the rich and powerful. Perhaps scientists too need to pay heed to some of the lessons learned from Greek mythology.

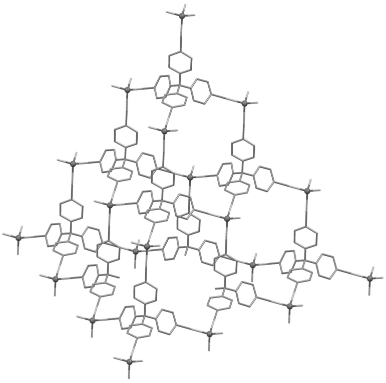
Participants in the crystallography school in Erice in 1985.

Gradually the community of crystal engineers began to grow. An important tutorial meeting in Erice, Sicily, in 1985, chaired by Aldo Domenicano, Istvan Hargittai and Peter Murry-Rust might already have sowed the seeds for some of the developments in crystal engineering in the late 1980s. Many scientists, who are currently prominent in the field, attended this meeting during their formative years. This meeting highlighted the fact that X-ray crystallography of small organic molecules was becoming easy, accurate and fast. In the 1990 Congress of the International Union of Crystallography in Bordeaux, there was free discussion on hydrogen bonds as agents of molecular association in crystals. The emphasis was shifting surely from structures of individual molecules to surveys of intermolecular packing and interactions, *crystal structures*. Along these lines, there were papers by Michael Zaworotko on hydrogen bonding and diamond networks, and by Dario Braga on organometallic cluster compounds in the early 1990s. Others too took up the issue of molecular aggregation in more general ways. A time line of crystal engineering over the last century is given at the end of this chapter and will give the reader a glimpse of some important developments.

Desiraju's 1989 book deals with the crystal engineering of organic solids. In a parallel development that was influenced by the idea of a crystal structure as a network, crystal engineering of metal-organic crystal structures was mooted.

1.4.3 *Metal-Organic Crystal Engineering*

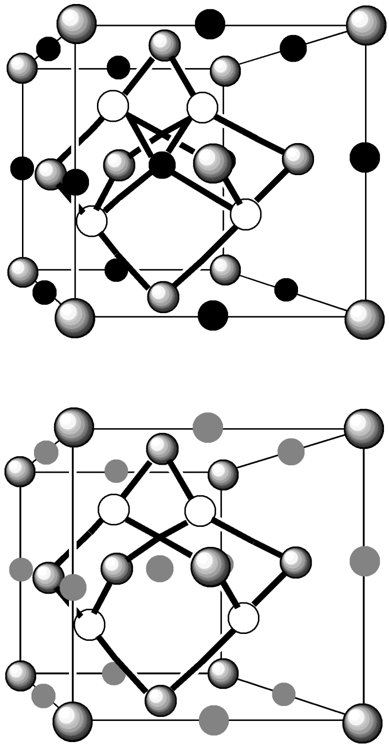
We have already seen that inorganic extended solids are typically described as networks (Section 1.3). This depiction was made popular by A. F. Wells, whose monumental book is now a classic. Wells defined crystal structures in terms of their topologies and reduced them to a collection of nodes (points) of particular geometry (tetrahedral, trigonal, planar) that are connected to each other with node connections (bonds, interactions). Any network consists of nodes and node connections. The resulting structures can also be calculated mathematically and can be infinite in one, two or three dimensions depending on the chemical nature of the nodes and node connections.



Tetrahedral network in $[Cu^I\{C(C_6H_4CN)_4\}]^+$

Richard Robson extended the work of A. F. Wells on inorganic extended solids to coordination compounds. By linking polycoordinate metal ions with polydentate ligands, it is possible to build up a polymeric structure. Therefore these compounds were called *coordination polymers*. They are described in detail in Chapter 7. Here, it will suffice to state that a network depiction for coordination polymers is intuitive. The metal centers act as nodes and the ligands behave as node connections. The first compound Robson made in 1989, $[Cu^I\{C(C_6H_4CN)_4\}]^+$, has a diamond network because it is constructed from a tetrahedral metal center (Cu^I) and a tetradentate ligand. The intention, fully realized, in this crystal engineering exercise was that the metal ion would bind to a tetrahedrally disposed set of four nitrile donors from separate ligand molecules, each of which in turn binds to four metal ions, extending the structure infinitely in three dimensions. The cavities created by this network are rather large and are filled with solvent and counterions.

We will describe the crystal structure of $Zn(CN)_2$ in Chapter 7. At this stage, it is sufficient to state that this solid too has a diamond network structure but both C and N atoms in the CN ligand can act as donors, and therefore each Zn^{II} ion is coordinated to two C-atoms and two N-atoms. This network is doubly interpenetrated, in other words two such networks catenate within each other with no formal link between them, similar to adamantane-1,3,5,7-tetracarboxylic acid which has a fivefold interpenetrated structure (Section 1.3) Noting that the affinities of Cu^I and Zn^{II} cations to C-atom and N-atom donors are different (Cu^I binds preferentially to C-donors), Robson conjectured correctly that if half the Zn^{II} sites in $Zn(CN)_2$ were replaced with Cu^I, an ordered structure would be obtained in which the Zn and Cu sites alternate strictly (the Zn coordinating to the N-donors and the Cu to the C-donors). He further extrapolated correctly that if a counterion of the correct size were chosen (he picked Me_4N^+), it would fit exactly into the cavities of the tetrahedral network so that interpenetration, as in $Zn(CN)_2$ would be avoided. Robson's work was followed by that of Omar Yaghi who, in 1995, first proposed that guest molecules could be absorbed and removed from the open pores of coordination compounds. These compounds were called metal-organic framework compounds or MOFs.



In 1994, G. R. Desiraju described an organic multi-component system in terms of networks. 1,3,5,7-Tetrabromoadamantane (large grey shaded) forms a 1:2 diamond network crystal with urotropin. There are two crystallographic sites for urotropin (black and unshaded). One of them (black) is loosely bound and can be substituted with CBr_4 (light grey) a molecule of the same size. These experiments are very similar to Robson's 1990 studies on $Zn(CN)_2$ in that both are based on retrosynthesis, a concept that was already well established in synthetic organic chemistry, but still had to become formalized in crystal engineering. Such formalization occurred with the publication of Desiraju's 1995 paper on supramolecular synthons (Chapter 3).

The fields of organic crystal engineering and coordination polymers were viewed, in the past, as being somewhat distinct but there is now a growing realization that they are conceptually very similar and also that they have borrowed from the same chemical thought streams. Retrosynthetic methods (Chapter 3), for example, are an integral part of crystal design strategies in both branches of the subject. In the modern day context, both these areas are considered to lie within the scope of crystal engineering.

1.4.4 *Properties of Crystals*

Crystal engineering is all about making crystals that have specific functions. It is about the systematics of crystal construction. In his legendary talk in 1959 entitled "There's plenty of room at the bottom", Richard Feynman alluded to the problem of synthesis as something a physicist might want to attempt. He asked "Is there a *physical* way to synthesize any chemical substance?" He continued and said that, in principle, no fundamental law of physics was violated if a molecule were assembled systematically atom by atom. Similarly, we can say that no law would be violated if a crystal is put together systematically molecule by molecule. In the end, this is what crystal engineering is all about. Ultimately we want to make crystals that have a particular property, and we want to get control over the ways in which molecules assemble.

Crystal properties are both chemical and physical. Many properties are directly related to the crystal structure. Chemical properties lead to a change in chemical composition of the crystal, which may be reversible or irreversible. Molecular crystals with particular chemical properties (reactivity, tautomerism, changes in color) find applications as sensors, devices, light sensitive materials, and in catalysis. Physical properties (gas inclusion, electrical, magnetic, optical, solubility) are more easily tailored and the majority of applications are in this category. Nonlinear optical responses of some organic solids that lack a crystallographic center of symmetry exceed that found in presently used inorganic substances. These crystals are used as frequency doublers and waveguides. Noncentrosymmetric crystals also find applications as ferroelectrics, piezoelectrics, pyroelectrics and as triboluminescent materials. Solid form control is important in industries connected with dyestuffs, pharmaceuticals and explosives. The importance of obtaining different solid forms of a drug molecule (polymorph, solvate, co-crystal) can be of huge commercial interest. A major application of molecular crystals today is in the engineering of open metal-organic framework structures (Chapter 7). These compounds have been compared to zeolites because they have framework structures with large spaces enclosed within. Compared with zeolites, however, the dimensions of the empty spaces in coordination polymers are large and the internal surface area is concomitantly large. Accordingly, these materials are able to absorb large quantities of gases. They can also be engineered so that they can selectively absorb gases from gas mixtures. Such applications can be immensely useful in separation and catalysis.

Richard Feynman (1918–1988).

1.5 Summary

This book is written so that it can be read all at once, or chapter by chapter. It is meant for senior undergraduates and beginning graduate students. In Chapter 2, we will discuss intermolecular interactions, the glue that holds molecules together in crystals. In Chapter 3 is outlined the main strategy for retrosynthesis of an

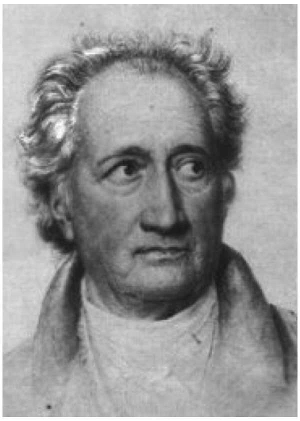
Reason is to the imagination as the instrument to the agent, as the body to the spirit, as the shadow to the substance.

Shelley

organic crystal. Crystal engineering is described as supramolecular synthesis. Chapter 4 provides a summary of the main issues connected with crystallization. Understanding the mechanism of crystallization is considered to be one of the holy grails of crystal engineering. In Chapter 5 is provided an account of polymorphs, or different crystal forms of the same compound. Is polymorphism the Nemesis of crystal engineering? Chapter 6 contains a description of multicomponent molecular crystals or co-crystals. Are these really different from single component crystals? Chapter 7 gives an account of coordination polymers or metal-organic framework compounds and will show how the study of these crystalline substances properly comes within the scope of crystal engineering. A glossary of useful terms is given at the end of the book. Nomenclature issues have always been lively in crystal engineering, and it is hoped that the annotations given in the glossary are both noncontroversial and useful. Also provided, at the end of each chapter, is a list of references for further study. This is a textbook and not a research book. Therefore, we have avoided mentioning references to the literature in the main body of the text. Representative problems are also given in each chapter.

Crystal engineering has been described as the designed synthesis of functional crystalline matter. In the end, however, crystal engineering is a form of synthesis and, in this respect, it is firmly a part of the chemical enterprise. Chemistry is the only important subject in which the researcher is free to make the object of his study. It was said by Berthollet that "La chime crée son objet". All synthesis is a combination of art and science, the substance and the shadow, and crystal engineering is no exception. Why do we make a crystal? Because it is there in the mind, waiting to be made; because the play of symmetry in the crystal is aesthetically pleasing; because it is difficult to make; because it is useful; because it is useless. Synthesis needs no justification. It is an integral part of chemistry. Some would say that synthesis is chemistry itself. Crystallography has its own fatal attractions. In the words of Goethe, who said in 1822, "Crystallography, considered as a science, gives rise to quite specific viewpoints. It is not productive, and it exists only for itself, having no consequences, especially now that one has encountered so many isomorphic substances. As it is really nowhere useful, it has developed largely into itself. But it does provide the intellect a certain limited satisfaction, and its details are

Claude Berthollet (1748–1822).



Johann Wolfgang von Goethe (1749–1832).

so diverse that one can describe it as inexhaustible and that is why it binds even first rate people so firmly and for so long." The sciences of chemistry and crystallography have had a deep and symbiotic relationship for a great many years. Crystal engineering is one the latest, and most exciting, examples of this symbiosis.

The first scientific meeting devoted exclusively to crystal engineering was organized by M. J. Zaworotko and K. R. Seddon in Digby, Nova Scotia, Canada in 1996.

Crystal Engineering Time Line

1921	W. H. Bragg relates the crystal structures of naphthalene and anthracene.
1935	J. D. Bernal advocates the study of groups of crystal structures. The forerunner of crystallographic databases.
1948	H. M. Powell describes the β-hydroquinone structure as a network.
1951	J. M. Robertson's paper on the crystal structures of polynuclear aromatic hydrocarbons.
1954	Crystal structure of the Hofmann complex by J. H. Rayner and H. M. Powell.
1955	R. Pepinsky uses the term *crystal engineering*, the first time anyone does so.
1959	R. Feynman's lecture on building a structure from bottom up. There's room at the bottom.
1964	G. M. J. Schmidt publishes a series of papers in *Journal of the Chemical Society* on the solid state chemistry of cinnamic acids and other alkenes. The topochemical principle.

1971	Schmidt formally introduces the term *crystal engineering* in his paper in *Pure and Applied Chemistry.*
1970–1985	Development of organic solid state chemistry in the Weizmann Institute (M. D. Cohen, M. Lahav, L. Leiserowitz), University of Illinois (D. Y. Curtin, I. C. Paul), University of Freiburg (G. Wegner) and University of Cambridge (J. M. Thomas).
1977	Crystal structure determination of Prussian Blue by A. Ludi *et al.* published in *Inorganic Chemistry*.
1988	First analysis of an interpenetrated organic solid. O. Ermer's paper in *Journal of the American Chemical Society* on adamantane-1,3,5,7-tetracarboxylic acid.
1989	Robertson revisited. Paper by G. R. Desiraju and A. Gavezzotti entitled *From molecular to crystal structure* in *Chemical Communications*.
1989	G. R. Desiraju's book *Crystal Engineering. The Design of Organic Solids* is published signifying the beginning of modern organic crystal engineering. This is still the only single author book on the subject.
1990	R. Robson's paper in *Journal of the American Chemical Society* on interpenetrated transition metal coordination compounds. The field of coordination polymers is born.
1990	M. C. Etter identifies the hydrogen bond as an important design element in crystal construction in her review in *Accounts of Chemical Research.*
1991	J. D. Dunitz terms the crystal as a *supramolecule par excellence* in his paper in *Pure and Applied Chemistry.*
1991	J. D. Wuest introduces the concept of molecular tectonics. This term was originally introduced by N. N. Greenwood in 1984 in the context of polyhedral boron clusters.
1993	Trial of Glaxo's action against Novopharm, a Canada-based generic company, for infringement of one of Glaxo's patents covering the block-buster anti-ulcer drug Zantac. The importance of polymorphism in crystal engineering becomes apparent.
1995	The relationship between crystal engineering and organic synthesis is highlighted in a review by G. R. Desiraju in *Angewandte Chemie.* Supramolecular retrosynthesis is introduced with the term *supramolecular synthon.*
1995	O. M. Yaghi describes selective binding and removal of guest molecules in a porous metal organic framework structure. Functional coordination polymers are launched.
1996	The first keynote lectures on crystal engineering in a Congress of the International Union of Crystallography are delivered by A. Gavezzotti and G. R. Desiraju in Seattle.
1996	The first scientific meeting devoted entirely to crystal engineering is organized by M. J. Zaworotko and K. R. Seddon in Nova Scotia.
1998	Crystal engineering becomes a microsymposium topic for the first time in a Congress of the International Union of Crystallography in Glasgow.
1999	The Royal Society of Chemistry launches the journal *CrystEngComm* with D. Braga as the chairman of the editorial board.
2001	The American Chemical Society launches the journal *Crystal Growth & Design* with R. D. Rogers as the editor-in-chief.
2004	M. J. Zaworotko and Ö. Almarsson describe the importance of pharmaceutical co-crystals in a review in *Chemical Communications.*

2004	S. Kitagawa describes third generation coordination polymers which the cavities in the metal-organic framework structure are responsive to guest shape.
2010	The first Gordon Research Conference in Crystal Engineering is held in New Hampshire.
2011	The first textbook devoted exclusively to crystal engineering is published and is co-authored by G. R. Desiraju, J. J. Vittal and A. Ramanan.

1.6 Further Reading

Books

J. M. Robertson, *Organic Crystals and Molecules*, 1953.
A. I. Kitaigorodskii, *Molecular Crystals and Molecules*, 1971.
J. D. Dunitz, *X-Ray Analysis and the Structure of Organic Molecules*, 1981.
G. R. Desiraju, *Crystal Engineering. The Design of Organic Solids*, 1989.
J. D. Wright, *Molecular Crystals*, 1995.
J.-M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, 1995.
G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, 1997.
J. W. Steed and J. L. Atwood, *Supramolecular Chemistry*, 2000.
J. Bernstein, *Polymorphism in Molecular Crystals*, 2002.
A. Gavezzotti, *Molecular Aggregation: Structure Analysis and Molecular Simulation of Crystals and Liquids*, 2007.
K. C. Nicolaou and T. Montagnon, *Molecules that changed the World*, 2008.
L.-L. Ooi, *Principles of X-ray Crystallography*, 2010.

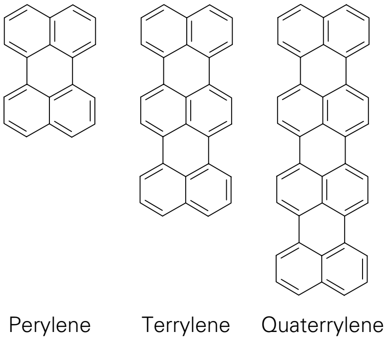
Papers

D. E. Palin and H. M. Powell, The structure of molecular compounds 5. The clathrate compound of quinol and methanol, *J. Chem. Soc.*, 571–574, 1948.
M. D. Cohen and G. M. J. Schmidt, Topochemistry 1. Survey. *J. Chem. Soc.*, 1996–2000, 1964, and the succeeding papers.
G. M. J. Schmidt, Photodimerization in the solid state, *Pure Appl. Chem.*, 27, 647–678, 1971.
L. Leiserowitz, Molecular packing modes. Carboxylic acids. *Acta Crystallogr., Sect. B*, 32, 775–802, 1976.
F. H. Allen, O. Kennard and R. Taylor, Systematic analysis of structural data as a research technique in organic chemistry, *Acc. Chem. Res.*, 16, 146–153, 1983.
O. Ermer Fivefold diamond structure of adamantane-1,3,5,7-tetracarboxylic acid, *J. Am. Chem. Soc.*, 110, 3747–3754, 1988.
G. R. Desiraju and A. Gavezzotti, From molecular to crystal structure. Polynuclear aromatic hydrocarbons, *J. Chem. Soc. Chem. Commun.*, 621–623, 1989.
B. F. Hoskins and R. Robson, Infinite polymeric frameworks consisting of three dimensionally linked rod-like segments, *J. Am. Chem. Soc.*, 111, 5962–5964, 1989.
M. C. Etter, Encoding and decoding hydrogen bond patterns of organic compounds, *Acc. Chem. Res.*, 23, 120–126, 1990.
J. D. Dunitz, Phase transitions in molecular crystals from a chemical viewpoint, *Pure Appl. Chem.*, 63, 177–185, 1991.
S. Subramanian and M. J. Zaworotko, Exploitation of the hydrogen-bond — recent developments in the context of crystal engineering, *Coord. Chem. Rev.*, 137, 357–401, 1994.
M. J. Zaworotko, Crystal engineering of diamondoid networks, *Chem. Soc. Rev.*, 23, 283–288, 1994.
D. Braga and F. Grepioni, From molecule to molecular aggregation — clusters and crystals of clusters, *Acc. Chem. Res.*, 27, 51–56, 1994.

1.7 Problems

You may need access to the internet to attempt many of these problems. You may also need special (not free) software in some cases.

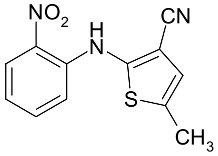
1. Refer to the definition of crystal engineering at the beginning of this chapter and verify that this definition addresses all three aspects of the subject: intermolecular interactions, crystal design and properties of molecular crystals.
2. What are the crystal structures of ZnS, CsCl, NbO and PtS? Topologically speaking, how do these compare with the well known structure of NaCl? In NaCl and in two of the four structures above, you can exchange cations and anions and still leave the structures unchanged. Which are these two structures?
3. Find out the crystal structure of palladium chloride, $PdCl_2$, and verify that it is a one-dimensional molecule.
4. What is a crystal unit cell? What are the unit cell dimensions (three lengths and three angles) for crystals of naphthalene and anthracene? Verify that all the dimensions, except one length, are practically the same for these crystals. What is the significance of the fact that $\alpha = \gamma = 90°$ in both these cases?
5. The unit cell parameters of perylene and quaterrylene are as follows: perylene, $P2_1/a$, $a = 11.27$, $b = 10.82$, $c = 10.26$ Å, $\beta = 100.55°$; quaterrylene, $P2_1/a$, $a = 11.25$, $b = 10.66$, $c = 19.31$ Å, $\beta = 100.6°$.



With this information, write down the space group and unit cell parameters of terrylene. This crystal structure is still unknown.

6. Refer to G. M. J. Schmidt's 1964 papers in the *Journal of the Chemical Society* given in the bibliography above. 2-Ethoxycinnamic acid crystallizes as three polymorphs α, β and γ where the Greek letters have the same meaning as they do in these papers. Write down the structures of the products that are obtained when crystals of each of the three forms are irradiated with UV light or sunlight?
7. Refer to the Cambridge Structural Database (www.ccdc.cam.ac.uk). From the CSD, retrieve the following information:
    (a) How many crystal structure determinations are there of benzene? In how many of these experiments was neutron diffraction used?
    (b) How many symmetry independent molecules are there in the asymmetric unit (Z′) for benzoic acid, naphthalene, phenol and cholesterol?

(c) How many polymorphs of the following compound are present in the CSD?



(d) How many co-crystals (multi-component molecular crystals) are there in the CSD for the anti-malarial drug artemisin?

8. Find out the crystal structure of 1,3,5,7-tetrahydroxyadamantane. Show how this structure is topologically related to the familiar CsCl structure.
9. Several workers have tried to provide up to date definitions as to what exactly a crystal is. Try and find some of these definitions. An official definition is provided by the International Union of Crystallography (www.iucr.org). From this definition, you will be able to find out why X-ray diffraction is so important in the examination of crystals.