

Crystal engineering: Outlook and prospects

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Crystal engineering continues to attract the interest of organic and physical chemists, crystallographers and materials scientists. This article discusses some current challenges in this area and outlines some prospects. Owing to the rapid recent advances, the scope of the present article is necessarily subjective.

CRYSTAL engineering or the design of organic solids with specific physical and chemical properties continues to elicit intense interest¹. This new subject encompasses a wide variety of research activity ranging from the understanding of crystal packing in organic molecular solids to the design of open network structures based on metal–ligand coordinate bonds, the so-called coordination polymers. On the other hand, one is able to analyse and understand with increasing certainty the vast amounts of accurate data currently available from crystallographic databases, while on the other, an appreciation of a phenomenon like polymorphism can lead to immediate benefits in applied areas such as pharmaceutical development². The work of Schmidt on topochemistry is considered by many to represent the formal beginnings of crystal engineering (Box 1). The seventies could be considered as something of a hiatus, but interest widened in the eighties to more general studies of intermolecular interactions. With a better appreciation of these interactions, the identification of a crystal as a supermolecule in the nineties appears natural. In the early 2000s, crystal engineering is moving from structure engineering to property engineering.

The brief chronological scheme outlines the progress of crystal engineering during the last 50 years, and more so since the late 1980s from when onwards the attention of the chemical community has become more fully focused on it.

Crystal structure from molecular structure

Around sixty years ago, Pauling and Delbrück stated that in any kind of molecular recognition, and this includes the recognition between identical molecules, it is the dissimilar rather than the similar functionalities that come into closest contact³. Because the supramolecular behaviour of a particular functional group depends on the nature and location of other groups in the molecule,

crystal structures of organic molecules need not necessarily be derived in a straightforward way from the functional groups present. Crystal engineering is, in this respect, distinct from traditional organic chemistry. Simple relationships between molecular and crystal structure are ideal but in practice, only obtained when *interference* between orthogonal sets of interactions is minimal. In such cases, the interactions are said to be insulated from one another but when and why such *insulation* occurs is still not evident. Accordingly, the crystal structures of many ‘simple’ organic compounds are hard to understand and harder to predict.

Since functional groups do not adequately reflect molecules → crystal transforms, how then does one attempt to understand recognition and crystallization events in chemical terms? In this regard, there have been attempts to identify multimolecular units that more accurately reflect the relationships between molecular and supramolecular structure. The descriptor *supramolecular synthon* signifies a larger structural unit, within the most robust and useful of which is encoded the optimal information inherent in the mutual recognition of molecules to yield crystals. Inherent in this term ‘synthon’ are ideas of size economy and maximum information content. Very large structural units will naturally contain more information, but these are accompanied by unnecessary detail, while very small units may lack sufficient and critical information regarding supramolecular structure. For example, the crystal structures of all the three isomeric aminophenols, **1–3**, contain the O–H···N and N–H···O synthon **4**. Knowing that the *ortho* and *meta* isomers, **1** and **2**, have a very different crystal structure from the *para* compound, **3**, one may then conclude that synthon **4** is too small to discriminate between alternative structural possibilities. A better, that is more representative, supramolecular synthon is **5**; this is found in the crystal structures of **1** and **2** but absent in the structure of **3**. In effect, the most useful supramolecular synthons combine form with compactness⁴.

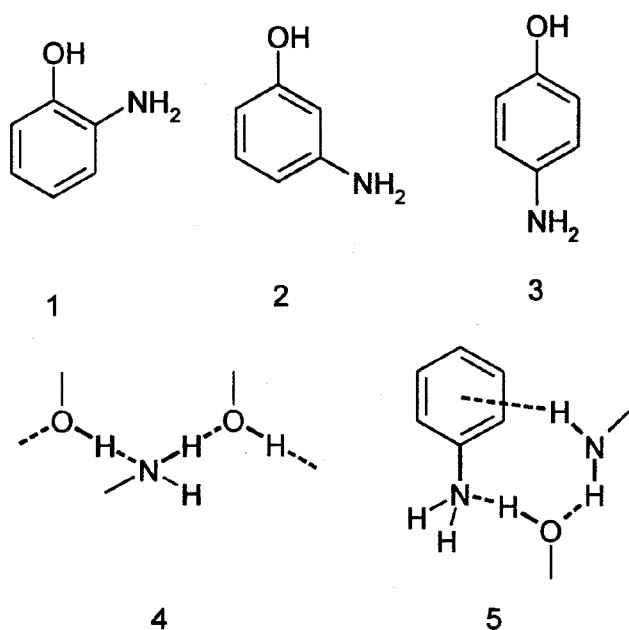
Weak intermolecular interactions and crystal packing

Conventional hydrogen bonding is the pivotal interaction in many crystal structures but a number of weaker and softer interactions have been shown to play a role

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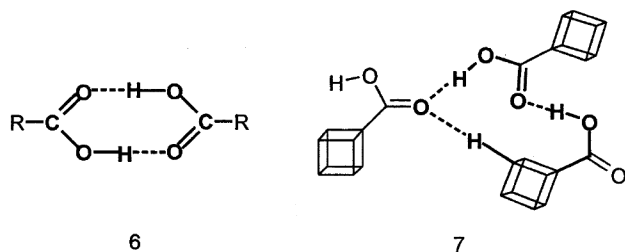
Box 1. Chronology of crystal engineering.

- 1951 J. M. Robertson's paper (*Proc. R. Soc. London*, 1951, **A207**, 101) on crystal structures of polynuclear aromatic hydrocarbons.
- 1964 G. M. J. Schmidt's series of papers (*J. Chem. Soc.*, 1964, 2000; 2014; 2041; 2051; 2060; 2068) on the solid state photochemistry of cinnamic acids and other alkenes – the topochemical principle.
- 1971 Introduction of the term *crystal engineering* by Schmidt (*Pure Appl. Chem.*, 1971, **27**, 647).
- 1970s till mid-1980s Development of organic solid state chemistry in the Weizmann Institute (reaction cavity and hydrogen bonding: M. D. Cohen, M. Lahav, L. Leiserowitz), University of Illinois (phase transformations, gas–solid reactions and crystal polarity: D. Y. Curtin, I. C. Paul), University of Freiburg (diacetylene polymerisation: G. Wegner, V. Enkelmann) and University of Cambridge (topotaxy: J. M. Thomas, W. Jones).
- 1988 First systematic analysis of an interpenetrated structure of a molecular solid. O. Ermer's paper on adamantane-1,3,5,7-tetracarboxylic acid, *J. Am. Chem. Soc.*, 1988, **110**, 3747.
- 1989 Robertson revisited. Paper by G. R. Desiraju and A. Gavezzotti entitled 'From molecules to crystal structure: Polynuclear aromatic hydrocarbons', *Chem. Commun.*, 1989, 621.
- 1989 G. R. Desiraju's monograph *Crystal Engineering. The Design of Organic Solids*, Elsevier, Amsterdam, 1989. This work showed that the subject of crystal engineering goes far beyond organic solid state chemistry, and is still the only single author book on the subject.
- 1990 R. Robson's paper on interpenetrated structures of transition metal coordination compounds, *J. Am. Chem. Soc.*, 1990, **112**, 1546.
- 1991 Identification of an organic crystal as a 'supramolecule par excellence' (J. D. Dunitz, *Pure Appl. Chem.*, 1991, **63**, 177) and a few years later by J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995.
- mid-1990s The subject enters mainstream organic chemistry. Crystal engineering is identified as a form of supramolecular synthesis. Three definitive reviews appear in this and related contexts: (a) G. M. Whitesides *et al.*, Noncovalent synthesis: Using physical organic chemistry to make aggregates, *Acc. Chem. Res.*, 1995, **28**, 37; (b) G. R. Desiraju, Supramolecular synthons in crystal engineering – a new organic synthesis, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2311; (c) J. F. Stoddart *et al.*, Synthetic supramolecular chemistry, *Acc. Chem. Res.*, 1997, **30**, 393.
- 1996 The first edited book on the subject appears. *The Crystal as a Supramolecular Entity* (ed. G. R. Desiraju), *Perspectives in Supramolecular Chemistry*, Wiley, Chichester, 1996, vol. 2.
- 1996 Crystal engineering is the theme of keynote lectures for the first time in a Congress of the International Union of Crystallography. Lectures are given by A. Gavezzotti and G. R. Desiraju at the Seattle Congress.
- 1996 First conference devoted exclusively to crystal engineering is held at Digby, Nova Scotia and is organized by M. J. Zaworotko and K. R. Seddon. The study of coordination polymers begins to develop as a distinct branch of crystal engineering, especially in North America (O. M. Yaghi, R. D. Rogers). Inorganic chemists get involved (A. Müller, J. Atwood, D. Braga).
- 1998 Crystal engineering makes its debut in the Erice series of conferences with a school organised by F.H. Allen and J.A.K. Howard. This is followed a year later by a very similar meeting organized there by D. Braga and A. G. Orpen.
- 1998 Launching of the first journal on the subject: *Crystal Engineering* (Elsevier).
- 1999 Crystal engineering becomes a microsposium topic for the first time in an I.U.Cr. Congress. G. R. Desiraju, M. J. Zaworotko and R. D. Rogers co-chair at the Glasgow Congress.
- 1999 The Royal Society of Chemistry launches its own journal *Cryst. Eng. Comm.* It is the second all-electronic journal of the RSC. The subject now has clear contours and may be distinguished from materials chemistry for which the society has a separate journal.
- 2000 The first dramatic application of crystal engineering – a crystalline sensor that can detect gaseous SO₂ at ppm level is described in a paper by van Koten *et al.* (*Nature*, 2000, **406**, 970). The subject is moving from structure engineering to property engineering.
- 2001 The subject has come of age. The American Chemical Society unveils its journal *Crystal Growth and Design*, to cover all aspects of crystal engineering.
- 2001 Crystal engineering and supramolecular chemistry in biological and material sciences is featured in a *Nature* review by G. R. Desiraju, *Nature*, 2001, **412**, 397.
- 2002 The first *CrystEngComm* discussion meeting on innovations in crystal engineering will be held at Bristol University, July, 2002 and will be sponsored by the RSC.



also in structure stabilization. This role can vary from unimportant to supportive to one that is actually intrusive. In this last case, the weak interactions may actually distort and modify the topology and arrangement of the conventional and stronger interactions⁵. Weak hydrogen bonding and polarization-induced heteroatom interactions are examples of these secondary interactions whose exact nature has still not been fully elucidated. As mentioned above, interaction insulation is always desirable and one would like to study the weaker interactions from this viewpoint.

The study of weak interactions will continue to be important in the design of supramolecular structures, because these interactions are able to alter predicted structures in dramatic ways⁶. Take for instance the crystal packing of carboxylic acids. The common mode of association of carboxyl groups is via the centrosymmetric dimer synthon **6**. However, in the family of cubane-carboxylic acids, the dimer synthon gives way to an



exotic pattern—carboxyl groups of alternating syn and anti-conformation form an infinite O—H...O hydrogen bonded catemer, **7**, that is stabilized by a C—H...O hydrogen bond from an activated cubyl C—H group. The assumption is that in the absence of the cubyl group, the

unusual catemer structure would not be obtained but rather that the more common dimer would be found.

Supramolecular synthetic strategies

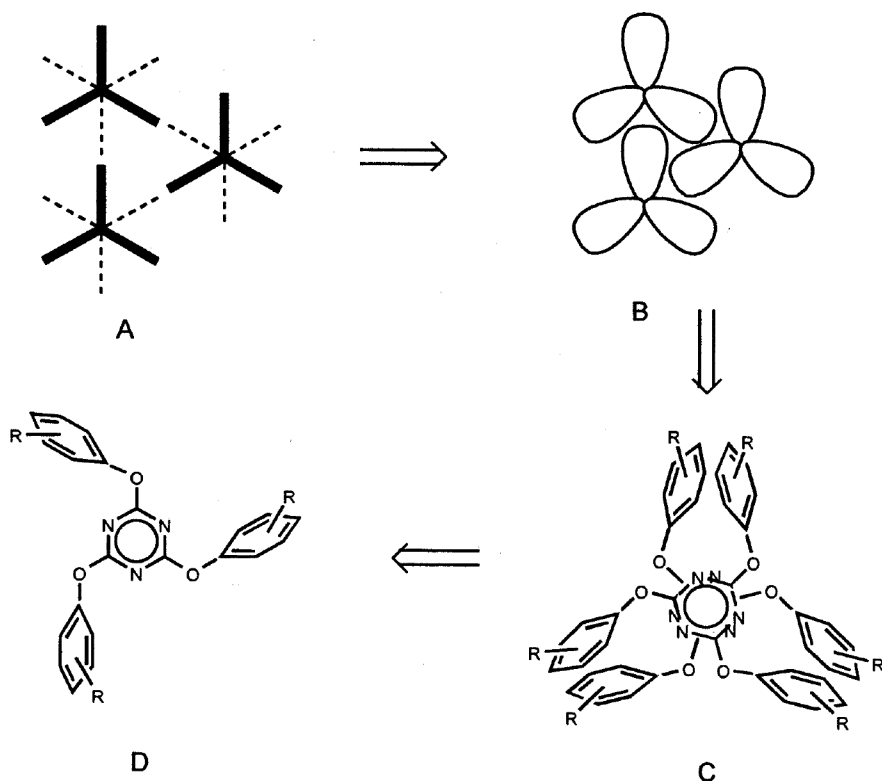
The study of a family of compounds provides insight into packing characteristics that may be exploited in the design of new and related structures. The identification of a crystal as a retrosynthetic target follows from the depiction of a crystal structure as a network with the molecules as the nodes and the supramolecular synthons as the node connectors. In this context, the organic diamondoid network solids are of relevance. Our interest in the study of such solids originated from observations of molecular-supramolecular equivalence in the tetraphenylmethane family of structures. For example, tetraphenylmethane, and CBr_4 form a 1:1 molecular complex, that is nearly isostructural with tetrakis-(4-bromophenyl)methane⁷. Following on these lines, we have recently described a diamondoid structure built up with $\text{I}\cdots\text{NO}_2$ interactions for diiododinitrotetraphenylmethane⁸.

Crystal structures from X-ray powder diffraction data

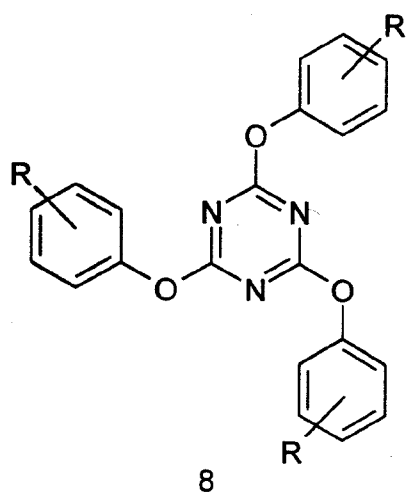
With the tremendous increase in the range of chemical systems being studied in crystal engineering, an all-too common occurrence is the failure to obtain diffraction quality single crystals. Clearly one would not like to abandon a research project for such a reason. The growth and development of methods of structure determination from X-ray diffraction patterns of polycrystalline samples is therefore becoming of increasing importance⁹. Among the difficulties encountered commonly in the use of such methods are the overlap of non-equivalent reflections in powder patterns, the indexing of patterns of low crystal symmetry and the dependence of the pattern on inhomogeneities in microcrystal size and orientation. Structures of purely organic compounds are difficult to solve because of the absence of strong scatterers, but direct space methods offer a new approach¹⁰. Synchrotron X-ray and high resolution neutron diffraction sources are very useful but are not commonly available and conventional X-rays are therefore used also.

Functionalized solids

Crystal engineering targeted at solids exhibiting large optical non-linearities has attracted much interest¹¹. The traditional design of NLO active materials has concentrated exclusively on dipolar molecules and in effect ignored the wealth of possibilities that could arise from two- and three-dimensional self-assembly. Diversified



Scheme 1.



investigations of more isotropic molecules, such as 2,4,6-triamino-1,3,5-trinitrobenzene, with attached octupolar and multipolar and non-linearities have been proposed but these investigations have been confined to the molecular rather than extended to the supramolecular or crystalline level.

A typical symmetry pattern that leads to crystalline octupolar non-linearity is the trigonal network **A** constituted with trigonal molecules (Scheme 1). Retrosynthetic analysis applied to **A** leads one to think in terms of synthons such as **B**. Crystalline triaryloxy substituted

1,3,5-triazines from stacked molecular diads called *Piedfort Units* (PUs) and such PUs, which in themselves are supramolecular species, **C** may be derived retrosynthetically from **B**. The ultimate molecular starting point of this supramolecular synthesis is a series of substituted 2,4,6-triphenoxy-1,3,5-triazines, **D**. To summarize, the retrosynthetic analysis $A \Rightarrow B \Rightarrow C \Rightarrow D$ has to ensure that the three-fold hierarchy is preserved at each stage of supramolecular construction from **D** to **A**. This is by no means trivial because it implies a carry over of molecular symmetry into the supramolecular structure. However, in a family of triazines, **8**, quasi-trigonal or trigonal networks are the rule rather than the exception¹², and measurable SHG powder signals of around $0.10 \times$ urea are obtained.

Polymorphism

Originally an enigma, then a curiosity, polymorphism¹³ today may be central to our understanding of crystallization mechanisms. Crystallization is inherently a very efficient process and nature seems to have developed ways and means to eliminate alternative pathways². Given the complementary nature of molecular recognition and the importance of enthalpic, entropic and kinetic factors, it would appear reasonable that the events during crystallization should be quite specific to the

molecule in question and that the possibility of obtaining two or more forms (especially in the same crystallization batch) is unlikely. Polymorphism is a complex phenomenon. Its occurrence is more frequent in compounds that are conformationally flexible and also contain groups that are able to form strong hydrogen bonds, like $-OH$, $-NH_2$, $-CO_2H$, and $-CONH_2$. The fact that these groups are commonly found in drug molecules makes this phenomenon of outstanding significance in pharmaceutical development.

Conclusions

The design of organic solids with potential applications as useful materials is an evolving subject. However, this new subject of crystal engineering contains features additional to those that are characteristic of molecule-based organic chemistry. Ability to plan and design crystal structures will depend very largely on thinking supramolecularly and on viewing a crystal structure as a blend of a very large number of interactions of various types and strengths. Within this complexity one must try to identify interactions or supramolecular synthons that will carry through across an entire family of structures with the aim of identifying a set of related molecules that yield a set of related crystal structures. The need to minimise interaction interference is therefore paramount. The resulting modularity in the crystal design process will render feasible three-dimensional structure control. The study of polymorphism is not a distinct endeavour from the control of crystal packing in

that the need to understand the nature of weak interactions is acutely felt in both cases. The challenging nature of many of these tasks should ensure lively activity in the future.

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Other key references are provided in the chronology.

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