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Crystal Engineering: Strategies and Architectures

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Abstract

The area broadly described as crystal engineering is currently expanding at a brisk pace. Imaginative schemes for supramolecular synthesis, and correlations between molecular structure, crystal packing and physical properties are presented in the literature with increasing regularity. In practice, crystal engineering can be many different things; synthesis, statistical analysis of structural data, *ab initio* calculations *etc.* Consequently, we have been provided with a new playing field where chemists from traditionally unconnected parts of the spectrum have exchanged ideas, defined goals and made creative contributions to further progress not only in crystal engineering, but also in other disciplines of chemistry. Crystal engineering is delineated by the nature and structural consequences of intermolecular forces, and the way in which such interactions are utilized for controlling the assembly of molecular building blocks into infinite architectures. Although it is important to acknowledge that a crystal structure is the result of a subtle balance between a multitude of non-covalent forces, this article will focus on design strategies based upon the hydrogen bond and will present a range of approaches that have relied on the directionality and selectivity of such interactions in the synthesis of predictable one-, two- and three-dimensional motifs.

Dr Christer B. Aakeröy, although a Norwegian citizen, was educated in Sweden where he obtained an M.Sc. at Uppsala University in 1986. He then embarked on further studies at the University of Sussex, England, where he acquired a D.Phil. in Chemistry in 1990. He was subsequently awarded a Scholarship from the Royal Swedish Academy of Sciences that enabled him to spend 8 months as a Research Fellow at the University of Minnesota in the laboratory of the late Professor M. C. Etter. From 1993 to 1996 he held a Lectureship in Chemistry at the Queen's University of Belfast, Northern Ireland. In September 1996 he accepted a position as Assistant Professor in Supramolecular Chemistry at Kansas State University, Manhattan, Kansas, where he continues to develop his research in crystal engineering, intermolecular interactions, molecular modelling and polymorphism.

1. Concept and background

Since the early days of structural and solid-state chemistry, many chemists have (sometimes unbeknown to themselves!) been working in the field of crystal engineering. Although the phrase itself did not appear until 1971 when it was introduced by Schmidt (1971), we only need to visit a recent definition by Desiraju (1989) to realise that structural chemistry and X-ray crystallography were involved with crystal engineering long before the concept itself had been explicitly verbalized:

> ...crystal engineering...the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desirable physical and chemical properties.

It is also becoming clear that this particular topic must hold considerable and widespread appeal and fascination because, all of a sudden, it seems as if everyone is doing crystal engineering! Manuscripts dealing specifically with 'designer-architectures' and with strategies for controlling and predicting structures are published on a regular basis, and several review articles (Lehn, 1988, 1990; Aakeröy & Seddon, 1993; Braga & Grepioni, 1996; Russel & Ward, 1996; Subramanian & Zaworotko, 1994; Desiraju, 1995*a*; Rebek, 1996) and books (Desiraju, 1989, 1995*b*; Vögtle, 1991; Lehn, 1995) have provided valuable overviews of the exciting and inspiring research efforts that have been presented during the last decade.

Before examining recent developments, it is useful to remind ourselves of the origins of the term 'crystal engineering'. During a study of photochemical dimerization reactions of cinnamic acid derivatives, Schmidt and co-workers established that the spatial relationship between neighbouring molecules played a dramatic role in determining reactivity (Cohen & Schmidt, 1964). These topochemical reactions were controlled by the structure of the material, *i.e.* the spatial arrangement of molecules in the solid. The ability to selectively change or optimize such reactions would therefore only come

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NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 1 of 18

about with control over the structure. Unfortunately, it turns out to be very difficult to foresee structural changes as a function of changes in molecular substitution patterns or in molecular geometry. Molecular shape does not necessarily manifest itself in a predictable manner in the crystalline lattice either in terms of space group, unit-cell dimensions or packing patterns. Since each crystal structure is the result of a delicate balance between a range of intermolecular forces, many of which are weak and non-directional, even a small change in the molecular structure, or isomerism, may lead to dramatic and unpredictable changes in the extended crystal structure. Hence, an improved understanding of the strength, directional behaviour, structural influence, in short, the very essence of non-covalent forces, becomes the underlying focus for initial research into crystal engineering.

Since intermolecular interactions govern molecular recognition at every level, every crystal structure is eventually the result of recognition processes which lead to thermodynamically favourable (albeit sometimes temporary) 3-D (three-dimensional) assemblies of molecules or ions. Bearing in mind that a crystalline material can, in theory, be assembled in an almost infinite number of ways (even within the constraints of crystal symmetry), these recognition mechanisms are extraordinarily selective, since most crystallites in every bulk sample display the same structural arrangement. This situation was recognized by Dunitz (1991) who succinctly described the crystal as the '*supramolecule per excellence*'. Indeed, each crystal represents the culmination of highly specific, reliable and reproducible molecular recognition. Consequently, each crystal structure contains important information about the way in which intermolecular forces compete and collaborate and eventually create an energetically balanced system. Therefore, it seems a shame to resort to rather crude phrases like 'packing forces' (which appear far too often in the literature) when attempting to rationalize and describe new structures. Instead, if we try to take a little bit more care in the analysis of structures, packing motifs and differences in molecular conformation, our crystals may release their inherent information to us in a more digestible and understandable format.

Nowacki (1942) examined space-group preference of *ca* 3000 structures and noticed that almost every other organic compound could be found in one of three space groups, $P2_1/c$, $P2_1$ and $P2_12_12_1$. He related this skewed distribution to the presence of specific symmetry elements within these space groups which, in turn, optimized electrostatic interactions between neighbouring molecules. At the same time, Kitaigorodsky (1961, 1973) began to study crystal systematics and the vast body of his work has arguably made him one of the key figures in developing a better understanding of crystal packing and structure analysis of organic compounds. His principles of close packing provided much needed organization of a rapidly growing pool of structural information and they neatly summarize the structural consequences of the balance between non-covalent forces within a crystalline lattice. Kitaigorodsky pioneered the notion that molecules strive to pack with maximum density (thus minimizing the free, 'empty', volume). In the course of this work, Kitaigorodsky also asked decisive questions about *e.g.* lattice dynamics, static crystals, imperfect crystals and phase transformations, and his contributions also gave inspiration and momentum to the development of molecular mechanics and force-field calculations.

Other notable contributions to the interpretation of observed intermolecular bond distances include Sutor's (1962, 1963) contention that attractive C—H···O hydrogen-bond interactions could play a role in determining extended crystal structures. This notion was initially met with considerable skepticism (Donohue, 1968), but was later completely vindicated using neutron diffraction data (Taylor & Kennard, 1982). Hassel & Romming (1967) made incisive observations about distances and preferential geometries for oxygen···halogen interactions in acyl halides. The question of how we can rationalize and interpret these, and other, unexpectedly short intermolecular distances is still hotly debated and both experimental and theoretical data have been furnished in order to shed more light on these arguments.

Systematic analyses of structural data continue to provide invaluable information about packing preferences, space-group bias and conformational partiality, and these studies have become even more powerful thanks to ongoing improvements and developments of the Cambridge Structural Database (Allen, Kennard & Taylor, 1983). Today, it makes perfect sense to expect that every structural paper is accompanied by a comparative study of related structures (if available), in order to place the characteristics of a new crystal structure in the proper context. In this way, unusual intra- or intermolecular features can be detected readily and the 'unexpected' can often stimulate new ideas or reinterpretations of 'well known' behaviour.

Consequently, crystal engineering is not just about finding quick routes to new materials with improved thermal stabilities, shorter response times or larger nonlinear optical coefficients. Equally important, and equally valid, is the task of searching for a better understanding of how fundamental laws of physics manifest themselves in ordered, three-dimensional, crystalline materials.

2. Strategies

2.1. *Looking for that molecular 'glue'*

Synthetic chemistry, organic as well as inorganic, is today at a highly advanced stage and the nature of the covalent bond, the primary tool in intramolecular synthesis, is well established. Supramolecular synthesis,

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 2 of 18

on the other hand, does not have the benefit of a lengthy history. Many non-covalent forces present in a solid are still ill-defined, poorly understood and difficult both to calculate and to measure. Quite often then we have to learn something about these forces in an indirect manner through an examination of crystal packing. Such observations may allow us to gain more insight into the relative strengths, selectivities and directionalities of hydrogen bonds, hydrophobic–hydrophilic interactions, halogen–halogen contacts, dispersive forces and the whole gamut of interactions often lumped together under the heading 'van der Waals forces'.

The hydrogen bond, primarily electrostatic in nature, has arguably been quoted most often as the architect in design strategies in crystal engineering. However, it can be misleading to analyse the overall structure of a material only in terms of hydrogen-bond geometries and donor/acceptor ratios. Competition, cooperation and balance between different intermolecular forces must all be considered, which makes this such a challenging field.

The presence and influence of hydrogen bonds in molecular and ionic solids have been catalogued in detail, and correlations between bond lengths and angles, and geometric variations as a function of donor/acceptor strengths have been presented for series of functional groups (Taylor & Kennard, 1983, 1984; Taylor, Kennard & Versichel, 1983; Jeffrey & Saenger, 1991). For some time, a hydrogen bond, D—H···A, was only considered possible (or important) if it involved a highly electronegative acceptor atom (A = O, N, F) in combination with a —NH*R* or —OH donor moiety. However, convincing evidence has been presented which indicates that attractive hydrogen-bond interactions can involve a wide variety of acceptors (A = S, Se, Cl, Br, I, π) and donor moieties (—CH, —SH). Olovsson and co-workers examined structures of simple organic and inorganic compounds over several decades (Kvick & Olovsson, 1968) and they were among the first to introduce the notion of a C—H···Cl interaction in 2-pyridone 6-chloro-2-hydroxypyridine (1/1) (Almlöf, Kvick & Olovsson, 1971). In a recent overview of some more exotic (but probably very common) hydrogen-bond interactions, Brammer, Zhao, Ladipo & Braddock-Wilking (1995) suggested some guidelines for characterizing three-centre, four-electron X—H···M interactions. For example, the bridging hydrogen is reasonably acidic and the metal involved is electron rich, typically with filled d orbitals. Furthermore, the X—H···M angle is usually close to linear and 18-electron complexes are also able to form these interactions. The X—H···M interaction can be identified experimentally through a shift in the ^{1}H NMR signal of the bridging H atom. There have also been many descriptions of three-centre, two-electron, agostic interactions X—H···M (where X = B, C, Si, P, S, Ge, Sn), which may be thought of as hydrogen bonds. These compounds are sometimes referred to as σ-bond complexes (Crabtree, 1993).

In addition, several theoretical examinations of more 'unusual' hydrogen-bond interactions have been presented. In a comparison of A···HF complexes (where A = S, O), it was found that a sulfur base is weaker and prone to adopt a more angular approach to the HF donor (Platts, Howard & Bracke, 1996). The observed geometries can be rationalized on the grounds of multipoles. The S···H bond, which is stabilized primarily by charge(H)–quadrupole (S) interactions, favours an angle of 90° (S···H—F), whereas the O···H monopole–monopole prefers a linear geometry.

Other intermolecular forces that have been proposed and debated include unexpectedly short halogen···halogen contacts, which may be interpreted as attractive in nature (Pedireddi, Reddy, Goud, Craig, Rae & Desiraju, 1994) or simply as a function of inherently anisotropic atoms (Price, Stone, Lucas, Rowland & Thornley, 1994). Recently, I···O_2N—*R* contacts (Desiraju, Pedireddi, Sarma & Zacharias, 1993) and cyano···halogen interactions (Reddy, Panneerselvam, Pilati & Desiraju, 1993; Desiraju & Harlow, 1989) have all been identified as influencing spatial orientation of substituted aromatic solids.

Even though electrostatic interactions are less pronounced in molecular solids, asymmetric molecules have non-spherical charge distributions which amplify the Coulombic component of the overall lattice energy of the solid. Higher-order moments, *e.g.* dipoles, quadrupoles *etc.*, also contribute *via* pairwise multipole interactions (which are highly directional), although these interaction energies decay rapidly with distance. Finally, since molecules and ions are fixed with respect to each other in a crystalline solid, some modification of charge distribution will take place on each molecule due to the influence of the charge on the nearest neighbours. The resulting attractions that may occur, inductive effects, are also short-range and directional, and are strongly dependent upon the polarizability of the molecule.

Any strategy for effective supramolecular synthesis requires some means for connecting neighbouring molecules into predictable arrangements. Consequently, we need to identify non-covalent connectors that are selective enough to be reliable and strong enough to be transferable between different systems. In short, we need to know how specific functional groups or moieties are going to interact given a choice of potential 'partners'. Much of the necessary ground work was carried out by groups at the Weizmann Institute and the thorough and systematic approach to the analyses of packing preference of classes of organic molecules presented by Leiserowitz and co-workers set important standards for how structural information should be classified and interpreted. The results obtained for carboxylic acids (Leiserowitz, 1976), substituted amides (Leiserowitz & Tuval, 1978) and other functional molecules have inspired many strategies in contemporary supramolecular synthesis.

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 3 of 18

2.2. *Cocrystals*

Some features of the solid state sometimes hinder our investigations of the influence of intermolecular forces upon the conformational and structural behaviour of molecular building blocks. In solution, interactions between a molecule and its surroundings can be investigated simply by varying the solvent. *Via* such systems we can study specific solvent–solute interactions, competitions and recognition processes in a systematic fashion. However, the solid phase of a particular compound is often uniquely defined (although polymorphism does expand the range of available solid phases to some extent) and, therefore, we are forced to rationalize the influence of non-covalent interactions on the packing and geometry of a specific molecule based upon one single-crystal structure determination, which is clearly not an ideal situation. One route towards a larger sample is *via* structural studies of closely related molecules, but the effects of intermolecular forces are often very subtle and even a slight chemical modification can have a profound impact upon structure, which makes it difficult to trace specific structural consequences to specific chemical moieties. Another route to developing a large number of potential test cases is provided by cocrystallization techniques. A cocrystal can be defined as a crystalline material that consists of different molecular (and electrically neutral) species held together by non-covalent forces.

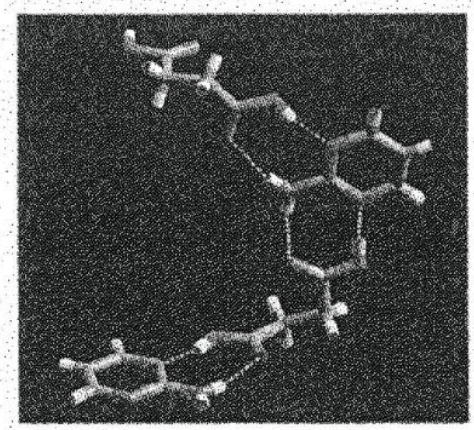


Fig. 1. The complementarity of hydrogen bonds in the cocrystal of 2-aminopyrimidine–succinic acid (1/2) (Etter & Adsmond, 1990).

Cocrystals are not necessarily easy to prepare since such a heteromeric system will only form if the non-covalent forces between two (or more) molecules are stronger than those between the molecules in the corresponding homomeric crystals. In general, it seems to be thermodynamically favourable to assemble similar molecules (pure *A* or pure *B*) in a 3-D solid compared with the corresponding process of packing dissimilar molecules into the same solid (*AB*). Cocrystals can be prepared either *via* evaporation of a heteromeric solution or by grinding the two components together (Etter & Adsmond, 1990; Pedireddi, Jones, Chorlton & Docherty, 1996). In the first case, the two components must have similar solubilities (otherwise the least soluble component will precipitate out exclusively), but this in itself is not a guarantee for success. It may be helpful to use molecules which can adopt alternative packing patterns whilst still satisfying the demands of the hydrogen-bond donors/acceptors that are present on the two (or more) components. Another important consideration when attempting to prepare cocrystals is to choose a compound which is already known to be polymorphic. Clearly, if a molecular compound exists in several polymorphs, it has demonstrated a structural flexibility and it is not as energetically locked into a single packing mode. Consequently, the chances of bringing such a molecule into a different packing arrangement in coexistence with another molecule is greatly enhanced (Aakeröy & Nieuwenhuyzen, 1997).

The use of cocrystals for studying packing patterns, hydrogen-bond motifs and intermolecular forces was

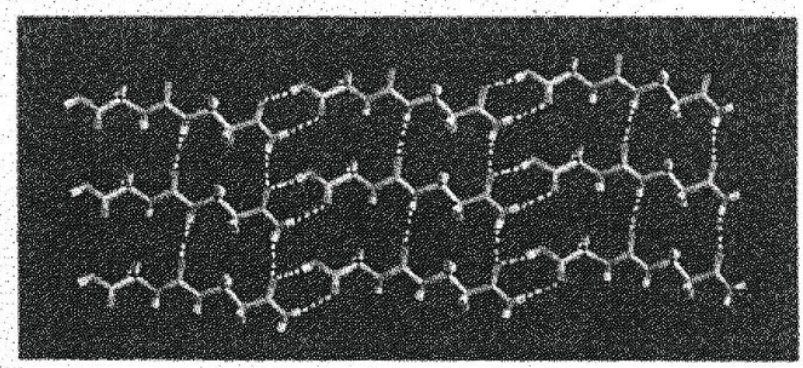


Fig. 2. A 2-D sheet in the crystal structure of *N*-(carboxymethyl)-*N*-(2-carboxyethyl)urea (Chang, West, Fowler & Lauher, 1993).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 4 of 18

brought to the forefront by Etter and co-workers (Etter & Baures, 1988; Etter, 1991; Etter & Adsmond, 1990). One high-impact manuscript describes the use of 2-aminopyrimidine as a means of probing hydrogen-bond preferences of carboxylic acids (Fig. 1). The affinity between carboxylic acids and the 2-aminopyrimidine moiety has since been employed in several design strategies. Structural studies of cocrystals have also served to underline how the competition and balance between intermolecular forces can be examined in an unbiased way (Ung, Bishop, Craig, Dance & Scudder, 1994; Smith, Gentner, Lynch, Byriel & Kennard, 1995).

Another lasting contribution by Etter and co-workers has been the construction of a language, based upon graph theory, for describing and analysing hydrogen-bond networks in three-dimensional solids (Etter, MacDonald & Bernstein, 1990; Bernstein, Davis, Shimoni & Chang, 1995). According to this methodology, any hydrogen-bond interaction can be classified into one of four groups: discrete dimers, chains, rings or intramolecular hydrogen bonds. A specific motif is then described in terms of the number of donors and acceptors that participate and the degree of the motif is determined by the number of unique hydrogen bonds that are present. With the aid of graph sets, it is possible to analyse even complex structures in a systematic and consistent manner, and this methodology (nomenclature) has been applied to hundreds of hydrogen-bonded structures over the last 5 years.

3. Form

3.1. *Molecular solids*

Molecular solids have been the most popular targets for crystal engineering, both in terms of structural analysis of existing data, as well as in the synthesis and characterization of new compounds. The relevant molecular building blocks have been 'glued' together with a variety of intermolecular forces and conventional hydrogen bonding is by no means the only interaction that will provide the desired structural outcome. Nevertheless, mutually complementary hydrogen-bonding sites have been employed in many elegant routes to low-dimensional motifs. Fowler, Lauher and co-workers (Zhao, Chang, Fowler & Lauher, 1990; Chang, West, Fowler & Lauher, 1993) utilized carboxylic, amide and urea functionalities in the preparation of anisotropic 2-D motifs (Fig. 2). The design strategies for these compounds are uncomplicated (thus appealing!) and make good use of the expected packing patterns for each individual functionality.

A combination of interactions can also be employed in a directed manner, as demonstrated in the 2-D layers of substituted alkoxy-1,4-benzoquinones (Keegstra, van der Mieden, Zwikker, Jenneskens, Schouten, Kooijman, Veldman & Spek, 1996). Neighbouring molecules are connected *via* C—H···O=C interactions and aligned through the hydrophobic ordering of alkoxy chains.

Studies of packing motifs in acyclic sugar amphiphiles (which may be used as simple structural models for biological membranes) identified commonly occurring homodromic rings generated by O—H···O hydrogen bonds (André, Luger, Fuhrhop & Rosengarten, 1993).

A monumental article by Ermer & Eling (1994) describes the hydrogen-bond complementarity of hydroxy (two acceptors–one donor) and amino (one acceptor–two donors) groups, and proceeds to illustrate how alcohols and primary amines can be combined in 1:1 cocrystals whilst forming predictable structural motifs, Fig. 3.

Hamilton and co-workers have shown that substituted bis(amidopyridines) can generate 2-D hydrogen-bonded layers (Garcia-Tellado, Geib, Goswami & Hamilton, 1991) and self-assembly of hydrogen-bonded helices is also possible with dicarboxylic acids and derivatives of bis-(2-amino-6-methylpyridine) (Geib, Vicent, Fan & Hamilton, 1993), Fig. 4. Stoddart and co-workers have built interwoven supramolecular cages (Ashton, Collins, Fyfe, Glink, Menzer, Stoddart & Williams, 1997), assembled through hydrogen bonds and π···π stacking.

Both Lehn (Lehn, Mascal, DeCian & Fischer, 1990), Fig. 5, and Whitesides (Zerkowski, MacDonald & Whitesides, 1994; Zerkowski, MacDonald, Seto, Wierda & Whitesides, 1994), Fig. 6, have employed combinations of triaminopyrimidine derivatives and barbituric acid in the design of molecular 'tapes' held together by selective hydrogen-bond interactions. Substituted 2-benzimidazolones have also been used in the preparation of infinite aggregates (Schwiebert, Chin,

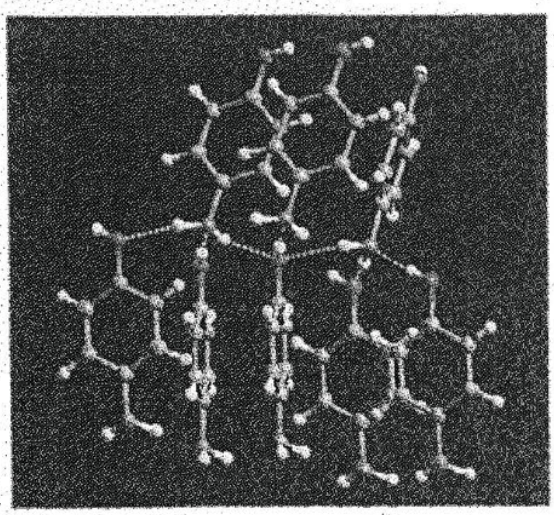


Fig. 3. The complementary of —NH$_2$ and —OH moieties create tetrahedral coordination centres in 4-aminophenol (Ermer & Eling, 1994).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 5 of 18

MacDonald & Whitesides, 1996). Many other connectors have been used in the assembly of low-dimensional motifs, e.g. 2-pyridones (Ducharme & Wuest, 1988), C—H···O/O—H···N pairwise interactions (Pedireddi, Jones, Chorlton & Docherty, 1996) and urea/quinone (Ge, Lilienthal & Smith, 1996), and the examples given here represent but a small portion of existing approaches to the design of molecular solids.

The preponderance of strategies for supramolecular synthesis prompted Desiraju (1995*a*,*b*) to introduce the term 'supramolecular synthons', defined as

> ...structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions.

Knowledge about supramolecular synthons is clearly as important to crystal engineering as is an understanding of reaction mechanisms and reagents in conventional covalent synthesis.

Although much progress has been made in the synthesis of specific structural features in molecular solids, detailed control over the assembly of low-dimensional motifs (chains, ladders *etc.*) remains an elusive goal and further work is required in order to increase the choice of reliable supramolecular synthons.

3.2. *Ionic organic compounds*

When looking for materials with specific physical properties, there are sometimes good reasons for moving from molecular to ionic solids. Typically, solubilities are different, and thermal and mechanical properties may also differ significantly, and depending upon the potential application, ionic compounds can provide advantages over molecular analogues. There may also be strategic reasons for working with materials containing two components, a cation and an anion. The design of a single molecule, capable of controlling the assembly selectively and specifically in three dimensions simultaneously, may require ingenious and complex synthetic programmes. However, in an ionic material, one of the ions can be used for creating a 2-D architecture and the final step, the link to 3-D, can be provided by a suitable counterion.

In recent years, several examples of engineering of ionic organic and organic–inorganic compounds with specific packing motifs have appeared. Most of these rely on hydrogen bonding as the active intermolecular tool and, furthermore, the majority of such structures are built around anionic aggregates. Since the hydrogen bond is primarily electrostatic in nature, the strength of such interactions involving charged species is enhanced and, as a result, the hydrogen bond becomes a powerful tool for linking ions together in a predictable manner.

Russel, Etter & Ward (1994*a*,*b*) utilized the complementarity of hydrogen-bond sites on guanidinium cations and substituted sulfonate anions in the preparation of materials containing infinite hydrogen-bonded sheets, Fig. 7. The precise topology of these motifs can be modified through appropriate substitution of the anion.

In our group we have developed predictable hydrogen-bonded architectures generated by anionic species. We have adopted a strategy of taking one step (one degree of freedom) at a time, thereby simplifying the synthetic component. The CSD is as always an invaluable starting point when looking for inspiration and existing information shows that carboxylic acids tend to form discrete dimers (zero-dimensional elements) in the solid state.

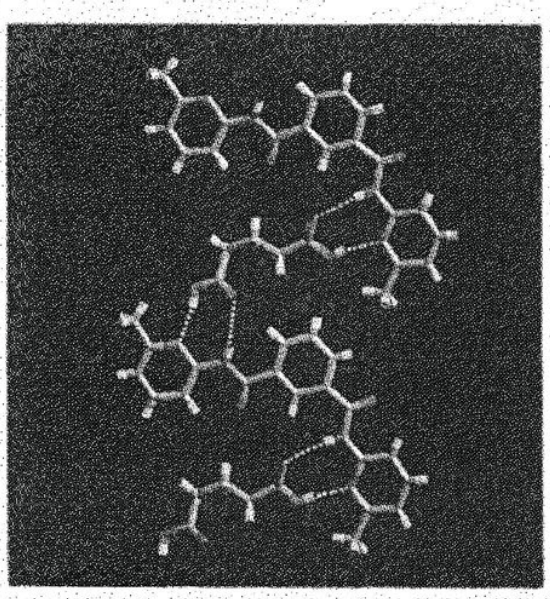


Fig. 4. An infinite spiral in 1,3-bis{(6-methylpyrid-2-yl)amino}carbonyl)-benzene glutaric acid (1/1) (Geib, Vicent, Fan & Hamilton, 1993).

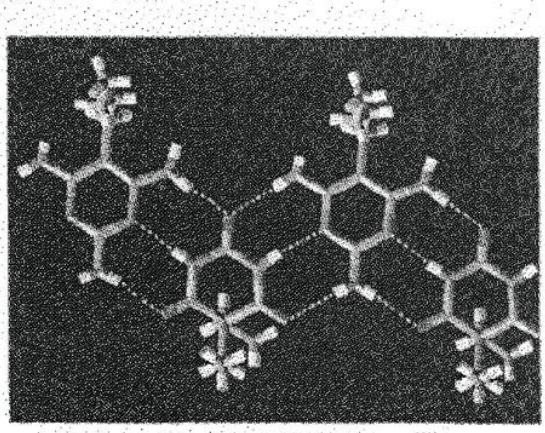


Fig. 5. An infinite hydrogen-bonded ribbon in 5-*tert*-butyl-2,4,6-triaminopyrimidine diethylbarbituric acid (Lehn, Mascal, DeCian & Fischer, 1991).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 6 of 18

Similarly, dicarboxylic acids are known to form infinite hydrogen-bonded chains (1-D elements) *via* $R_2^2(8)$ motifs, almost irrespective of the overall geometry of the molecule. Moving from molecular to ionic motifs simply requires deprotonation of the acid which creates an asymmetric anion with a carboxylate 'tail' (with strong hydrogen-bond acceptors) and a carboxylic 'head', acting as a powerful hydrogen-bond donor. Typically, monoanions of dicarboxylic acids have a propensity to form infinite chains through a very short and near-linear O—H···O hydrogen bond between the 'head' and 'tail' of adjacent anions. Two O—H···O interactions between neutral species are thereby replaced with one O—H···O interaction between anions, but the overall structural outcome is unchanged, a 1-D motif. An additional bonus is given by the fact that this chain is inherently polar, which may have useful implications for the physical properties of the resulting material. The next step involves combining 1-D elements into 2-D features in a reliable manner. In these anions there are several hydrogen-bond acceptors available, so by introducing a donor group on the anion, preferably positioned so that it can provide a link between neighbouring chains, it should be possible to create infinite anionic layers. With

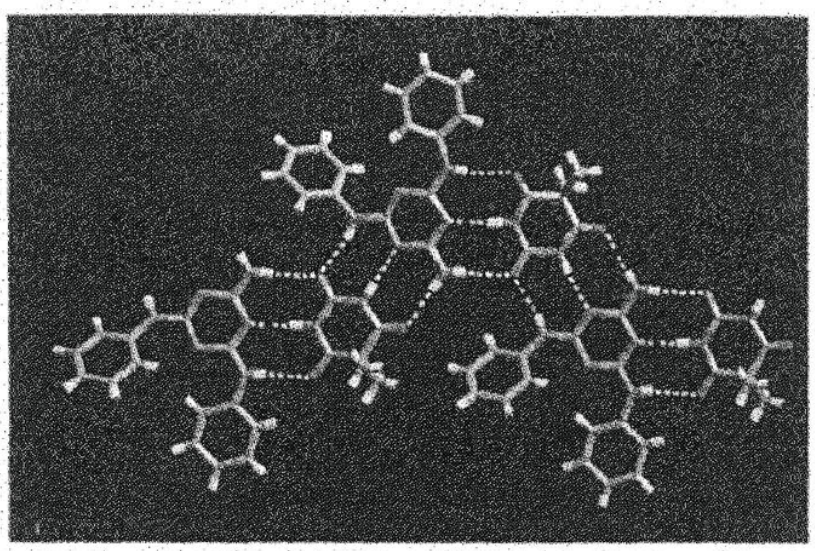


Fig. 6. A hydrogen-bonded tape in 5,5-dimethylbarbituric acid *N,N*-diphenylmelamine (Zerkowski, MacDonald & Whitesides, 1994).

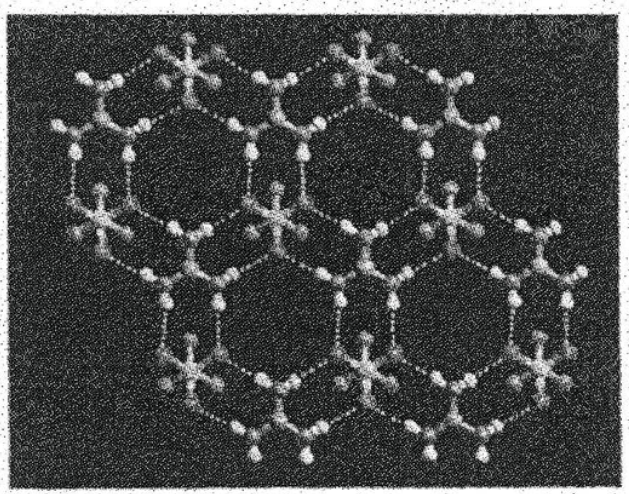


Fig. 7. An infinite hydrogen-bonded sheet in guanidinium trifluoromethanesulfonate (Russel, Etter & Ward, 1994*a*).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 7 of 18

this task in mind, we characterized a number of structures of hydrogen tartrate (Aakeröy, Hitchcock & Seddon, 1992; Aakeröy & Hitchcock, 1993) and hydrogen malate salts (Aakeröy & Nieuwenhuyzen, 1994, 1996). These data, in combination with existing information from the CSD, show that the expected anionic chains are almost invariably formed. Secondly, the additional —OH groups (two in the case of tartaric acid, one in the case of malic acid) generate robust O—H···O hydrogen bonds between neighbouring chains, which give rise to the desired 2-D anionic network, Fig. 8. Although the 2-D arrangement of anions is reliable, two different network 'types' are possible. If adjacent chains are aligned in a parallel fashion (giving rise to a highly polar structure), the layer tends to be planar, or near-planar. If, on the other hand, neighbouring chains are aligned in an antiparallel fashion, the anionic layer is normally buckled, Fig. 9. Obviously, the existence of flat vs buckled anionic layers, as well as the degree of distortion away from a planar geometry, is governed by the structural influence of the cation.

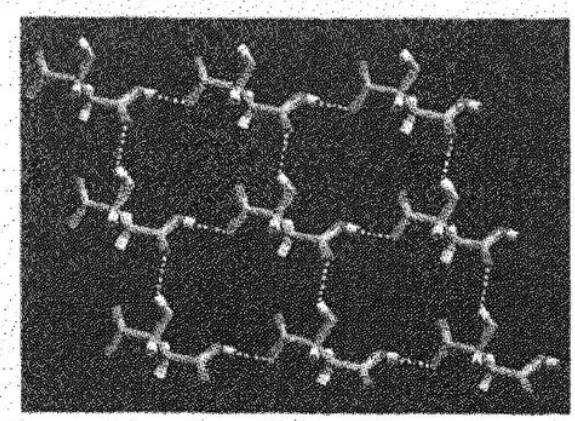


Fig. 8. A layer of anions in 3-chlorobenzylammonium hydrogen-L-malate. The horizontal chains are aligned in a parallel manner (Aakeröy & Nieuwenhuyzen, 1996).

At this stage we have established that hydroxydicarboxylic acids (exemplified by tartaric and malic acid) may be used as reliable building blocks of infinite 2-D motifs. The advantage of employing ions as building blocks now becomes apparent since the final step in our design strategy, moving from 2-D to 3-D, can be achieved through a suitable choice of cation. The cation can act as a bridge which actively associates with neighbouring anionic layers through directional intermolecular interactions. Examples of structures where the cation forms a bridge between anionic layers are imidazolium hydrogen-L-tartrate, Fig. 10, and 3-hydroxy-6-methylpyridinium hydrogen-L-malate, Fig. 11. In the first case the links are generated by two N—H···O interactions and in the second case through one N—H···O and one O—H···O hydrogen bond. These particular cations were chosen since they contain hydrogen-bond donors at opposite ends of a rigid spacer which were expected to generate crosslinks between neighbouring anionic layers. Alternatively, if the cations only have one hydrogen-bond donor (or several donors in close proximity) they would be expected to attach themselves to one side of the layer and simply act as spacers, as a means of varying the interplanar distance between the infinite anionic layers, Fig. 12.

The use of similar building blocks in crystal engineering (notably in the design of non-linear optical materials) has received widespread attention and many groups are making important contributions to our

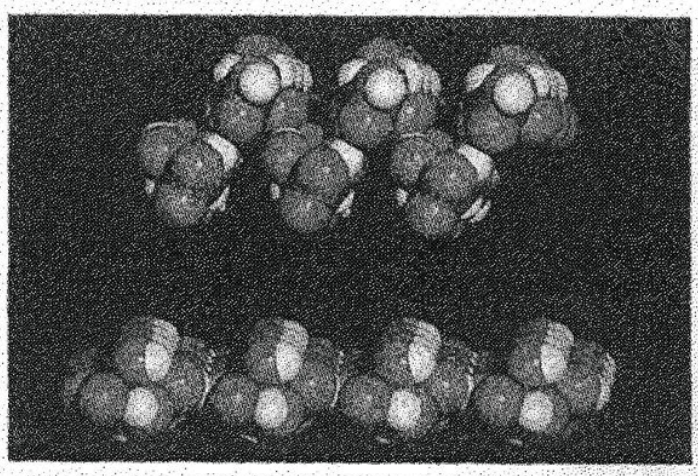


Fig. 9. Edge-on view of the two 'types' of anionic layers in hydrogen malate and hydrogen tartrate structures. Above, a buckled layer (antiparallel chains) and below, a flat layer (parallel chains) (Aakeröy & Nieuwenhuyzen, unpublished results).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 8 of 18

understanding of exercising precise control over interplanar distances, layer topology and other structural features that eventually determine the physical properties of these materials (Zyss, Pecaut, Levy & Masse, 1993; Watanabe, Noritake, Hirose, Okada & Kurauchi, 1993; Kadirvelraj, Umarji, Robinson, Bhattacharaya & Guru Row, 1996; Bhattacharaya, Dastidar & Guru Row, 1994; Lefur, Bagieu-Beucher, Masse, Nicoud & Levy, 1996).

Although these structures contain several predictable structural features, they do not represent materials over which we can claim complete control. For example, we do not yet know how a cation can induce parallel or antiparallel alignment of anionic chains. Furthermore, we cannot control the orientation of one anionic layer with respect to another and this is clearly of great importance since parallel sheets would give rise to highly polar and strongly anisotropic materials.

An important aspect of crystal engineering pertains to the uncovering of practical guidelines for estimating the structural outcome when combining different functional groups. In order to achieve this, it is helpful to study a simple system that can give rise to a small number of well defined structural motifs. With this in mind, we synthesized and characterized several organic salts based upon the oxamate anion, $[H_2NCOCOO]^-$ (Aakeröy, Hughes & Nieuwenhuyzen, 1996). This particular anion was selected since it possesses complementary hydrogen-bond donors and acceptors that can lead to three dimeric motifs. *Ab initio* calculations showed very small energetic differences between these 'postulated' patterns, indicating that oxamate anions can aggregate in at least three different ways which, in turn, can give rise to distinctive anionic extended motifs. In fact, all three dimeric features have appeared in crystalline oxamates. Furthermore, the anions invariably give rise to either 1-D motifs, Fig. 13, or infinite 2-D layers, Fig. 14. As discussed previously, the detailed arrangement of anions and cations is determined by specific cation–anion interactions. By grouping cations together depending upon what type of anionic motif they are associated with, we can identify some common geometric characteristics which lead us to propose simple guidelines for predicting oxamate structures. Primary ammonium ions with three hydrogen-bond donors positioned in close proximity to each other (the $[-NH_3]^+$ moiety) will form hydrogen bonds to at least two different anions and, in doing so, bring anions close together (*via* N—H···O interactions), which in turn forces the anions into a layered arrangement. On the other hand, secondary or tertiary ammonium ions can only bring together a smaller number of anions which may be insufficient to cause the formation of an infinite 2-D sheet. In these cases, *e.g.* imidazolium oxamate, the anions instead create 1-D motifs. In addition, cation size may also be important, since a small cation will inevitably bring neighbouring anions within close proximity of each other and this will also encourage anionic layer formation. This is exemplified by the crystal structure of potassium oxamate hydrate (Aakeröy, Hughes & Nieuwenhuyzen, 1996). Conversely, a bulky cation will expand the size of the lattice and will therefore increase the distance between anions, which should result in the formation of 1-D anionic motifs.

The hydrogen bond is arguably of sufficient strength to link neighbouring ions together into infinite architectures, even in the presence of different cations and in competition with other non-covalent interactions, and it is likely that there will be many more forays into the design of desired structural functionalities in organic salts.

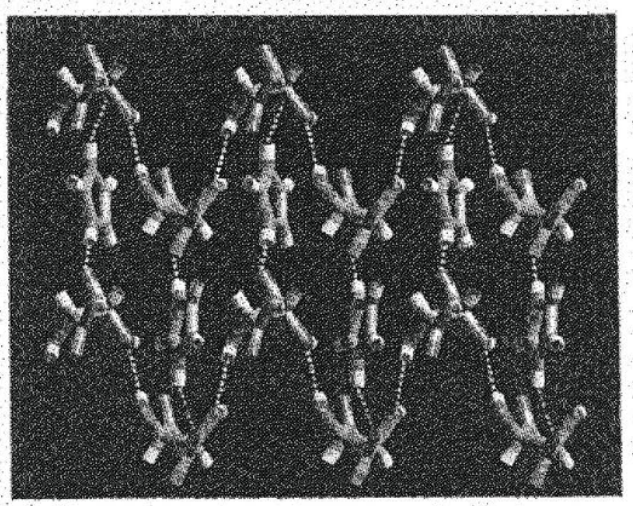


Fig. 10. Edge-on view of buckled anionic layers held together by cations in imidazolium hydrogen-L-tartrate (Aakeröy & Hitchcock, 1993).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 9 of 18

3.3. *Metal complexes*

Many approaches to the programmed design of metal-containing compounds with predictable dimensions have recently been presented. For example, Robson and Hoskins outlined the possibilities of creating infinite 2-D and 3-D metal-containing frameworks based around metal-4,4′-bipyridine derivatives (Robson, Abrahams, Batten, Gable, Hoskins & Liu, 1992). Interpenetration of such 2-D sheets can give rise to 3-D solids with channels and cavities of specific dimensions. Zaworotko and co-workers have employed similar building blocks in the design of porous 'coordination-polymers' with diamondoid structures (Copp, Subramanian & Zaworotko, 1992; Subramanian & Zaworotko, 1995; Robinson & Zaworotko, 1995; Zaworotko, 1994), Fig. 15.

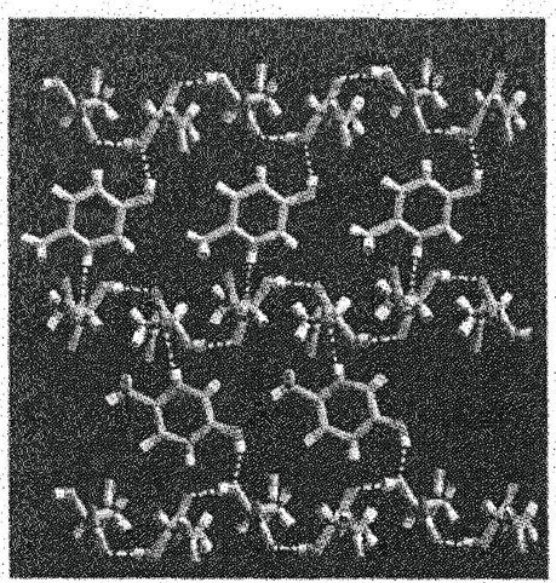


Fig. 11. Edge-on view of sheets of cations and anions held together by hydrogen bonds in 3-hydroxy-6-methylpyridinium hydrogen-L-malate (Aakeröy & Nieuwenhuyzen, 1994).

Lehn and co-workers have generated some extraordinary structures covering silver(I) helicates (Garrett, Koert, Lehn, Rigault, Meyer & Fischer, 1990), circular double helicates (Hasenknopf, Lehn, Kneisel, Baum & Fenske, 1996), supramolecular macrocycles (Drain, Russel & Lehn, 1996) and zinc(II) porphyrins assembled into cages (Drain, Fischer, Nolen & Lehn, 1993). Many of these motifs are built with a combination of well established coordination chemistry (coordination number, geometry *etc.*) and site-specific and self-complementary hydrogen-bonds. Mingos and co-workers (Burrows, Mingos, White & Williams, 1996; Chowdhry, Mingos, White & Williams, 1996) have utilized intermolecular connectors, *e.g.* thiourea//carboxylate, diaminopyridine//uracil *etc.*, as a way of linking neighbouring metal complexes into extended 'tapes' and sheets, Fig. 16. On the one hand, the presence of a metal complex provides access to properties which cannot be obtained with molecular solids alone, but at the same time, the organic connectors provide the basis for new pre-organized structural arrangements. This strategy can be applied to both organometallic and coordination compounds.

The hydrogen-bonding capability of polycarboxylic acids has been used extensively in the design of preordered cationic metal complexes. For example, terephthalic acid was used by Kimura, Ikeda, Shionoya & Shiro (1995) as a link between substituted zinc(II)

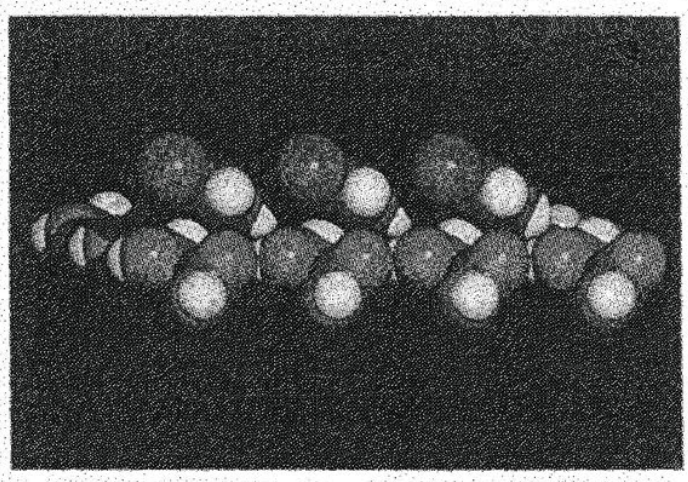


Fig. 12. Cations, acting as spacers, attached to one side of the flat anionic layer in 4-chlorobenzylammonium hydrogen-L-malate (Aakeröy & Nieuwenhuyzen, 1996).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 10 of 18

complexes of cyclene. Both ends of the dianion coordinate to a zinc ion in a neighbouring complex. James, Verspui, Spek & van Koten (1995) employed CCH···Cl—Pt hydrogen bonds to create infinite chains in an organoplatinum compound. Munakata and co-workers prepared hydrogen-bonded copper(I) complexes with large channels occupied by cations, using the well known dimeric 2-pyridone synthon (Munakata, Wu, Yamamoto, Kuroda-Sowa & Maekawa, 1996).

Dance and co-workers have made extensive use of the 'phenyl factor' (interactions between adjacent aromatic groups) in inorganic supramolecular chemistry.

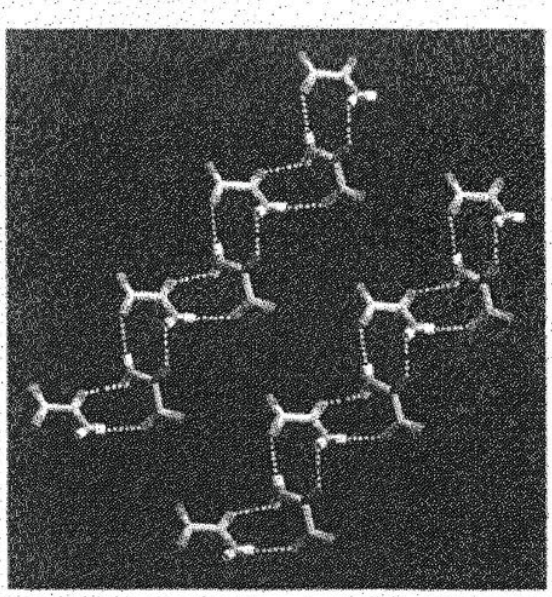


Fig. 13. Adjacent ribbons of anions in piperidinium oxamate (Aakeröy, Hughes & Nieuwenhuyzen, 1996).

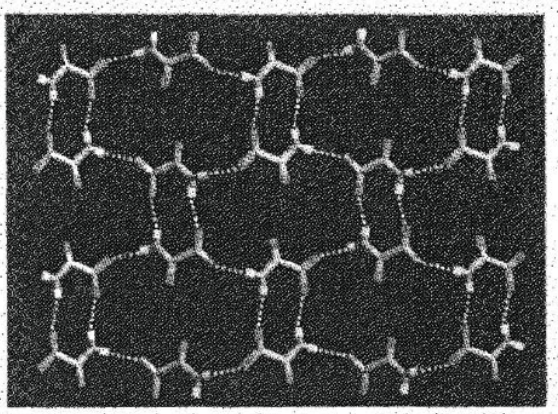


Fig. 14. The infinite layer of anions in 4-chlorobenzylammonium oxamate (Aakeröy, Hughes & Nieuwenhuyzen, 1996).

Calculations of the non-bonded Ph···Ph interaction energies in a series of $[M(SPh)_4]$ derivatives show that such interactions make a significant contribution to the overall lattice energy of the solid and thus can play a vital part in the assembly and orientation of these complexes (Dance, 1995). This has been illustrated by the commonly occurring 'sextuple embrace' involving three phenyl rings on neighbouring $[Ph_4P]^+$ cations (Banda, Cusick, Scudder, Craig & Dance, 1989). Aryl rings are positioned such that one or two H atoms are pointing towards the π-cloud of an adjacent ring resulting in an edge-to-face interaction. Alternatively, H atoms are positioned over C atoms in the adjacent π-system, leading to offset face-to-face interactions. There are several hundred examples of this motif in crystals containing $[Ph_4P]^+$ cations, which clearly shows the anisotropic, directional and, thus, supramolecular behaviour of this building block.

Braga, Grepioni and co-workers have been at the forefront of developing an organometallic 'branch' of crystal engineering through a combination of synthesis, database analysis and packing-energy calculations (Braga & Grepioni, 1996). Based upon structural data for hexanuclear carbonyl cluster anions, they were able to demonstrate that the relative size of the component ions is a determining factor in the assembly process of the solid (Braga, Grepioni, Milne & Parisini, 1993). Very significantly (but often overlooked) they also showed that the formal charge associated with each ion was very effectively distributed over the ions, thus making cation···cation or anion···anion interactions perfectly acceptable. Braga and co-workers also encapsulated a paramagnetic chromium species within an organic, anionic framework with the aid of CH···O interactions (Braga, Grepioni, Byrne & Wolf, 1995).

There is no reason why this particular branch of crystal engineering will not expand at an exponential rate. Organometallic chemistry has for a long time been preoccupied with molecular structure, but if a fraction of this attention is devoted to intermolecular interactions in organometallic compounds, we will uncover a wealth of information in the next few years. It will also be interesting to examine to what extent the introduction of additional interactions, *e.g.* metal–ligand, Lewis acid–base, will facilitate, or hamper, structure predictions.

3.4. *Polymorphism*

You are working with a seemingly flawless design strategy, every synthon stays intact, the synthesis is straightforward and the product crystallizes into beautiful well shaped crystals. All you need to do is to solve the structure and your approach is instantly validated. Surely, nothing can go wrong at this stage? Well, this may depend upon how far you are prepared to look.

Possible complications may be introduced by the obdurate riddles furnished by polymorphism. Not only

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 11 of 18

must we uncover how to control the delicate balance between a multitude of weak interactions, but once the material appears it may make a mockery of our design and rationalizations by appearing in several guises!

Although polymorphism is a well known phenomenon (be it pervasive or not), it is still difficult to define accurately. Suggested criteria for assessing polymorphs include statistically different unit-cell dimensions, differences in crystal packing or distinctly different physical properties. In addition, several sub-classes have been discussed, ranging from pseudo-polymorphs *via* conformational polymorphs (Bernstein & Hagler, 1978) to disappearing polymorphs (Dunitz & Bernstein, 1995)! Although in some cases these discussions spill over into either faith or semantics, there is no doubt that the question of structural purity is, from a materials perspective, of equal importance to chemical purity. Furthermore, this is not just an esoteric academic topic, which was clearly illustrated in a recent high-profile court case involving one of the best selling drugs world-wide (Leadbeater, 1991). With several billion dollars at stake (which does tend to make people pay attention), we can expect much more interest in this field over the next few years, not just from the pharmaceutical industry.

If we define polymorphism provisionally as different crystalline forms of the same chemical compound (with identical composition!) leading to measurable differences in physical properties, what means do we have for identifying such systems? X-ray crystallography (single-crystal and powder) is often the method of choice, but hot-stage microscopy, spectroscopy or thermochemistry are commonly used for recognizing and characterizing polymorphic forms. As a matter of routine, differences in solubility and crystal morphology should also be noted and reported for different polymorphs since these properties can be of great practical importance, *e.g.* for bioavailability and filterability, respectively. An excellent review by Threlfall (1995) provides an extensive overview of various experimental techniques for studying polymorphs of organic compounds.

The frequency of occurrence of polymorphism is another question which remains largely unanswered and although it is arguably true to say that the more time we spend looking for polymorphs, the more often we will come across the phenomenon, we also need to know where to look. For example, aromatic hydrocarbons rarely exhibit polymorphism which, *prima facia*, may seem counter-intuitive since such compounds are held together by relatively weak forces that are often considered to display much less pronounced directionality and structural specificity. However, this serves to illustrate that weaker non-covalent interactions, *e.g.* C—H$\cdots\pi$ or $\pi\cdots\pi$, working in concert, can display exceptional selectivity.

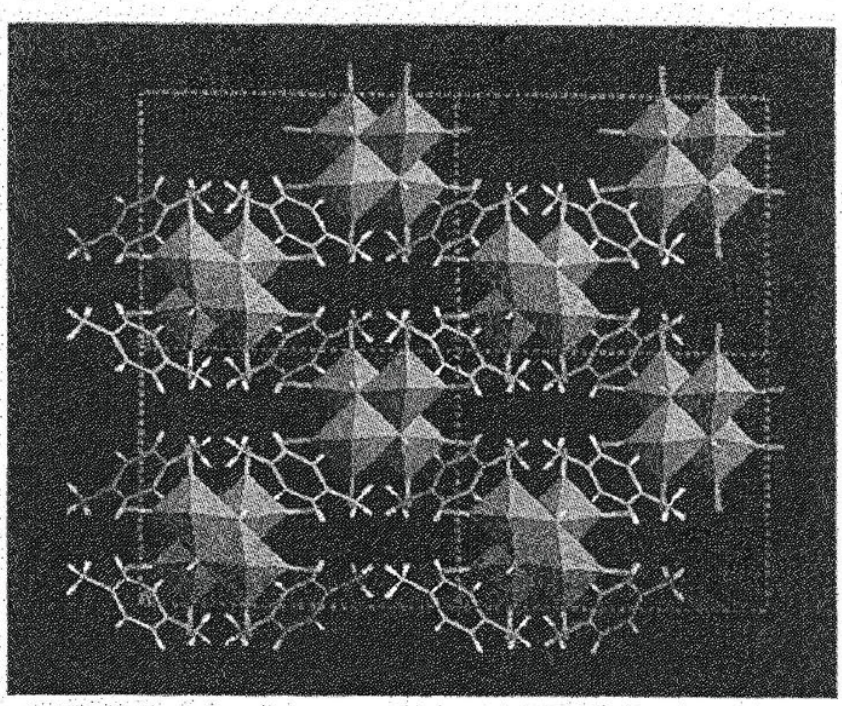


Fig. 15. An example of a diamond structure based upon tetrakis($(\mu_3$-hydroxo)tricarbonylmanganese) 4-xylene clathrate (Copp, Holman, Sangster, Subramanian & Zaworotko, 1995).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 12 of 18

In some polymorphic systems, the dominating synthon (strongest intermolecular interaction) stays intact, but the relative orientation of one motif with respect to another is changed. However, there are also examples of systems where the expected synthon is rejected in favour of an alternative arrangement. For example, one polymorph of 3-hydroxybenzoic acid (3HBA) does contain the commonly occurring hydrogen-bonded dimeric motif, whereas in the second polymorph (3HBA), the dimer is abandoned in favour of a new motif, Figs. 17(*a*) and 17(*b*) (Gridunova, Furmanova, Struchov, Ezhkova, Grigorieva & Chayanov, 1982). This structural pair illustrates that the same compound can exist in both centrosymmetric (3HBA) and non-centrosymmetric structures (3HBA).

Polymorphism brings, at first glance, added complications to crystal engineering and structural chemistry. On the other hand, polymorphic systems provide excellent opportunities to study specific chemical entities in different crystalline environments (Bernstein & Hagler, 1979). By comparing differences in experimentally determined thermodynamic quantities and trends displayed by calculated lattice energies for a series of polymorphs, energy differences between observed molecular conformations can be estimated. Subsequent analyses of the results may highlight the influence of different functional groups on the overall crystalline arrangement of each material and this represents a case where experiment and theory are combined into a powerful probe of intermolecular interactions.

Finally, from a crystal engineering or solid-state chemistry perspective, structural purity is as important as chemical purity. Unfortunately, it is rather rare that a single-crystal X-ray diffraction study is accompanied by a powder diffraction experiment in order to establish that the chosen crystal is, indeed, representative of the bulk material. A single crystal is, after all, just that, one crystal. Furthermore, crystals with the same morphology may have different structures and crystals with different morphology may have the same structure! The structural homogeneity of a crystalline material can be assessed very easily and rapidly: (i) simulate the X-ray powder pattern from the existing single-crystal data, (ii) record the X-ray powder pattern on the bulk sample and (iii) if there is a good match between the simulated and experimental patterns, we can be much more confident that the crystal structure that has been obtained is typical for the bulk material. Of course, this does not preclude the possibility of finding other polymorphic forms if the compound is prepared under different conditions or in a different location (!), but at least we have carried out a more comprehensive analysis of our material. If it is worth spending time on design and crystal engineering, it is probably worth finding out if the material is structurally pure!

4. Function and future

What types of properties do we seek in our new 'designer' materials and what level of predictability can we realistically expect in the near future? The field itself does hold much promise, but what if we are unable to deliver real crystalline materials that are cheaper than current materials or that can perform certain tasks more efficiently, more selectively or with greater speed than existing candidates? Will the whole area be reduced to

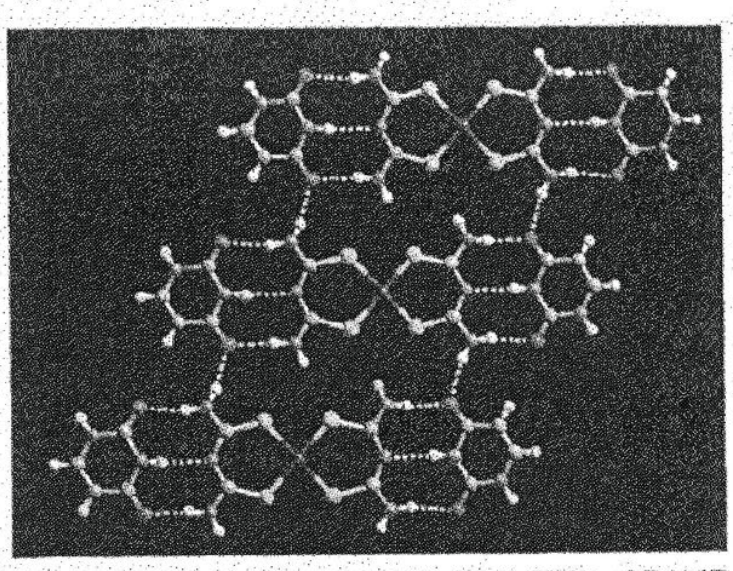


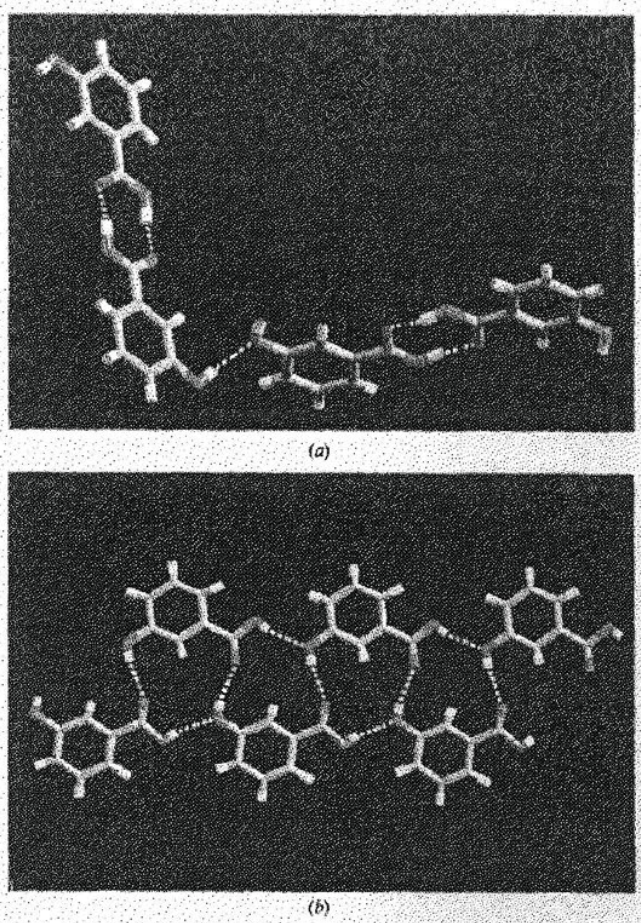
Fig. 16. An infinite Ribbon of nickel complexes, propaged *via* hydrogen bonds in bis(dithiobiuret-*S*,*S*')nickel(II) diuracil dihydrate. Water molecules removed for clarity (Houlton, Mingos & Williams, 1994).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 13 of 18

the design and synthesis of compounds with 'aesthetically pleasing' packing motifs with no regard to functionality and properties?

An outsider could be of the opinion that crystal engineering is only about making yet more 'pretty structures', but it is important to realise that supramolecular synthesis is still very much in its infancy. It is necessary to collect structural information, to search the CSD for recurring packing motifs and to test the reliability and robustness of simple non-covalent interactions. Furthermore, none of this has to be performed on complicated synthetically challenging compounds. On the contrary, a simple system (amenable to small geometric or chemical variations) is likely to furnish more easily extractable information about competition and balance between intermolecular forces. We have certainly become more aware of the importance of looking at the 'chemistry beyond the molecule' (Lehn, 1990) and this will allow us both to identify new synthons and to learn more about exotic weaker intermolecular interactions. However, eventually, we will need to supply materials for applications and practical devices.

Broadly speaking, control over molecular orientation, packing patterns and lattice dimensions would provide us with the ability to improve or fine-tune any physical property determined by structure. On one hand, successful crystal engineering would allow us to understand such 'basic' physical properties as solubility and thermal stability. For example, the observation that *para* isomers almost invariably have higher melting points than *meta* isomers (Gavezzotti, 1995) is still in need of a rational explanation. Other important functions such as second-order optical effects and piezoelectric behaviour are determined by space group, centrosymmetric (of1)–noncentrosymmetric (on) and the relative alignment and



(*a*)

(*b*)

Fig. 17. (*a*) Hydrogen-bonded dimers, linked by O—H···O hydrogen bonds in the centrosymmetric polymorph of 3-hydroxybenzoic acid (Gridunova, Furmanova, Struchov, Ezhkova, Grigorieva & Chayanov, 1982). (*b*) Crystal packing in the non-centrosymmetric polymorph of 3-hydroxybenzoic acid (Gridunova, Furmanova, Struchov, Ezhkova, Grigorieva & Chayanov, 1982).

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 14 of 18

orientation of individual molecules/ions within the solid. Clearly, with control of the spatial arrangement of molecules and ions, we would be in a strong position to make better functional materials.

In the case of non-linear optical materials, the earliest studies were carried out primarily on inorganic materials such as potassium dihydrogenphosphate (KDP) and lithium niobate(V). Although KDP is commonly used for second harmonic generation (SHG) in commercial laser systems, it is not an ideal material since its non-linear response is relatively low. Subsequently, much attention was diverted to the design of organic molecules that, individually, would exhibit enormous non-linear effects. Unfortunately, much less attention was paid to intermolecular interactions and crystal properties and, as a consequence, many carefully designed molecules only became short-lived entries on the most current top-ten list of molecular SHG activity. Today, after a decade of intense interest in supramolecular synthesis, it may be worthwhile to revisit some of those classes of molecules. Our understanding of the structural effects of intermolecular forces and of the way in which we may influence the balance between them has improved considerably and the tools of crystal engineering may bring new enthusiasm to the design of improved SHG-active materials. Furthermore (and against the backdrop of polymorphism), should we throw away our carefully synthesized molecular solid, designed for SHG, simply because, at the first attempt, it crystallizes in a symmetric space group? Probably not.

The ability to control lattice dimensions immediately brings attention to correlations between the shape and size of the molecular scaffolding and the subsequent properties of that material. Even with a chemically 'unreactive' architecture, we can design functional solids. Porous materials (3-D materials) with variable cavity sizes, infinite channels or with specific interplanar separations (for 2-D structures) can be useful in applications concerned with 'separation techniques', 'selectivity', 'inclusion' or 'intercalation', all of which have considerable commercial potential. Do zeolites and clays represent the final summits of sophistication in 3-D and 2-D materials, respectively? There is no obvious reason to believe that they do and consequently there should be room for improvements in terms of both physical properties and chemical reactivity. Although ultimately we want control over the assembly of 3-D solids, there is much to be said for attempting to make low-dimensional solids. A single-crystal containing well defined 2-D molecular motifs is inherently highly anisotropic and will display physical properties that are strongly dependent upon the direction of the incident input or stimulus. The response to an external electromagnetic signal can therefore be modulated, or even cancelled, simply by rotating the crystal with respect to the incident 'probe'. If we can make precise alterations to the interplanar separations in such materials (whilst leaving the fundamental chemistry intact), we have a way of directly correlating lattice dimensions with physical properties. In principle, there is little difference between the attempted assembly of 1-D, 2-D or 3-D motifs. Clearly, the ability to prepare low-dimensional supramolecular assemblies is as important as 3-D crystal engineering, since the practical relevance of many materials is directly derived from their structural anisotropy.

There are other areas where supramolecular synthesis may provide a fresh approach to solving long-standing problems. Colours of organic compounds are commonly thought to be a function of molecular electronic structure alone, but there are examples of organic solids where the colour is determined by crystal packing. This phenomenon, crystallochromy (Klebe, Graser, Hädicke & Berndt, 1989), has been observed in *e.g.* phthalocyanines (Wagner, Loutfy & Hsiao, 1982). A theoretical study of some perylenes (Kazmaier & Hoffmann, 1994) also showed that the bandwidth of the valence and conduction bands is a direct function of the stack angle and, thus, the degree of overlap between adjacent molecules within the stack. The observed colour differences of many perylene pigments must be a function of crystal packing as they have very similar absorption spectra in solution (Klebe, Graser, Hädicke & Berndt, 1989). With this in mind, supramolecular design of new photoconducting materials for xerographic applications is another field with considerable potential.

We may also revisit topochemistry where Schmidt carried out his first experiments in 'crystal engineering'. The fact that crystalline solids are, by definition, ordered solids means that we can utilize these media as a way of imparting stereochemical control over the reaction. For example, in solution, disubstituted penta-1,4-diene-3-ones may undergo photochemically induced isomerization reactions which lead to mixtures of *cis–trans* products. However, in the solid state, where each molecule is locked in place, typically only one product is obtained (Green & Schmidt, 1970). Not only does the solid state impart positional restrictions on molecules, but inherently flexible molecules will also be confined, which may provide control over the stereochemistry of the product.

Another area which may fall into the realm of crystal engineering is the 'responsibility' for providing better insight into the way in which intermolecular recognition processes govern spatial orientation, space-group partiality *etc.* Sometimes it may also be necessary to re-evaluate or re-interpret existing information. Until quite recently it was commonly thought that molecules with large dipole moments align in an antiparallel fashion. Since such a packing arrangement will lead to an overall cancellation of individual contributions to the overall polarity of the solid, this notion may well have had a rather detrimental effect upon synthetic efforts and the search for polar solids. However, Whitesell and co-

NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 15 of 18

workers (Whitesell, Davis, Saunders, Wilson & Feagins, 1991) have demonstrated that there is no correlation between a high dipole moment and a propensity for centrosymmetric space groups, especially if directional intermolecular forces, *e.g.* hydrogen bonds, are present. This is an important statement which could affect existing approaches to the design of new polar solids. These issues will be addressed by scientists concerned with the utilization and understanding of intermolecular forces.

Computational chemistry and molecular simulation will continue to add to our understanding of how to predict unknown structures, polymorphs and physical properties of 'hypothetical' materials. An in-depth overview of computational chemistry in the context of crystal engineering is beyond the scope of this article. Several authors have outlined many of the possibilities and challenges of theoretical supramolecular chemistry (Gavezzotti, 1990; Gavezzotti & Filippini, 1995, 1996; Holden, Du & Ammon, 1993; Hagler & Bernstein, 1978). Gavezzotti (1994) asked the crucial question in a recent review, 'Are crystal structures predictable', and the current answer would have to be 'Sometimes'. Such a reply is unlikely to set the academic world ablaze with excitement, but it is nevertheless a realistic viewpoint (although the answer may also depend upon your definition of the term 'crystal structure'). Despite the complexities of these problems, progress has been made both with dynamic and static methods. Perlstein (1992, 1994) has used a Monte Carlo cooling method in combination with empirical potentials for calculating intermolecular energies. The 3-D structure is built up from substructures (*e.g.* stacks and layers) which are in local energy minima. Karfunkel & Gdanitz (1992) employed simulated annealing to generate collections of low-energy structures by searching the lattice energy hypersurface. Gavezzotti (1991) has calculated interaction energies of clusters of rigid molecules using force-field methods and the clusters are then translated in space or coupled together to give the 3-D crystal structure. Price & Wibley (1997) showed that the observed crystal structures of several heterocycles corresponded to calculated minima in the lattice energy. Particular attention was paid to the electrostatic contributions which were calculated from an *ab-initio*-based distributed multipole model of the charge density.

Considerable advancement has been made in the *a priori* prediction of crystal structures and further progress would be greatly facilitated if existing databases continue to be developed with new search algorithms and statistical tools. More importantly, if the CSD also contained information about enthalpies of fusion, enthalpies of melting, solubilities and thermal stabilities, we would have an immensely powerful research tool that would contain essential data for further statistical and quantum mechanical studies. Obviously, this information is not available for more than a small fraction of all structures in the CSD, but it would still represent a crucial step in the right direction.

Finally, leaving the commercial applications perspective aside, we should also remind ourselves that one of the most important targets for crystal engineering is to provide improved understanding of the very essence and consequences of non-covalent forces. We need to know more about their relative strengths and preferred geometries, we need to pinpoint their physical origin and we need to establish appropriate criteria for recognizing these interactions.

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NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 16 of 18

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NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 17 of 18

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NOVARTIS EXHIBIT 1048
Novartis v. Regents, IPR2023-01346
Page 18 of 18