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Crystal engineering, Where from? Where to?

Dario Braga

Dipartimento di Chimica G. Ciamician, Università di Bologna, Via Selmi 2, 40126 Bologna, Italy. E-mail: dbraga@ciam.unibo.it

It is hard to give a definition that does justice to the breadth of crystal engineering today. But a useful working description might see modern crystal engineering as the bottom-up construction of functional materials from molecular or ionic building blocks. Crystal engineering has its roots in chemistry with important interfaces with physics and biology, as well as applications in materials sciences, the drug industry and nanotechnology. In short, crystal engineering is a rapidly expanding *global* discipline practised by scientists with diverse interests in the modelling, synthesis, evaluation and utilization of crystalline solids.

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When did we make our first "crystal by design"? There was a moment of inspiration during the Italo-Israeli Meeting in 1992.[1] Peggy Etter had shown in her talk that benzene could be used to template the hydrogen bonding of six 1,3-cyclohexanedione molecules into a hexameric "cyclamer".[2a] When, soon after, Fabrizia Grepioni spoke about the packing analogy between solid benzene and bisbenzene chromium $(C_6H_6)_2Cr$ Peggy suggested the possibility of substituting benzene for bisbenzene chromium in the dione cyclamer. The idea was beautifully simple and we did *almost* succeed when we finally tried it. However, since shape is not everything in chemistry, the oxidation of $(C_6H_6)_2Cr$ to $(C_6H_6)_2Cr^+$ had led to something similar to, but not quite the same as, Etter's cyclamer.[2b] Nonetheless, we had learned that crystal design was indeed possible and, with this, joined the rapidly growing community of *crystal makers*.

Various factors drove the emergence of crystal engineering during the 1990s. There was a demand for more practical objectives for basic research, given the restrictions upon funding. Meanwhile, small molecule crystallography was becoming increasingly accessible to non-specialists – so maybe the crystallographers were looking for a new challenge. Technically, point detectors were increasing the speed of data collection by an order of magnitude, while computers were becoming smaller and cheaper, allowing easy manipulation of molecular images on-screen. At the same time, the Cambridge Structural Database[3] was becoming more user-friendly and the storehouse of intermolecular interactions easily available for crystal design.

But the cultural factor in the growth of crystal engineering was perhaps the most important. The supramolecular perception of chemistry generated a true "paradigm shift": from one focused on atoms and bonds between atoms to one focused upon molecules and bonds between molecules. Supramolecular chemistry has dissolved all the traditional barriers between the subdivisions of chemistry (organic, inorganic, organometallic, biological), focusing attention on the *collective* properties generated by the assembly of molecules and also on the relationship between such collective properties and those of the individual components.

The paradigm shift

When applied to crystalline solids, the paradigm shift leads directly from supramolecular chemistry to crystal engineering. Who could deny that J. M. Lehn's[4] definition of a supermolecule ("organized entity of higher complexity held together by intermolecular forces") works just as well for a (molecular) crystal? The collective properties of such a giant *supermolecule* result from the convolution of the properties of the individual molecular/ionic building blocks with the periodical distribution of intermolecular non-covalent bonding of

Dario Braga is Professor of Chemistry at the University of Bologna in Italy. He has always been interested in solids and in the relationship between molecular and crystal properties. His interests are, at present, focused on making crystalline materials by design for applications in solid–solid and solid–gas solvent-free reactions. He collaborates with several companies in Italy and abroad on problems of crystal polymorphism. Dario Braga is the author of about 300 papers and reviews. He is the Scientific Editor of *CrystEngComm* and a member of the Advisory Board of *ChemComm.* He has been involved in the planning and organization of several International European Schools and Meetings on crystal engineering.

The term ‘crystal engineering’ is traditionally attributed to G. Schmidt (Pure Appl. Chem., 1971, **27**, 647). “...*we shall, in the present context of synthetic and mechanistic photochemistry, be able to ‘engineer’ crystal structures having intermolecular contact geometries appropriate for chemical reaction*…”. However, the proceedings of the American Physical Society Meeting held in Mexico City in August 1955 (*Phys. Rev.*, 1955, **100**, 952) report an abstract entitled “Crystal Engineering: a new concept in crystallography”, by R. Pepinsky of the Pennsylvania State University: “*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’*… Pepinsky’s goal was that of exploiting complex ions in the application of direct methods for structure determination, in particular the absolute structure of optically active ions. Although the scopes of modern crystal engineering are much broader, it is interesting to note that the idea of *making crystals by design* was there already fifty years ago: the purposed modification of a crystal structure to enhance anomalous scattering for diffraction image seeking can be regarded as an early application of the *crystal engineering* principles.

I am grateful to Dr. K. Larsson (Chalmers University of Technology, Göteborg, Sweden) for informing me of this “ancient literature” discovery.

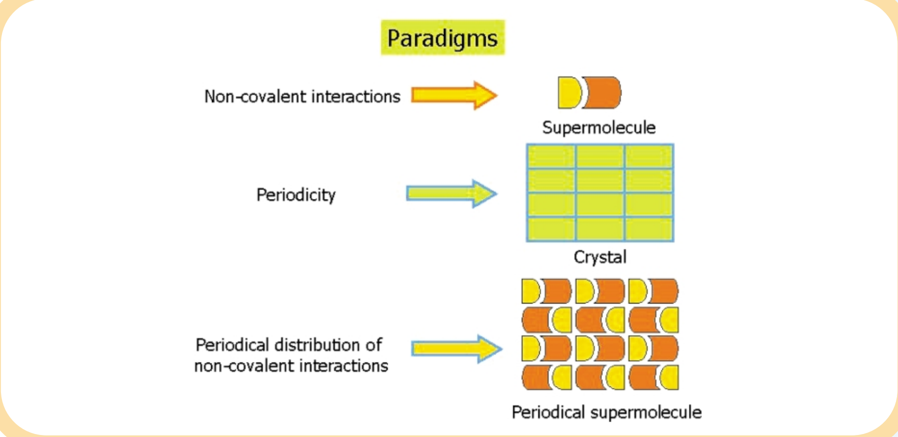

Fig. 1 From molecule to periodical supermolecule: the collective properties of molecular crystal result from the convolution of the properties of the individual molecular/ionic building blocks with the periodical distribution of intermolecular non-covalent bonding of the crystal.

the crystal (see Fig. 1). This had been anticipated in Etter’s papers[5] and in Desiraju’s 1988 book,[6] and hinted at as early as 1973 in Kitagorodsky’s investigations of molecular crystals.[7] A concurrence of thoughts and objectives fostered the birth of modern crystal engineering as the chemistry of *periodical supermolecules*.

The identification of a crystal as a retrosynthetic target[8] marked this evolutionary step: the *new* crystal engineer was a chemist, actually a supramolecular solid state chemist, with interests ranging from synthetic chemistry, to crystallography and solid state chemistry. Though they have their origins in organic chemistry, these ideas have found an extraordinarily fertile soil in the fields of metal-organic and coordination chemistry.[9]

Put simply, crystal engineering is *making crystals by design*. This definition implies the ability to assemble molecular or ionic components into the desired architecture by engineering a target network of supramolecular interactions. These interactions can be covalent bonds between atoms, as well as coordination bonds between ligands and metal centers, Coulombic attractions and repulsions between ions, and non-covalent bonds between neutral molecules (van der Waals, hydrogen bonds, *etc.*) or – of course – any combination of these linkages. These bonding interactions span a very wide energy range: from the tiny energies involved in the van der Waals interactions between neutral atoms in neutral molecules to the high ones involved in breaking and forming of covalent bonds (see Fig. 2). The difference in bonding types offers a practical way to differentiate target materials, and hence synthetic strategies, as a function of the energy involved in the bond breaking-bond forming processes that lead from building block to superstructure. On this premise, a judicious choice of the supramolecular links and of the building block features (electronic, spin, charge state and geometry) allows “bottom-up” preparation of molecule-based materials for a variety of applications.[10]

It is worth stressing that crystal-oriented synthetic strategies do not differ, in their essence, from classical chemical experiments in which molecules are modelled, synthetic routes devised, products characterised and their properties measured. However, this step-wise process needs, in a sense, to be repeated twice: first, in order to prepare the building blocks (whether molecules or ions), and then to arrange the building blocks in a desired way to attain and/or control crystal properties. This latter step invariably requires the characterisation of a solid product for which routine analytical and spectroscopic laboratory tools are much less useful than in the case of solution chemistry. In fact, the crystal engineer has to master methods that are not routine in chemistry labs (DSC, TGA, AFM, STM, SSNMR, XPD, *etc.*).

Interfaces – crystal engineering and co-ordination chemistry, green chemistry and drug discovery

Coordination chemistry has also gone *supramolecular*, evolving from a coordination chemistry focused on molecular complexes to a *periodical* coordination chemistry focused on networks of complexes. The basic idea is that of expanding coordination in one, two and three dimensions by means of

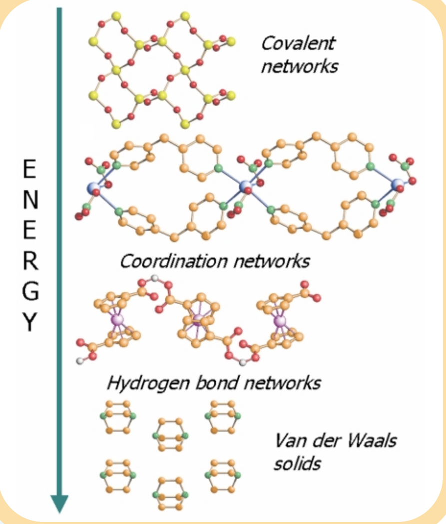

Fig. 2 Bonding interactions between building blocks span a very wide energy range: the difference in bonding types offers a practical way to differentiate target materials, and hence synthetic strategies, as a function of the energy involved in the bond breaking-bond forming processes that lead from building block to superstructure.

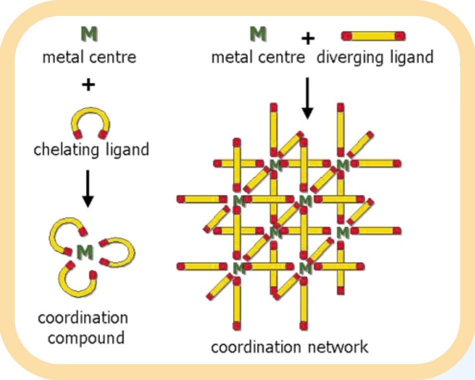

Fig. 3 The transition from molecular to periodical coordination chemistry. From coordination complexes (top) to coordination networks (bottom): the use of bidentate ligand spacers allows construction of *periodical* coordination complexes.

polydentate ligands which, instead of convergent chelation, could give divergent polydentation joining metal centres in extended networks as schematically represented in Fig. 3. Coordination networks (also called coordination polymers) constitute by far the largest class of engineered crystal structures.

A popular motivation for this work is the design and preparation of zeolite-type nanoporous structures with voids and channels that can be used for sensing, trapping, and storing small molecules (see Fig. 4).[11] There is a catch, though, and this is the self-filling of voids in the structures by network interpenetration. Even when interpenetration does not occur, the edifice may not resist removal of solvent or guest molecules. Therefore, the two main design challenges in this sub-area are:

- understanding the factors controlling self-entanglement
- designing nanoporous materials that withstand uptake and release of substances[9]

Solvent-free reactions between molecular crystals and gases, as well as between two molecular solids, to yield molecular crystalline products are also of interest in the quest for environmentally friendly processes (green chemistry).[12] Examples of both types of processes are shown in Fig. 5.[13] Both uptake/release of small molecules by a nanoporous material and the reaction between a molecular crystal and molecules (whether from gas phase or in the solid state) to yield a new crystalline material are *supramolecular reactions* whereby non-covalent interactions between guest and the host are broken and formed.

Solid-state covalent reactions, on the other hand, bring back Schmidt's pioneering ideas of pre-arranging molecules in the solid state in order to obtain reactions.[14] This topochemical approach, however, is not a *dogma*: in many cases molecules need to travel a long distance within crystals in order to react.[15]

Meanwhile, fuelled by patenting concerns, the interest of pharmaceutical companies in the appearance (or disappearance) of polymorphic forms of a given substance has increased tremendously.[16] Crystalline polymorphs, *e.g. different periodical supermolecules* of the same component molecule, could have different physico-chemical properties (solubility, thermal resistance, workability, particle size *etc.*) and could thus be treated as different substances for many practical purposes. The controlled preparation and characterization of different crystal forms has thus become a major issue of solid-state chemistry, and not only for organic substances. However, one may wonder whether the existence of a multiple answer to the crystal design and construction paradigm could be seen as the "dark side" of crystal engineering.

Learning how to generate polymorphs *on purpose* by a judicious choice of the crystallization conditions is a way to master non-covalent interactions. There are also notable implications in theoretical solid-state chemistry where the challenge becomes that of *predicting* the outcome of a crystallization process (see J. D. Dunitz recent Focus Article[17]).

Crystal engineering, where to?

Where is crystal engineering going? It continues to expand across scientific borders. Having grown from its "organic" cradle, crystal engineering now spans all areas of chemistry, with relevant interdisciplinary interactions with biology, informatics and physics.

In the area of biology, for example, crystal engineering involves the investigation of the interaction between biological matrices and crystalline phases and the transfer of this knowledge to lab practice.[18]

Clearly, the motivation behind a crystal engineering project may be utilitarian and economical or, equally, aesthetic and/or fuelled by quintessential scientific curiosity. Crystal engineering is a *global* discipline practised by scientists with diverse interests but all sharing the idea of "making crystals with a purpose".

Needless to say, crystals were prepared "with a purpose", and thoroughly investigated, long before the advent of modern crystal engineering. What was lacking, perhaps, was a common scientific language and a unifying perception of crystals not as something *different from* molecules but rather as gigantic supermolecules that could be manipulated with the tools of chemistry. In this respect, while topological analysis of weak and strong non covalent interactions, design strategies with hydrogen and coordination bonds, characterization of solid compounds are all well charted areas, the quest for novel properties engineered at

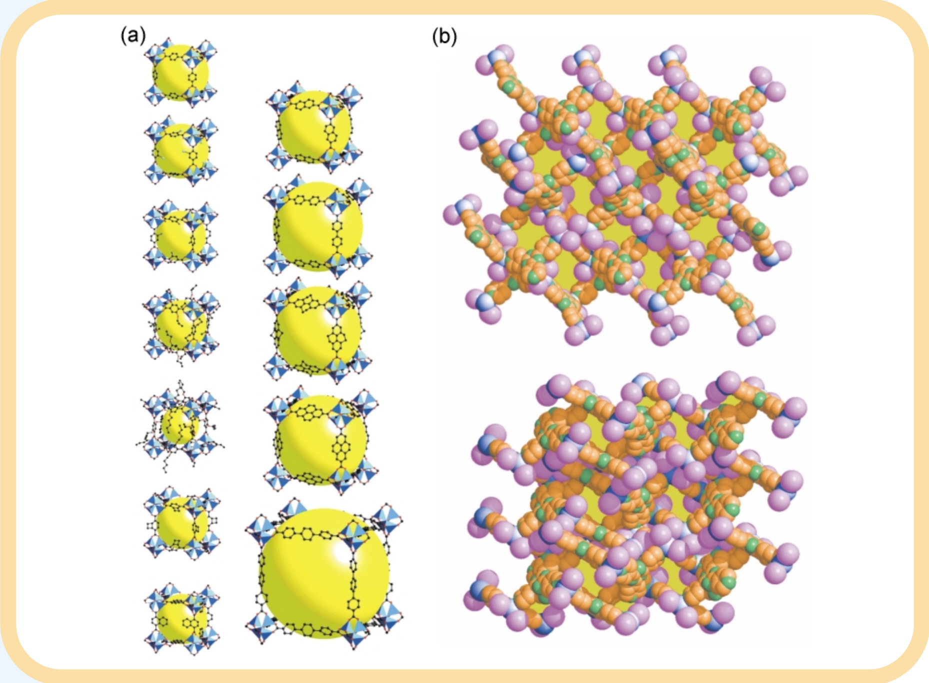

Fig. 4 Coordination networks: (a) "Paddle wheel" clusters M(O$_2$CR)$_4$ have been used to produce low-density structures that can take up a large amount of guest molecules; the large sphere indicates the empty space in the crystal structure. Reproduced by permission of the Royal Society of Chemistry.[11a] (b) "Sponge-like" behaviour of the coordination network obtained from 2,4,6-tris-(4-pyridyl)triazine and ZnI$_2$: the network shrinks/swells upon release/uptake of guest molecules.[11b]

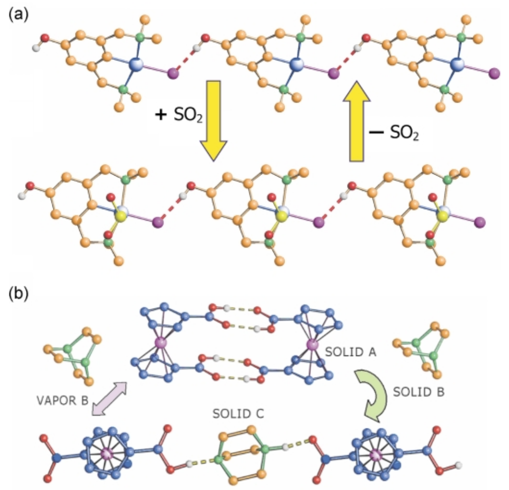

Fig. 5 Solid-gas and solid-solid reactions. (a) the Pt(II) complex reversibly binds gaseous SO_2 in the solid state by Pt–S bond formation and cleavage. Uptake and release of SO_2 does not destroy the crystalline ordering.[13a,b] (b) *Mechanochemical* and gas–solid assembly of a hybrid organic–organometallic solid compound accompanied by reorganization of the hydrogen bonding pattern.[13c]

molecular and supramolecular levels has only recently begun.[10] One can expect developments in diverse and complementary areas: nano-computing, catalysis (in nano- and meso-cavities), protonics (fuel cells), storage (fuel storage), biomimesys and implantology, sieves, sensors and traps (environmental chemistry), polymorphism (drugs delivery and uptake) just to mention a few. Focusing research on these topics will also help directing basic research towards long term practical applications and will increase co-operation between the academic and industrial sectors.

However, the "black magic" of crystallization[19a] remains a challenge. No recipe exists to *predict* the shape or size, let alone space group, of the crystals that will eventually form from a solution of a new chemicals, nor whether the crystals will be thermodynamically stable or metastable, or will undergo phase changes with temperature or pressure, or include solvent molecules upon crystallization. We are unable to predict whether crystallization will yield a powder, or single crystals, or amorphous materials, or all these together. Everything can be solid but not every solid obeys Bragg's law. Indeed, many of the most interesting materials are disordered or amorphous[18c] and their characterization and evaluation is an open challenge.

Engineering requires transferability and reproducibility. There is no doubt that crystals can be *engineered* at the molecular level, but in order for a crystal to "exist", to have any practical meaning, it must grow to size. Even the smallest fragment, visible only under a microscope, requires the self-arrangement of billions of molecules.[19b] This is the fascination that never ends.

Acknowledgements

For reasons of space I am unable to cite relevant contributions of many colleagues. I hope all those who have contributed to make crystal engineering fascinating and diverse will accept a collective acknowledgment. I would also like to express my thanks to Fabrizia Grepioni for her help and useful suggestions.

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