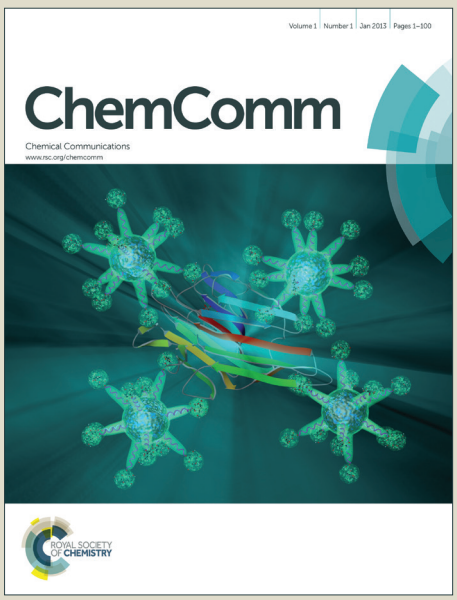
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Molecular crystals by design?

Edward R. T. Tiekink[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

In this Viewpoint, the impact of the paper published by Gautam R. Desiraju and Angelo Gavezzotti (*J. Chem. Soc., Chem. Commun.*, 1989, 621) upon the development of *Crystal Engineering*, now recognised a key discipline in contemporary chemical/pharmaceutical/materials science, is discussed.

So much has happened in molecular crystallography in the 25 years since the publication entitled "*From molecular to crystal structure: polynuclear aromatic hydrocarbons*" by Gautam R. Desiraju[1a] and Angelo Gavezzotti[1b] in *Chem. Commun*.[2a] and the full version published in *Acta Crystallogr. B* relatively soon thereafter;[2b] this work is hereafter referred to as "DG". It is salutary to contemplate that in 1989, Charge Coupled Devices (CCD's) for X-ray measurements were still under development with data collections still largely relying on single-point detector systems so that experiments were measured in terms of days, even weeks, rather than minutes as now; low temperature measurements were generally employed for specialist experiments only. University Departments had expert crystallographers, who often had their own custom-made programs for data reduction and analysis/interpretation – PLATON[3a] was not yet all pervasive and Crystallographic Information Files (CIF's) were just starting to come to the fore.[3b] Manuscript submission was still by hard-copy *via* "snail-mail"; e-mail was known but not yet the Internet, RSS Feeds, *etc*. The Cambridge Structural Database had yet to incorporate its 100,000th high quality structure.[3c] Against this backdrop of ever increasing automation, the wide-availability of standardised and robust software, and the sense that given knowledge of the chemical composition of a new compound, a reasonable assumption could be made of its structure, that is, molecular structure, crystallography as a discipline was destined to change.[3d] However, while it may be true that molecular structures might be predicted with some confidence, the situation with crystal structures is still very much a frontier and the lack of knowledge in this aspect of fundamental science, that is the unpredictability of the way molecules self-assemble into crystals, has famously been described as a scandal.[3e]

Crystal engineering can succinctly be described as the rational assembly of molecules into crystals optimised for specific applications. Applications will vary depending on the constituent species, for example metal-containing or not, and cover a broad range from tailoring solubility/stability for pharmaceutical applications, engineering pore-size in Metal-Organic Frameworks (MOF's) for gas separation/storage, to generating magnetic, luminescent, *etc*. materials. "All", then, that is required for crystal engineering is the control of supramolecular assembly but this might be likened to "herding cats". The magnitude of problem confronting crystal engineers in the organic solid-state as opposed to MOF's[4a] is realised when Crystal Structure Prediction (CSP) or *in silico* crystallography indicates that many, often very many, alternative packing arrangements might be differentiated by relatively small energies,[4b] not to mention issues associated with solvation, proton transfer and disorder.

Building upon the shoulders of some of the pioneers of the organic solid-state such as Bragg, Bernal, Robertson and Kitaigorodskii,[5a-d] in 1989 the DG paper described a delineation of the common crystal packing patterns for polyaromatic hydrocarbons (PAH's), *i.e*. disk-shaped molecules with a large cross-section relative to thickness, based on both geometric and energy criteria. Four prototypes for crystal packing were identified, namely the herringbone, sandwich herringbone, a flattened herringbone and a layered motif. These are exemplified by the crystal structures of naphthalene, pyrene, coronene and tribenzopyrene in Figs 1a-d, respectively.[6]

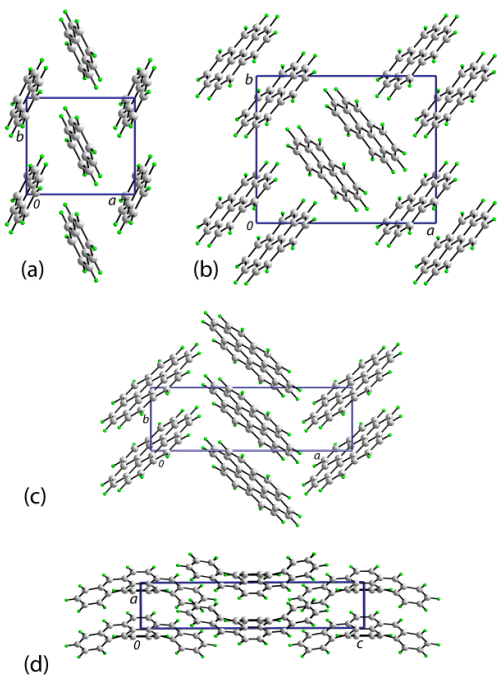


Fig. 1 Views of the crystal packing in four prototype structures of PAH's: (a) naphthalene, (b) pyrene, (c) coronene and (d) tribenzopyrene.

In terms of unit cell metrics, the four motifs can be classified in terms of the length of the shortest axis, always the unique direction, with the remaining axes of appropriate length to accommodate the size and shape of the respective molecule. Thus, the short axis for the layered, 'graphitic', motif is < 4.2 Å. The flattened herringbone motif features shortest axes in the range 4.6 to 5.4 Å. The herringbone motif, with non-parallel nearest neighbours, is characterised by shortest axes in the range 5.4 – 8.0 Å, and these are > 8.0 Å in the sandwich herringbone motif, which comprise diads. From the foregoing, these data clearly correlate with relative orientations of the molecules along the unique axis, and this naturally impacts upon the manner by which the molecules associate.

In the motifs with parallel or close to parallel stacking of molecules, face-to-face π…π interactions predominate and conversely, inclined arrangements favour edge-to-face C–H…π interactions. In the sandwich herringbone motif both π…π interactions, between the molecules comprising the diad, and C–H…π interactions are formed between diads. Having established a qualitative relationship between the nature of the intermolecular interactions and crystal structure the question then arises, why? What feature(s) of a given molecule determines the structural motif adopted in the condensed phase? In an attempt to answer this fundamental question, the DG work classified individual molecules in terms of their surface area, showing those with a large surface area relative to molecule thickness favour face-to-face π…π interactions and conversely, edge-to-face C–H…π interactions are more likely for molecules with a reduced relative surface area. The molecular surface area is also correlated with packing energy and calculations on individual atoms within a molecule allow their assignment as being able to promote face-to-face stacking or to induce a glide relationship between molecules leading to edge-to-face C–H…π interactions. Put simply, molecules with a greater relative proportion of carbon atoms will tend to form face-to-face π…π interactions and those with a smaller proportion will form edge-to-face C–H…π interactions.

Over and above the rationalisation of literature PAH's, the DG work went on to predict features of the crystal structures for molecules that had not yet been structurally characterised. Subsequently, one of these structures appeared in the literature, namely, 1,2-benzopyrene,[7] which, adopting a herringbone sandwich motif, fitted in nicely with prediction.

In summary, in the DG work[2] both qualitative and quantitative correlations are presented between the size and shape of close to planar molecules largely devoid conformational flexibility with their crystal packing patterns. Complementing the rationalisation of structure were predictions of hitherto unknown structures. While perhaps limited in scope in terms of the molecules investigated, the idea of trying to rationalise and predict crystal structures based on the nature of the molecule is one of the fundamental questions in crystallography. The real significance of the DG work is in the challenge it poses to develop an overarching theory relating molecular to crystal structure. This question is being addressed in two key fashions: the nature of intermolecular interactions and global crystal packing considerations. Each of these is evaluated in turn in the following.

In rationalising the structural motifs adopted by various PAH's, well known π…π and, then, less well studied C–H…π[8a] stabilising forces were considered. Since the DG publications,[2] increasing attention has been devoted to delineating the different ways molecules associate in crystals, *i.e*. how molecules recognise each other. Complementing all-organic π-systems, are those incorporating a metal, *e.g*. a chelate ring, which may form analogous π(chelate)…π(chelate)[8b,c] and C–H…π(chelate) interactions.[8d-f] Anions[8g] and lone pairs of electrons,[8h-j] have been shown to interact with π-rings. Other forms of interaction are well-documented such as halogen bonding,[8k] and others such as tetrel,[8l] pnictogen[8m] and chalcogen,[8n] bonding increasingly being recognised and employed in the description of crystal structures. Indeed, quite intricate analyses of crystal packing are now possible based on the above but these reveal little about the energy of individual interactions let alone the reason why they form in some structures but not in others. Complimenting the above is conventional hydrogen bonding such as O–H...O, N, and other forms, *e.g*. involving C–H hydrogen as a donor. Hydrogen bonding considerations led to the elegant concept of the *supramolecular synthon*,[9] referring to the idea that crystallisation is first and foremost a kinetic event and that the most directional intermolecular interaction will be the first to form within a specific aggregate and this will be carried through to the entire crystal structure.

The concept of supramolecular synthon features prominently in one of the most fertile areas of crystal engineering of organic molecules, *viz*. co-crystals, in particular as they apply to the pharmaceutical industry.[10a] Here, disparate molecules may be connected in a crystal by the consistent adoption of a specific, pre-designed supramolecular synthon. An obvious example comes to mind in the "reliable" matching of carboxylic acid and pyridyl residues *via* a {…HOC(=O)…N(pyridyl)} *hetero*synthon;[10b] often a weak pyridyl-H…O=C hydrogen bond turns this into an eight-membered heterosynthon. A survey of the Cambridge Structural Database[10c] shows this synthon to occur in 98% of crystal structures where both carboxylic acid and pyridyl residues are present, but when competing hydrogen bond donor/acceptor groups are absent. The prevalence of this heterosynthon decreases to 77% when all structures containing both carboxylic acid and pyridyl residues are considered. Here is the *first* difficulty in designing crystal structures: there is no hard and fast heirarchy[10d] of supramolecular synthons that can be employed by the crystal engineer to design crystals. Even the normally referred to as "robust and directional" conventional hydrogen bonding, upon which much crystal engineering endeavours are predicated, can be subject to polymorphism, including synthon polymorphism, and even usurped by other, nominally weaker, intermolecular interactions as in the case, for example, of the much discussed crystal structure of alloxan.[10e,f] As things stand, at best, it might be possible to employ the supramolecular synthon approach to deliberately associate selected molecules in a specific fashion into an aggregate within a crystalline manifold but no control is possible over the way these aggregates associate to form the crystal structure.

The *second* difficulty in designing crystal structures is in reality the real challenge, but is often neglected. Whatever the nature of recognisable association between molecules, the energy of the specific interaction is invariably smaller, perhaps by two

orders of magnitude, than the electrostatic potential between molecules themselves. In order to control the pattern of molecular assembly in three-dimensions, one must overcome the energy associated with the global crystal packing of molecules.

It is salient at this point to recall that 83% of all molecules crystallise in one of five close packing space groups ($P\bar{1}$, $P2_1$, $P2_1/c$, $C2/c$, $P2_12_12_1$ and $Pbca$; and alternative settings).[9c] Stated simply, in this geometric approach, the majority of molecules are going to pack in a crystal structure so as to minimise free space, crudely expressed in the idea that bumps in molecules will match hollows in neighbours but leading inevitably to some voids. Aristotle is attributed as having stated "*horror vacui*", translated widely as "Nature abhors a vacuum". This idea is more directly applied to the design of crystal structures by a quote Dunitz and Gavezzotti, *viz*. "As far as the packing energy is concerned, empty space is wasted space".[11] This geometric scenario clearly allows for polymorphism and certainly accounts for supramolecular polymorphism.

Taken to an extreme, if it was the dictate that limited free-space be allowed in a crystal that solely determines the ultimate crystal structure adopted by a molecule, the aforementioned intermolecular interactions arise a consequence of the global crystal packing of molecules. Consistent with this are the following two observations. For organic molecules, the number of nearest neighbours, the molecular coordination number, is often 14 but can range from 8 to 22,[12a] and compares to a value of 12 for ideal spheres. Despite the fact that many organic molecules have low symmetry, have odd shapes, *etc*., the crystal packing efficiencies are close to 0.74, *i.e*. close to that for ideal spheres.[12b] In the geometric scenario, molecules assemble to optimise electrostatic potentials, leading in the crystal structure and residues projecting toward the 26% "free space" available and adjust their positions to optimise interactions/minimise repulsions. Paraphrasing a comment by Dunitz and Gavezzotti focussing on hydrogen atoms at the periphery of molecules in crystal structures,[12c] the residues are already in close proximity and are hardly going to adopt repulsive configurations. In other words, many, even all, intermolecular interactions, interpreted as molecular recognition events in the supramolecular synthon approach, arise as a consequence of the global crystal packing even if there are measureable or calculable energies of attraction associated with these.[12d]

The real situation is likely to lie somewhere between the two views of crystal packing. Crystallisation is a dynamic process and involves nucleation which implies supramolecular recognition of some form – *via* supramolecular synthons and/or between bumps and hollows – and this persists as a crystal grows. Whatever the mechanism of crystal growth, the rationale design of fragments within crystals is clearly possible through the supramolecular synthon approach – the many success stories cannot be a coincidence. As an aside, it should be noted that this is crystal engineering *in* a crystal not crystal engineering of *a* crystal as no control over the overall crystal structure, *e.g*. a specific crystal system let alone space group.

Crystal Engineering is a burgeoning field with practitioners drawn from many disciplines – it is now difficult to contemplate life without crystal engineering. For the organic solid-state, significant progress has been made in identifying different modes of association between molecules and using this information to specifically associate molecules into larger aggregates within crystals. However, control over the overall crystal structure still remains a challenge deserving of continued effort.

Postscript. Fortunately, the two protagonists of the original DG paper are still making significant contributions to the understanding of the organic solid-state. For further insight in the way molecules assemble in the solid-state, and more, two recent personal accounts are highly recommended reading.[13,14]

Our research in crystal engineering is supported by the High Impact Research MoE Grants UM.C/625/1/HIR/MoE/SC/-03 and -12 from the Ministry of Higher Education, Malaysia.

Notes and references

[a] *Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia. Fax: 60 3 7967 4193; Tel: 60 3 7967 6775; E-mail: Edward.Tiekink@um.edu.my*

1 (a) website for Prof. Dr G. R. Desiraju: http://sscu.iisc.ernet.in/gautam_r_desiraju.html; (b) website for Prof. Dr A. Gavezzotti: http://users2.unimi.it/gavezzot/.

2 (a) G. R. Desiraju and A. Gavezzotti, *J. Chem. Soc., Chem. Commun.*, 1989, 621; (b) G. R. Desiraju and A. Gavezzotti, *Acta Crystallogr., Sect. B: Struct. Sci*., 1989, **45**, 473.

3 (a) A. L. Spek, *Acta Crystallogr*., *Sect. D: Biol. Crystallogr*., 2009, **65**, 148; (b) S. R. Hall, F. H. Allen and I. D. Brown, *Acta Crystallogr., Sect. A: Found. Cryst*., 1991, **47**, 665; (c) F. H. Allen, *Acta Crystallogr., Sect. B: Struct. Sci*., 2002, **58**, 380; (d) E. R. T. Tiekink, *Z. Kristallogr*. 2002, **217**, 373; (e) J. Maddox, *Nature*, 1988, **335**, 760.

4 (a) M. O'Keeffe, *Chem. Soc. Rev*., 2009, **38**, 1215; (b) S. L. Price, *Chem. Soc. Rev*., 2014, **43**, 2098.

5 (a) W. H. Bragg, *Proc. Phys. Soc. London*, 1921, **34**, 33; (b) J. D. Bernal and D. Crowfoot, *J. Chem. Soc*., 1935, 93; (c) J. M. Robertson, *Proc. R. Soc. London, Ser. A*, 1951, **207**, 101; (d) A. Kitaigorodskii, *Acta Crystallogr*. 1965, **18**, 585.

6 K. Brandenburg, DIAMOND. Crystal Impact GbR, Bonn, Germany, 2006.

7 G. Reck, B. W. Schulz, Private Communication to the Cambridge Structural Database, 2006.

8 (a) M. Nishio, Y. Umezawa, J. Fantini, M. S. Weiss and P. Chakrabarti, *Phys. Chem. Chem. Phys*., 2014, **16**, 12648; (b) Z. D. Tomić, D. N. Sredojević and S. D. Zarić, *Cryst. Growth Des*., 2006, **6**, 29; (c) D. N. Sredojević, Z. D. Tomić and S. D. Zarić, *Cryst. Growth Des*., 2010, **10**, 3901; (d) M. K. Milčić, V. B. Medaković, D. N. Sredojević , N. O. Juranić and S. D. Zarić, *Inorg. Chem*., 2006, **45**, 4755; (e) E. R. T. Tiekink and J. Zukerman-Schpector, *Chem. Commun.*, 2011, **47**, 6623; (f) S. K. Singh, M. G. B. Drew and N. Singh, *CrystEngComm*, 2013, **15**, 10255; (g) A. Frontera, P. Gamez, M. Mascal, T. J. Mooibroek and J. Reedijk, *Angew. Chem. Int. Ed*., 2011, **50**, 9564; (h) T. J. Mooibroek, P. Gamez and J. Reedijk, *CrystEngComm*, 2008, **10**, 1501; (i) I. Caracelli, J. Zukerman-Schpector and E. R. T. Tiekink, *Coord. Chem. Rev*. 2012, **256**, 412; (j) I. Caracelli, I. Haiduc, J. Zukerman-Schpector and E. R. T. Tiekink, *Coord. Chem. Rev*., 2013, **257**, 2863; (k) A. Priimagi, G. Cavallo, P. Metrangolo and G. Resnati, *Acc. Chem. Res*., 2013, **46**, 2686; (l) A. Bauza, T. J. Mooibroek and A. Frontera, *Angew. Chem. Int. Ed*., 2011, **52**, 12317; (m) S. Scheiner, *Acc. Chem. Res*., 2013, **46**, 280; (n) M. E. Brezgunova, J. Lieffrig, E. Aubert, S. Dahaoui, P. Fertey, S. Lebegue, J. G. Angyan, M. Fourmigue, E. Espinosa, *Cryst. Growth Des*., 2013, **13**, 3283.

9 G. R. Desiraju, *Angew. Chem. Int. Ed*., 1995, **34**, 2311.

10 (a) Ö. Almarsson and M. J. Zaworotko, *Chem. Commun*., 2004, 1889; (b) T. Shattock, K. K. Arora, P., Vishweshwar and M. J. Zaworotko, *Cryst. Growth Des*., 2008, **8**, 4533; (c) F. H. Allen, *Acta Crystallogr., Sect. B: Struct. Sci*., 2002, **58**, 380; (d) J. A. Bis, P. Vishweshwar, D. Weyna and M. J. Zaworotko, *Molec. Pharm*., 2007,

4, 401; (e) J. D. Dunitz and W. B. Schweizer, *CrystEngComm*, 2007, **9**, 266; (f) T. S. Thakur, M. T. Kirchner, D. Blaser, R. Boese, G. R. Desiraju, *CrystEngComm*, 2010, **12**, 2079.
11 J. D. Dunitz and A. Gavezzotti, *Acc. Chem. Res*., 1999, **32**, 677.
12 (a) E. V. Peresypkina and V. A. Blatov, *Acta Crystallogr*., *Sect. B: Struct. Sci*., 2000, **56**, 501; (b) J. D. Dunitz, G. Filippini and A. Gavezzotti, *Helv. Chim. Acta*, 2000, **83**, 2317; (c) J. D. Dunitz and A. Gavezzotti, *Chem. Soc. Rev*., 2009, **38**, 2622; (d) J. D. Dunitz and A. Gavezzotti, *Cryst. Growth Des*., 2013, **13**, 5873.
13 G. R. Desiraju, *J. Am. Chem. Soc*., 2013, **135**, 9952.
14 A. Gavezzotti, *CrystEngComm*, 2013, **15**, 4027.