Crystal Engineering: from Structure to Function

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Modern crystal engineering has emerged as a rich discipline whose success requires an iterative process of synthesis, crystallography, crystal structure analysis, and computational methods. By focusing on the molecular recognition events during nucleation and growth, chemists have uncovered new ways of controlling the internal structure and symmetry of crystals and of producing materials with useful chemical and physical properties.

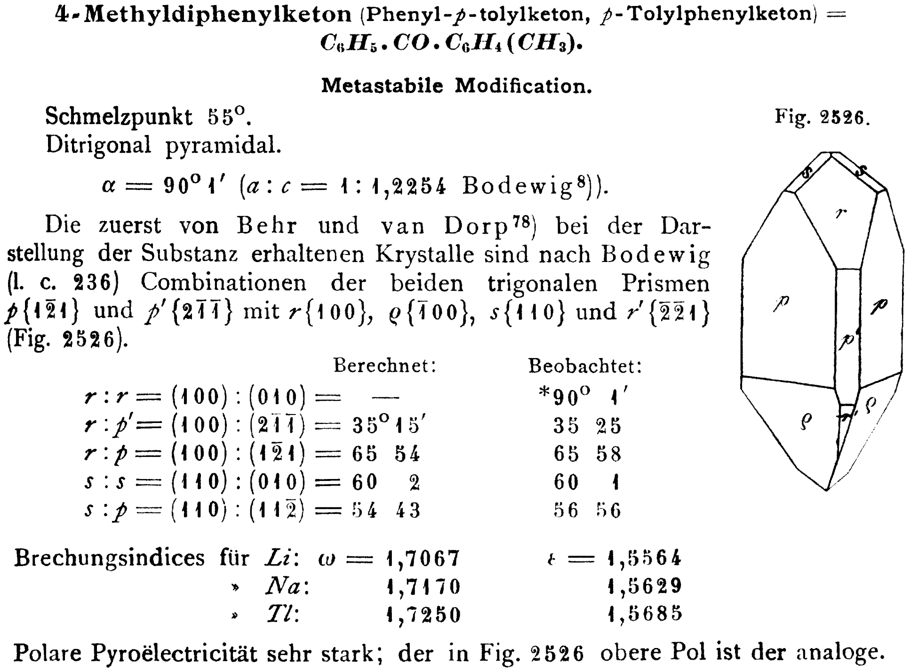
Legend has it that modern crystallography owes its roots to an accidental discovery reported in 1781 by the French physicist René Just Haüy (*1*). While admiring a friend's mineral collection, Haüy dropped a particularly large crystal of Iceland spar (calcite), which cleaved into equivalent fragments. With keen insight, Haüy recognized that internal structure was related to external form, and after spending the next years smashing his mineral collection and those of his friends, he reckoned that all crystals were composed of a limited number of building blocks that were stacked together in simple ways. With the subsequent development of optical goniometry, polarized light microscopy, and other physical techniques, 19th-century chemists and crystallographers focused on macroscopic properties of crystals such as birefringence, optical activity, pyroelectricity (electric polarization caused by temperature change), and, later, piezoelectricity (electric polarization under external stress), which was discovered by Pierre and Jacques Curie in 1880. These efforts culminated in Paul Groth's *Chemische Krystallographie* (*2*), which documents in five volumes what was known about the external form and physical properties of more than 7000 organic and inorganic crystals that had been characterized by the beginning of the 20th century (Fig. 1).

Groth's treatise and Haüy's deconstruction of macroscopic crystalline objects provide instructive contrasts with the modus operandi of modern-day solid state organic chemists and "crystal engineers," who have embraced the notion of the supramolecular synthon (*3*) as the critical design element for generating new materials. In its renaissance, as inaugurated by G. M. J. Schmidt and coworkers in the 1960s (*4*), solid state organic chemistry has focused on the molecular building blocks and their connections with the anticipation that reliable functional group interactions can be used to assemble a variety of useful molecular materials.

The synthesis of organic molecules relies on the strength of covalent bonds and on the relative rates of bond-forming processes to lead, in a rational, step-wise process, to the final product. It is therefore no surprise that many organic chemists have, until recently, shied away from crystal synthesis. For the supramolecular synthetic chemist, the specific goal is a macroscopic property, and the final product is often a moving target that changes each time the crystal synthesis yields something different from that predicted by the imperfect models we use. The fundamental difficulty for this field is that molecular crystals are held together by a multitude of weak interactions, and a huge number of free energy minima (polymorphs) exist within a few kilojoules/mol of the global minimum. The process of crystal engineering is therefore an iterative one that involves synthesis, crystallography, crystal structure analysis, and computational methods.

Ever since Pauling, chemists have used crystal structures to look for trends in both intra- and intermolecular bonding. Today, even polycrystalline samples of moderately complex molecules are amenable to structure determination from laboratory x-ray data (*5*, *6*), and the Cambridge Structural Database (*7*) houses more than 250,000 organic and metal-organic crystal structures. This database contains numerous examples of almost every kind of intermolecular contact and has been used by materials chemists to identify important trends in crystal packing.

Statistical analyses of crystal structures have reinforced our notions concerning directionality of many strong interactions, but they cannot provide even a crude assessment of the energetics of functional group interactions. Evaluations of even moderately weak interactions have there-



4-Methyldiphenylketon (Phenyl-*p*-tolylketon, *p*-Tolylphenylketon) = $C_6H_5 . CO . C_6H_4(CH_3)$.

Metastabile Modification.

Schmelzpunkt 55°.
Ditrigonal pyramidal.

$\alpha = 90^\circ 1'$ ($a : c = 1 : 1{,}2254$ Bodewig[8])).

Die zuerst von Behr und van Dorp[78]) bei der Darstellung der Substanz erhaltenen Krystalle sind nach Bodewig (l. c. 236) Combinationen der beiden trigonalen Prismen $p\{1\bar{2}1\}$ und $p'\{2\bar{1}\bar{1}\}$ mit $r\{100\}$, $\varrho\{\bar{1}00\}$, $s\{110\}$ und $r'\{\bar{2}\bar{2}1\}$ (Fig. 2526).

	Berechnet:	Beobachtet:
$r : r = (100) : (010) =$	—	*90° 1′
$r : p' = (100) : (2\bar{1}\bar{1}) =$	35° 15′	35 25
$r : p = (100) : (1\bar{2}1) =$	65 54	65 58
$s : s = (110) : (010) =$	60 2	60 1
$s : p = (110) : (11\bar{2}) =$	54 43	56 56

Brechungsindices für	$\omega =$	$\epsilon =$
Li:	1,7067	1,5564
» *Na*:	1,7170	1,5629
» *Tl*:	1,7250	1,5685

Polare Pyroëlectricität sehr stark; der in Fig. 2526 obere Pol ist der analoge.

Fig. 2526.

Fig. 1. Groth's entry for a metastable modification of 4-methylbenzophenone, showing the noncentrosymmetric crystal morphology and describing the interfacial angles between principal faces, the refractive index dispersion, and pyroelectric properties of this material. [From vol. V of (*2*), copyright 1919.]

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fore suffered because crystal packing results from a competition between shape (packing efficiency and repulsion), specific functional group interactions, longer range electrostatic interactions, and cooperative effects (e.g., induction, charge transfer) involving larger aggregates (*8*). Scatter plots showing geometric parameters for weakly interacting groups are often diffuse, making it difficult to make firm conclusions about the nature of such interactions. In this context, the most notable example is the C–H · · · O "hydrogen bond." Although there are numerous cases in which short C–H · · · O contacts fit the established criteria for hydrogen bonds (*9*), the diffuse nature of scatter plots for many C–H · · · O interactions suggests that observations of short C–H · · · O contacts are often secondary consequences of stronger interactions in the crystal.

As a further complication, parameterizations of potential functions from lattice parameters and heats of sublimation are typically not transferable from one crystal class to another. This lack of transferability becomes clearer upon closer inspection. Potential energy sums for even simple molecular crystals typically contain several hundred terms; for many of these, the sign of the energy is not even known, and the strong correlation between terms in the energy expressions makes unique and widely applicable solutions difficult to achieve. Crystal packing is obviously complicated, and successful parameterization for a weak interaction requires that one knows the "correct" parameters for all the other interactions in the crystal. One promising approach is to combine empirical parameters with quantum mechanical results (e.g., electrostatic multipoles) (*10*), but the close energy spacing of viable polymorphic structures remains a great difficulty (*11*).

In a recent blind test of the principal computer programs used for predicting crystal structures, the experimental crystal structures were predicted (within reasonable error) for each of the four compounds presented to the "contestants" (Fig. 2) (*12*).

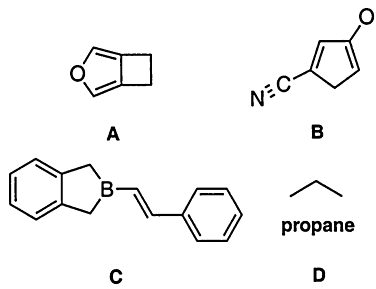

Fig. 2. Chemical structures of compounds used in a blind test of the principal computer programs for crystal structure prediction.

Nevertheless, none of the programs succeeded in predicting all four structures, and none of them predicted a second known polymorph for compound A. At present, it appears that the principal utility of these computational methods is to inform our intuition about the possible polymorphs that might be obtained for a given molecular structure.

Despite the difficulties in predicting crystal structures, synthetic chemists have focused on the most reliable supramolecular synthons (the functional group pairs that bind molecules together) and have generated molecular scaffolds that project these functional groups in one, two, and three dimensions. Hydrogen bonds (*13*), metal-ligand interactions (*14*), ion pairs, and other strong donor-acceptor interactions have been exploited to generate new and versatile frameworks, sometimes with astonishing results.

Porous Networks

Several workers have focused on the preparation of porous frameworks that may have applications in separations and as sensors, catalysts, and storage devices. Although zeolites fill a niche for industrial-scale cracking of petroleum and other catalytic processes, organic and metal-organic frameworks present unique opportunities for generating lightweight, functional materials in which chemical and/or catalytic properties can be incorporated in a rational way during the solid state synthesis. A key issue in the design of three-dimensional networks containing large voids is the degree of interpenetration of the polygonal building blocks that make up the crystalline framework (*15*). To make the largest void possible, it is necessary to minimize the degree of interpenetration of the networks, but until recently this was regarded as incompatible with long "linkers" between the coordinating centers (Fig. 3). Several approaches have been used to circumvent the problem of interpenetration, including (i) crystallization in the presence of a guest that packs efficiently within the desired, noninterpenetrated structure (*16*), (ii) the use of branching substituents that prevent concatenation (*17*), and (iii) the incorporation of specific topological features that discourage or forbid interpenetration (*18*).

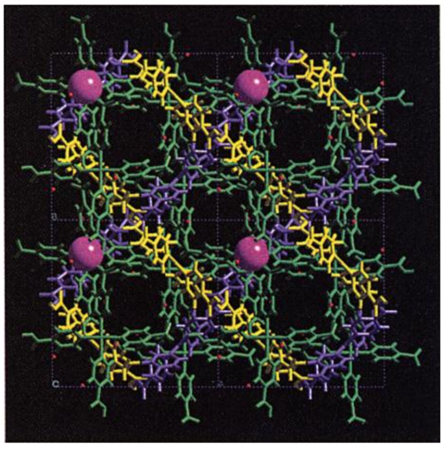

Fig. 3. A network of a square planar Pt complex with nicotinic acid and isonicotinate exhibiting threefold interpenetration (*44*). If there had been no interpenetration, voids would have occurred between selected platinum atoms, shown in magenta. Efficiently packed structures such as this are ordinarily favored over noninterpenetrated structures.

Perhaps the most spectacular of the network solids is a recently reported series of 16 metal-organic bis-carboxylate structures with noninterpenetrating pore sizes that range from 3.8 to 28.8 Å (*19*). By combining strong metal-carboxylate interactions and rigid linkers, Yaghi and co-workers were able to form octahedral zinc complexes with spacers as large as terphenyl between the metal centers (Fig. 4A). Some of the larger frameworks formed interpenetrated networks, but in this work Eddaoudi *et al.* found crystal growth conditions that yielded a noninterpenetrated network for each of the different linkers. Upon solvent exchange and evacuation, these materials maintain the same crystal structures and readily absorb gases. In particular, one structure (Fig. 4B) contains pores that are optimally sized for methane absorption. With its free volume (in the evacuated form) of 77.5%, this material absorbs a remarkable 240 cm^3 of CH_4 at standard temperature and pressure per gram [155 cm^3 (STP)/cm^3] at 36 atm and 298 K. Combined with its thermal stability, this absorptive capacity positions this material and congeners as potentially safe methane storage media for the automobile industry.

Symmetry Lowering in Solid Solutions, Mixed Crystals, and Channel Inclusion Compounds

Nature's abhorrence of a vacuum is paralleled, albeit to a smaller degree, by the propensity for molecules to crystallize so that their molecular dipole moments cancel one another. This bias may often simply reflect the shape complementarity of efficiently packed molecules, but regardless of its origin, the upshot is that most crystals are centrosymmetric, or at least nonpolar, and many crystal chemists have taken the challenge of synthesizing crystals with macroscopic dipole moments. Although many have focused on the purely scientific endeavor of understanding and overcoming this natural bias, the useful physical properties of polar crystals [e.g., piezoelectricity, nonlinear optical (NLO) effects] (*20*) continue to attract broad attention among solid state chemists who are interested in forming technological devices.

Each type of material presents its own particular challenges. With ferroelectric crystals (*21*), in which external electric fields trigger a macroscopic conversion to a nominally degenerate orientation state, the concern is with order parameters in the presence and absence of applied electric fields and with the kinetics and reversibility of domain reorientation. For NLO materials, the challenge is to order the individual constituent molecules into a polar array that achieves the proper orientation of the principal components of the second (or third) order nonlinear optical susceptibility tensors and to ensure that the material is stable to radiation fields. With the aid of ab initio calculations, it has been possible to optimize molecular hyperpolarizabilities (*22*) before assembling the NLO chromophores into polar arrays (*23*).

Many chemists have taken molecular or supramolecular approaches to generating polar materials (*24*), but solid solutions or mixed crystals provide an important avenue for tailoring the properties of molecular solids and for altering the symmetry of a material. Although Kitaigorodskii had earlier asserted that in solid solutions substitution of "guest" for "host" would occur in a symmetric fashion (*25*), scientists at the Weizmann Institute showed in the late 1980s that the orientation and distribution of impurities or additives was often anything but symmetric (*26*, *27*). Because crystallization is an inherently kinetic phenomenon and because the symmetry of a crystal's surface is lower than that of the bulk, additives are incorporated into emergent growth sectors that are terminated by faces for which guest attachment is favored. On opposite faces of the crystal, the additives can be oriented with opposite senses, and the ensuing polarity can give rise to useful properties such as second harmonic generation, even at impurity concentrations as low as 0.01% (*28*).

This sea change in our understanding of crystal growth and solid solution formation has manifested itself in many ways. If grown as pure materials and in the absence of specific types of disorder, high-symmetry crystals exhibit no birefringence (refractive index anisotropy) when viewed down their high-symmetry axes with a polarizing microscope (*29*). But solid solutions using such high-symmetry materials as hosts exhibit interference colors that arise from the birefringence caused by different orientations of guest molecules in the different sectors. In such "optically anomalous crystals," the birefringence provides a record of the crystal growth process as well as a method for studying the molecular recognition processes at the growing crystal surfaces. Such molecular recognition processes may be visualized and characterized even for crystals of low symmetry if the guest contains a chromophore or luminophore, as with crystals of benzamide containing luminescent Nile red dye (Fig. 5) (*30*). Because such dyes are typically included at the parts per thousand to parts per million level, x-ray diffraction is practically useless for determining their structures, but optical probes (e.g., linear dichroism, linear birefringence, fluorescence polarization) can provide reasonable models for the molecular recognition processes. Such dye inclusion compounds have recently been used to form tunable solid state lasers (*31*); incorporation of laser dyes into NLO-active hosts appears to be a promising avenue of research.

With certain one-dimensional channel inclusion compounds such as perhydrotriphenylene (PHTP), the same sort of molecular recognition processes described above can give rise to polar arrangements of guests, even in the absence of impurities or additives. For unsymmetric guests that can pack in the channel in head-to-head (HH), head-to-tail (HT), and tail-to-tail (TT) arrangements, the relative energetics of these three types of contacts (and in particular, the difference between HH and TT pairs) dictate the orientation of guests emerging from opposite ends of these crystals. For 1-(4-nitrophenyl)piperazine in PHTP, for example, strong –$NO_2 \cdots$ H–N– interactions, weaker –N–H ··· H–N– interactions and unfavorable –$NO_2 \cdots O_2$N– interactions give rise to a self-correcting crystal growth mechanism in which opposite ends of the crystal are decorated with nitro groups (*32*). A Markov chain model predicts that the crystal will have the opposite polarity at each end, and this was verified by measuring the sign of the electrooptic effect in different regions of the crystal. Solution of this crystal structure has required no less than a tour de force based on diffuse x-ray scattering and models of dis-

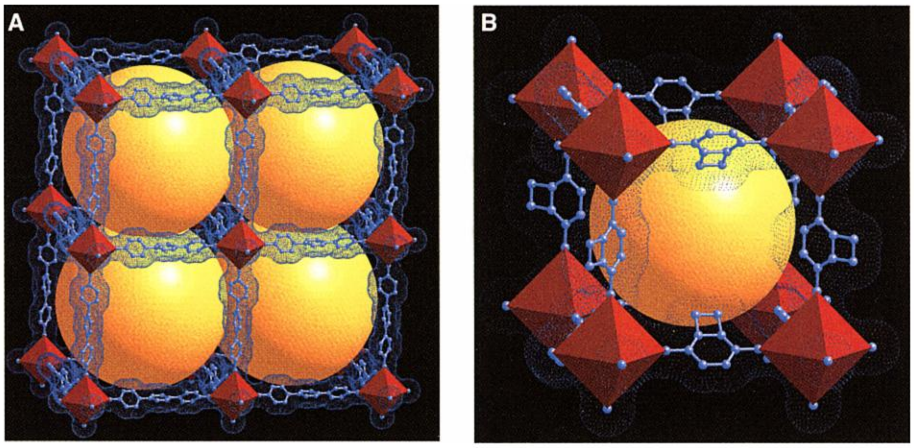

Fig. 4. Octahedral zinc (red) complexes with organic bis-carboxylates (blue). The yellow spheres indicate the free volume of the pores. The complex containing terphenyl linkers (**A**) has the lowest density (0.21 g/cm^3) and largest free volume (91.1%) of any crystalline material. The complex utilizing 1,2-dihydrocyclobutabenzene-3,6-dicarboxylic acid (**B**) has optimally sized pores for methane storage.

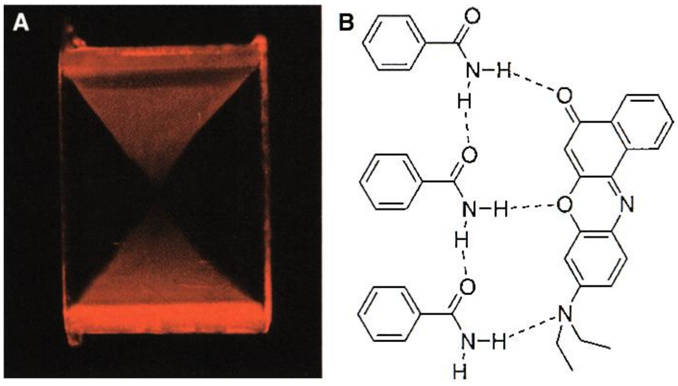

Fig. 5. (**A**) Photomicrograph of benzamide crystal containing luminescent Nile red in $\{10\bar{2}\}$ growth sectors (top and bottom). (Crystal grown and photographed by M. Kurimoto.) (**B**) Tentative structural model for host-guest recognition based on linear dichroism and solvatochromism of the dye. [Adapted with permission from (*30*), copyright 2001, American Chemical Society.]

order in different parts of the crystal (*33*). Other work on PHTP inclusion compounds has demonstrated that certain short-chain guests can undergo rapid end-for-end exchange, allowing the populations of HH, HT, and TT pairs to be determined at equilibrium with solid state nuclear magnetic resonance (*34*). Coupled with the generality of the Markov chain model, this empirical method for assessing pair-wise functional group interactions should facilitate a rational approach for preparing polar inclusion compounds.

Organic Crystals in Action

Because their utility does not rely on excitation of carriers, nonresonant NLO materials allow ultrafast response times and large repetition rates required for optical communications systems that use wavelength conversion devices in their multiplexing schemes (*35*). In the realm of sensors, actuators, and switching or memory devices, however, there is much potential for solid state processes with slower response times, such as ferroelectric domain reorientation, piezoelectric effects, photochromism, photochemical reactions, or combinations of these and other effects. A recent report of photochemically induced color change accompanied by a change in crystal shape exemplifies the sophisticated blending of solid state chemistry and physics that is required to formulate devices such as photodriven nanoscale actuators (*36*). Reversible nanometer-scale actuation has also been achieved upon absorption of SO_2 by organoplatinum crystals (*37*). In all of these materials, an essential design element is the control of fatigue resistance, which is intimately associated with the stress and strain that develops as the crystal changes its internal arrangement of atoms or macroscopic shape. High local stress is a controlling feature of many solid state reactions (*38*), so considerations of the elasticity of a solid are of paramount importance when designing materials whose properties require substantial reorganization on the molecular scale.

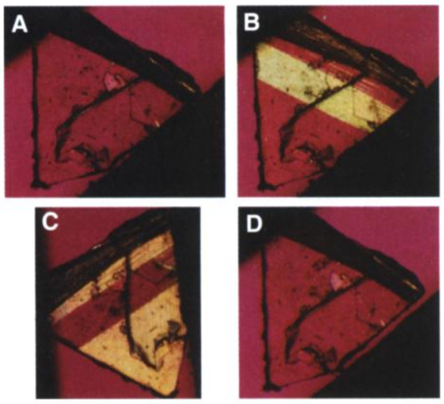

Fig. 6. Ferroelastic inclusion crystal containing 2,10-undecanedione (80%) and 2-undecanone (20%) in a urea host framework showing reversible domain reorientation in the presence of the 2-undecanone impurity. **(A)** Before stress under crossed polars and λ plate. **(B)** Under stress showing domain reorientation (white region). **(C)** Under stress after rotation to show that the newly formed region extinguishes light as a single crystal. **(D)** After release of stress, showing reversible return to the original domain orientation.

Here again, solid solutions or mixed crystals provide avenues for tailoring the properties of a solid. Impurities can change the state of strain of a crystal (*39*), which is an important consideration in designing ferroelectric materials. They can also facilitate the domain-switching process itself by breaking up large networks of connected molecules that impose cooperative barriers to such switching. In a series of ferroelastic urea inclusion compounds, in which domain reorientation occurs upon application of an external anisotropic force, introduction of an impurity that disrupts a specific hydrogen bonding network transforms a plastic (irreversible) domain-switching process into an elastic (reversible) one (Fig. 6) (*40*). Because many of the most useful ferroelectric materials are inorganic solids or minerals, such fine-tuning of the properties is not ordinarily possible, so there appears to be considerable promise for organic analogs, especially inclusion compounds, which allow substantial variation in one or more of the components. And as the design of porous materials becomes more sophisticated, so too should the prospects for switching devices and sensors that couple gas absorption with macroscopic changes in symmetry, polarity, or domain orientation.

Progress in crystal engineering will continue to require imaginative advances in several fields of chemistry, physics, and materials science. At the heart of this endeavor is the process of crystallization itself; a better understanding of nucleation and aggregation, template effects (*41*), epitaxy (*42*), and the role of solvent molecules (*28*) and external fields is essential for the controlled synthesis of materials that may exhibit polymorphic structures or a range of crystal habits, sizes, and orientations. The ultimate incorporation of oriented crystals into useful devices (*43*) will require even further transformation of the process of crystal growth from an art into a science.

References and Notes

1. J. G. Burke, *Origins of the Science of Crystals* (Univ. of California Press, Berkeley, CA, 1966), pp. 83–85.
2. P. A. Groth, *Chemische Krystallographie* (Verlag von Wilhelm Engelmann, Leipzig, 1906–1919), vol. I–V.
3. G. R. Desiraju, *Angew. Chem. Int. Ed.* **34**, 2311 (1995).
4. G. M. J. Schmidt, *Pure Appl. Chem.* **27**, 647 (1971).
5. K. D. M. Harris, M. Tremayne, P. Lightfoot, P. G. Bruce, *J. Am. Chem. Soc.* **116**, 3543 (1994).
6. K. D. M. Harris, M. Tremayne, B. M. Kariuki, *Angew. Chem. Int. Ed.* **40**, 1626 (2001).
7. Cambridge Structural Database, available at: www.ccdc.cam.ac.uk.
8. J. D. Dunitz, A. Gavezzotti, *Acc. Chem. Res.* **32**, 677 (1999).
9. G. Desiraju, T. Steiner, *The Weak Hydrogen Bond: Applications to Structural Chemistry and Biology* (Oxford Univ. Press, Oxford, 1999).
10. C. B. Aakeröy, M. Nieuwenhuyzen, S. L. Price, *J. Am. Chem. Soc.* **120**, 8986 (1998).
11. J. Bernstein, R. J. Davey, J.-O. Henck, *Angew. Chem. Int. Ed.* **38**, 3441 (1999).
12. J. P. M. Lommerse *et al.*, *Acta Crystallogr. B* **56**, 697 (2000).
13. V. A. Russell, M. C. Etter, M. D. Ward, *J. Am. Chem. Soc.* **116**, 1941 (1994).
14. B. Moulton, M. J. Zaworotko, *Chem. Rev.* **101**, 1629 (2001).
15. R. Robson, *J. Chem. Soc. Dalton Trans.* **2000**, 3735 (2000).
16. K. Biradha, Y. Hongo, M. Fujita, *Angew. Chem. Int. Ed.* **39**, 3843 (2000).
17. S. V. Kolotuchin, E. E. Fenlon, S. R. Wilson, C. J. Loweth, S. C. Zimmerman, *Angew. Chem. Int. Ed.* **34**, 2654 (1995).
18. M. Eddaoudi, J. Kim, M. O'Keefe, O. M. Yaghi, *J. Am. Chem. Soc.* **124**, 376 (2002).
19. M. Eddaoudi *et al.*, *Science* **295**, 469 (2002).
20. D. Y. Curtin, I. C. Paul, *Chem. Rev.* **81**, 525 (1981).
21. O. Auciello, J. F. Scott, R. Ramesh, *Physics Today* **51**, 22 (July 1998).
22. S. R. Marder, D. N. Beratan, L. T. Cheng, *Science* **252**, 103 (1991).
23. S. R. Marder, J. W. Perry, *Adv. Mater.* **5**, 804 (1993).
24. K. T. Holman, A. M. Pivovar, M. D. Ward, *Science* **294**, 1907 (2001).
25. A. I. Kitaigorodskii, *Organic Chemical Crystallography* (Consultants Bureau, New York, 1961), p. 233.
26. M. Vaida *et al.*, *Science* **241**, 1475 (1988).
27. J. M. McBride, *Angew. Chem.* **101**, 391 (1989).
28. I. Weissbuch, L. Addadi, M. Lahav, L. Leiserowitz, *Science* **253**, 637 (1991).
29. B. Kahr, J. M. McBride, *Angew. Chem. Int. Ed.* **31**, 1 (1992).
30. B. Kahr, R. W. Gurney, *Chem. Rev.* **101**, 893 (2001).
31. M. Rifani *et al.*, *J. Am. Chem. Soc.* **117**, 7572 (1995).
32. O. König *et al.*, *J. Am. Chem. Soc.* **119**, 10632 (1997).
33. T. Weber, M. A. Estermann, H.-B. Bürgi, *Acta Crystallogr. B* **57**, 579 (2001).
34. M. D. Hollingsworth, A. R. Palmer, *J. Am. Chem. Soc.* **115**, 5881 (1993).
35. A. Yokoo, I. Yokohama, H. Kobayashi, T. Kaino, *J. Opt. Soc. Am. B* **15**, 432 (1998).
36. M. Irie, S. Kobatake, M. Horichi, *Science* **291**, 1769 (2001).
37. M. Albrecht, M. Lutz, A. L. Spek, G. van Koten, *Nature* **406**, 970 (2000).
38. J. M. McBride *et al.*, *Science* **234**, 830 (1986).
39. M. D. Hollingsworth *et al.*, *J. Am. Chem. Soc.* **124**, 2094 (2002).
40. M. E. Brown, M. D. Hollingsworth, *Nature* **376**, 323 (1995).
41. M. D. Hollingsworth *et al.*, *Science* **273**, 1355 (1996).
42. M. D. Ward, *Chem. Rev.*, **101**, 1697 (2001).
43. F.-J. Meyer zu Heringdorf, M. C. Reuter, R. M. Tromp, *Nature*, **412**, 517 (2001).
44. C. B. Aakeröy, A. M. Beatty, D. S. Leinen, *Angew. Chem. Int. Ed.* **38**, 1815 (1999).

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