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Conformational Polymorphism in Organic Crystals

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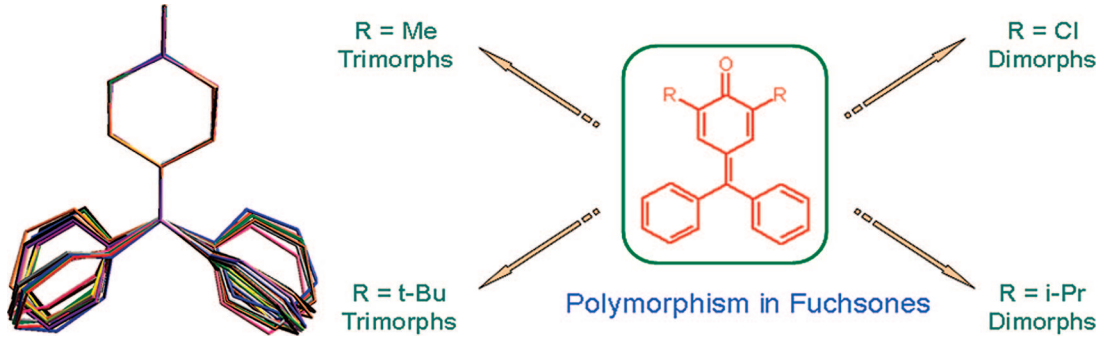

Polymorphs are different crystalline modifications of the same chemical substance. When different conformers of the same molecule occur in different crystal forms, the phenomenon is termed conformational polymorphism. Occasionally, more than one conformer is present in the same crystal structure. The influence of molecular conformation changes on the formation and stability of polymorphs is the focus of this Account.

X-ray crystal structures of conformational polymorphs were analyzed to understand the interplay of intramolecular (conformer) and intermolecular (lattice) energy in the crystallization and stability of polymorphs. Polymorphic structures stabilized by strong O−H···O/N−H···O hydrogen bonds, weak C−H···O interactions, and close packing were considered. 4,4-Diphenyl-2,5-cyclohexadienone (**1**) and bis(*p*-tolyl) ketone *p*-tosylhydrazone (**3**) are prototypes of C−H···O and N−H···O hydrogen-bonded structures. Distance−angle scatter plots of O−H···O and C−H···O hydrogen bonds extracted from the Cambridge Structural Database indicate that polymorphs with a larger number of symmetry-independent molecules (high Z') generally have better interactions when compared with the polymorphs with lower Z' values, with the implication that these symmetry-independent molecules have different conformations. Since molecular conformer (E_{conf}) and crystal lattice (U_{latt}) energy differences are of the same magnitude in organic crystals (typically <5 kcal mol^{-1}), situations wherein these two factors compensate or cancel one another are illustrative. Calculation of conformer and lattice energies using Gaussian 03 and Cerius^2 in 23 recently published polymorph sets shows that a strained conformer (higher E_{conf}) is stabilized by stronger interactions or better crystal packing (lower U_{latt}) in two-thirds of the cases, whereas there is no energy balance in the remaining structures.

Organic molecules with flexible torsions and low-energy conformers have a greater likelihood of exhibiting polymorphism because (1) different conformations lead to new hydrogen -bonding and close-packing modes and (2) the tradeoff reduces the total energy difference between alternative crystal structures. As a test case, polymorph promiscuity in fuchsones (**6**) is related to the conformational diversity at the *exo*-methylene phenyl rings and the small energy difference computed for dimethyl fuchsone polymorphs. These ideas find application in the design of putative pharmaceutical polymorphs and crystal structure prediction.

Introduction

Molecular conformation is a subtle but important property in the chemistry of the organic solid state.[1] Rotations about single bonds (intramolecular torsions) are worth 1−3 kcal mol^{-1} but can be as high as 8 kcal mol^{-1} due to steric factors or restricted rotation.[2] This Account discusses the relationships between conformational changes in a molecule and the formation and stability of crys-

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talline polymorphs that contain these different conformations. Hydrogen bonding is perhaps the most important discriminating cohesive force in directing the crystallization of organic molecules.[3] The nature of strong or conventional hydrogen bonds (4−15 kcal mol^{-1}), such as O−H···O, N−H···O, or O−H···N, is well-studied in organic and biological structures.[4] Weak hydrogen bonds (1−4 kcal mol^{-1}), for example, C−H···O, C−H···N, and N−H···π, are equally significant in crystal packing.[5,6] The weakest van der Waals and dispersive interactions (0.5−1.0 kcal mol^{-1}) are worth about the thermal energy of atoms at 300 K ($RT \sim 0.6$ kcal mol^{-1}). Notably, the energies of *intra*molecular torsions and *inter*molecular nonbonded interactions lie in the same range (0.5−10 kcal mol^{-1}). Therefore, there is an immediate possibility that conformationally flexible systems are prone to polymorphism.

In typical cases, a crystal form with a favorable single bond torsion finds an alternative polymorph where a slightly disfavored torsional geometry is compensated by a better C−H···O or van der Waals interaction. Alternatively, an extreme deformation of one torsion angle or several small deformations may be allowed in a new polymorph that optimizes a strong hydrogen bond geometry. Thus, molecular conformation and hydrogen bonding can influence each other and in turn the overall crystal packing. In a classical example, the flat conformation of *ortho*-H biphenyl is favored in the solid state although it lies ~1.5 kcal mol^{-1} above the lowest (gas-phase) energy conformation, which has an inter-ring twist angle of 44°.[7] The herringbone T-motif stabilizes the metastable planar conformation in biphenyl crystal structures. Brock and Minton[8] referred to the stabilization of strained conformers by crystal packing forces as a systematic effect, a term that continues to be used in the literature.[2]

Crystallization may be viewed as the directed assembly of close to an Avogadro number of molecules in an ordered, periodic, and infinite lattice.[9] However, crystal structures are not necessarily the global free energy minima of solid-state supramolecular assemblies.[10] That polymorphs[11,12] represent metastable structures on the free energy landscape was stated by Ostwald[13] over a century ago in his famous Rule of Stages, "When leaving a metastable state, a given chemical system does not seek out the most stable state, rather the nearest metastable one that can be reached with minimum loss of free energy." In a contemporary interpretation, Desiraju[14] formulated this dichotomy in crystallization as the formation of kinetic and thermodynamic products (crystals) via a Curtin−Hammett-like reaction pathway.

McCrone[15] defined polymorphism as "the existence of a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state. Figure 1 illustrates how changes in molecular conformation lead to different supramolecular arrangements of conformational polymorphs.[16] In crystallography terminology, Z' is the number of formula units in the unit cell (Z) divided by the number of independent general positions for that space group.[17] For the present discussion, Z' is the number of crystallographically unique molecules or conformers that will tessellate in space to build the crystal structure. Hydrogen bonding, systematic effects, and multiple conformers in crystalline polymorphs of some organic molecules (Figure 2) are discussed in this Account. Industrial interest in polymorphism is rapidly growing because it impacts pharmaceutical form discovery, patenting, and drug formulation.[18,19] Crystal engineering and

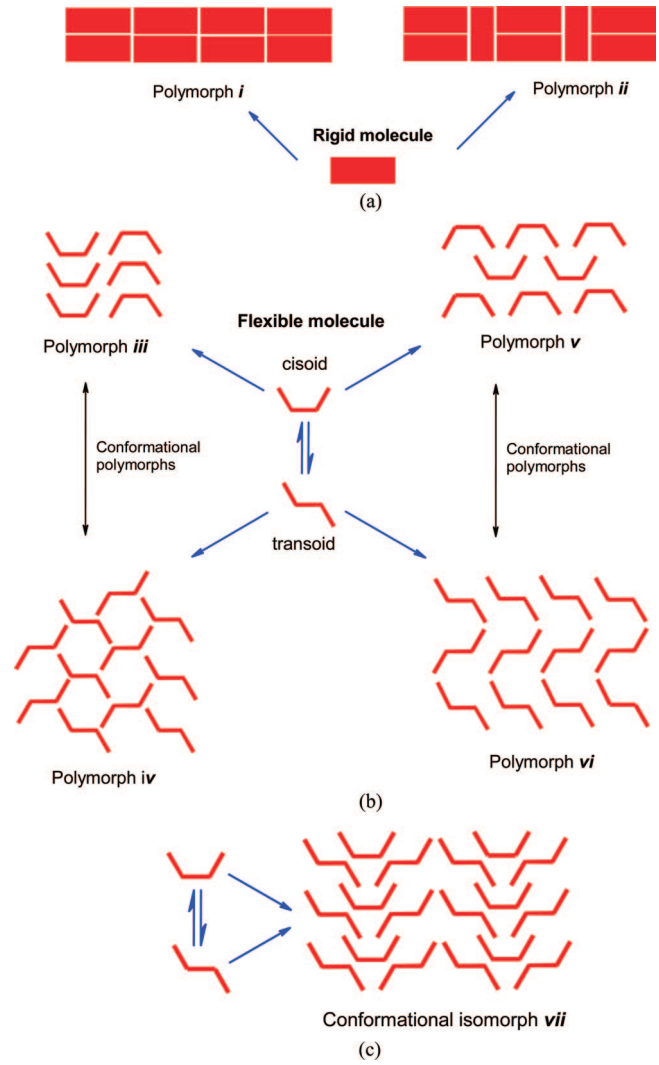

FIGURE 1. (a) Schematic representation of polymorphs *i* and *ii* for a rigid molecule, (b) a conformationally flexible molecule has a greater number of packing arrangements, *iii*−*vi*, and (c) two symmetry-independent molecules ($Z' > 1$) in conformational isomorph *vii*.

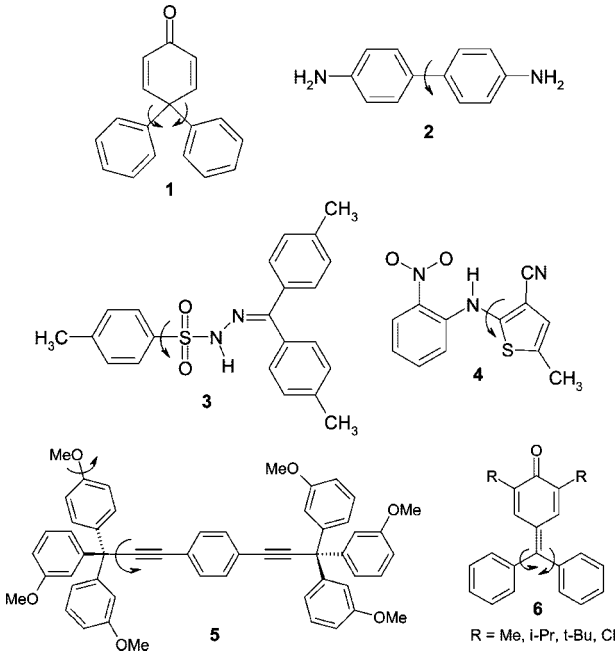

FIGURE 2. Some conformationally flexible molecules that exhibit polymorphism. The main bond torsions are indicated with arrows.

supramolecular isomerism in coordination polymers[20] and the interplay of hydrogen bonding and coordination geometry in malleable metal−organic systems[21] are reviewed elsewhere.

Conformational Polymorphs

Our first encounter with polymorphism was serendipitous. Photochemical rearrangements of 4,4-diphenyl-2,5-cyclohexadienone (**1**) have been studied for decades,[22] but its crystal chemistry was unexplored until 1998.[23] Compound **1** appeared to be a proof-of-concept molecule for crystal engineering of the benzoquinone C−H···O tape.[24] However, reality proved to be a surprise. Dienone **1** afforded three concomitant polymorphs,[25] ***A***, ***B***, and ***C***, upon crystallization from EtOAc/*n*-hexane. Addition of CH_2Cl_2 to the same solution afforded form ***D***, and a fifth form (***E***) was crystallized from EtOH/CH_2Cl_2.[26] Crystal structures ***C*** and ***E*** "disappeared" after our initial result. They converted to form ***B***, an occupational hazard for crystallization chemists.[27] The four polymorphs of **1** set a record of 19 molecular conformers (Figure 3) in X-ray crystal structures and the high Z' of 12 in form ***C*** (see molecules in Figure S1, Supporting Information) is rare among organic polymorph sets in the Cambridge Structural Database[28] (Table 1).

The abundance of polymorphism in **1** was traced to the presence several low-lying conformers (0−2 kcal mol^{-1}) through rotation about the $C_{quinone}$−C_{phenyl} single bond. Conformer energies (E_{conf}) vary as ***B*** < ***D*** < ***A***, whereas form ***A*** < ***D*** < ***B*** in lattice energy (U_{latt}) values (Table 2).[29] From the dynamic equilibrium mixture of conformers at ambient to 100 °C ($\Delta E_{conf} \approx RT$), one or more conformations crystallize in a particular form at supersaturation conditions. Because of different orientations of phenyl rings, the (Ph)C−H···O═C interactions have different geometry (2.2−2.8 Å, Figure S2, Supporting Information) and strength in different crystal structures. The formation of polymorphs ***A***−***D*** mediated via one or more conformers and C−H···O helix and dimer synthons ***I***−***III*** (Figure 3) is therefore understandable, at least in hindsight.

Very simple, almost classic, molecules can have a rich structural chemistry. Rafilovich and Bernstein[30] reported four polymorphs of benzidine (**2**). Forms **I**−**IV** have rare and unusual Z' values of 4.5, 3, 1.5, and 4.5 (BENZIE, Table 1). Form **III** transformed to ***I*** at 90−100 °C in an endothermic solid−solid phase change measured by differential scanning calorimetry (DSC) and hot stage microscopy (HSM), making it an enantiotropic system according to the heat of transition rule.[31] Form ***II*** is the thermodynamic phase of benzidine. The 15 planar and twisted conformers in tetramorphs of **2** (the planar half-molecules reside on the inversion center) arise due to rotation about the central biphenyl bond.[8] Different notations (Roman or Arabic numerals or letters) are in vogue to designate polymorphs. Polymorphs are indicated with bold face, italic font in this Account.

Intramolecular and intermolecular energy compensation, or systematic effects, are easier to quantify in conformational polymorphs ***1***−***3*** of bis(*p*-tolyl) ketone *p*-tosylhydrazone (**3**) because $Z' = 1$ in each structure. An unusual structural feature in **3** is that the first polymorph contained the expected N−H···O═S dimer but N−H···O hydrogen bonding is completely absent in forms ***2*** and ***3*** (Figure 4). Such polymorph pairs of a hydrogen-bonded structure and another non-H-bonded form of the same molecule are uncommon. The use of available strong hydrogen bond donors and acceptors is almost axiomatic.[32] Among molecules that can make O−H···O, N−H···O, and O−H···N hydrogen bonds, there are only two reported examples of H-bonded and close-packed (no H bonds) polymorph pairs.[33,34]

Forms ***1*** and ***3*** of molecule **3** were assigned as kinetic and thermodynamic states.[35] (1) The less stable polymorph was isolated first according to Ostwald's rule. (2) Form ***3*** has higher density and melting point than form ***1*** (1.29, 1.24 g cm^{-3}; 159−160, 142−143 °C). (3) Lattice energy of polymorph ***3*** is lower than that of form ***1*** (Table 3). Crystallization of form ***2*** could not be reproduced[27] subsequent to the isolation of stable polymorph ***3***. Of the three torsion angles τ_1, τ_2, and τ_3 in tosylhydrazone **3** (Figure 5), the maximum variation is at the

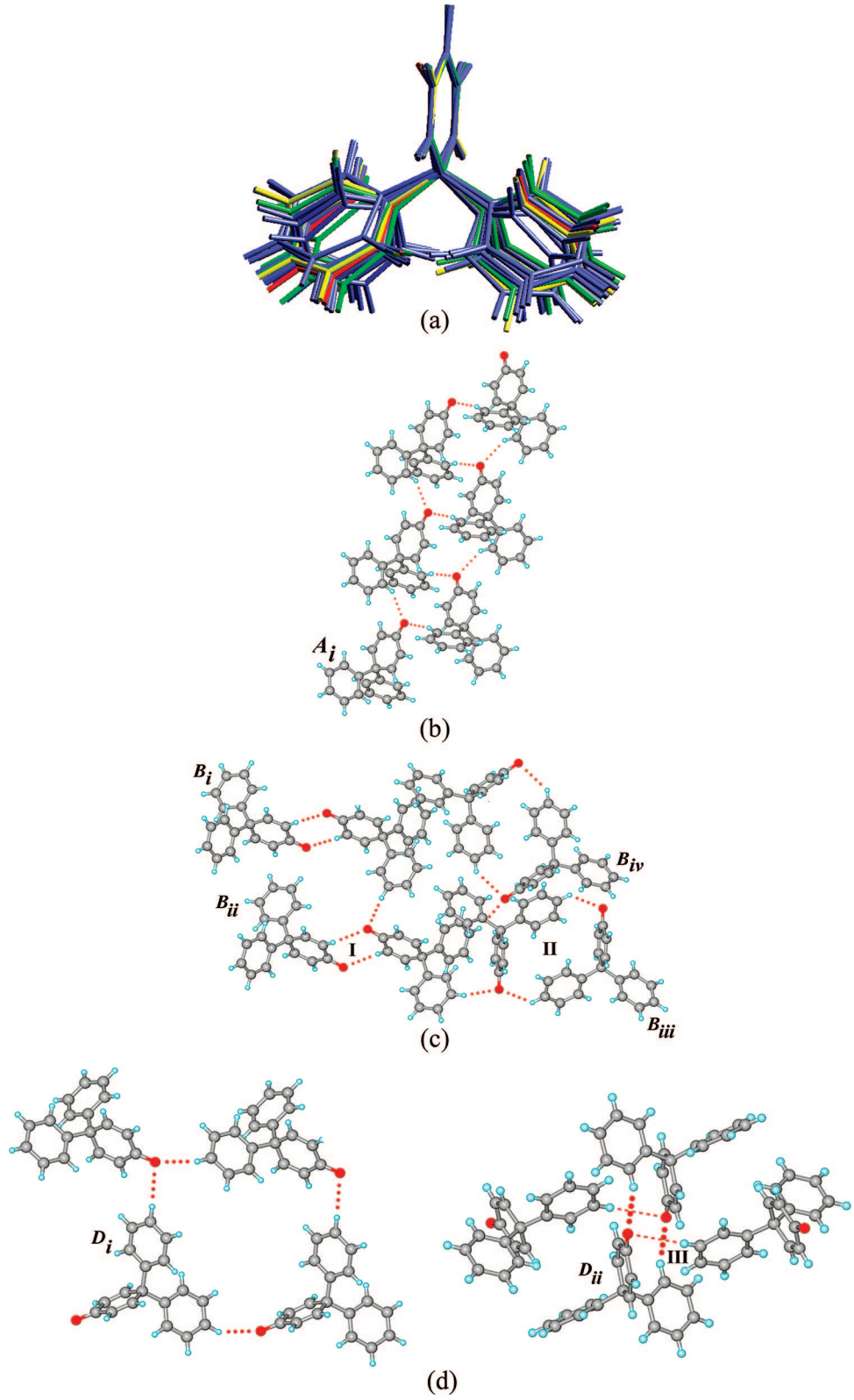

FIGURE 3. (a) Overlay of 19 symmetry-independent conformers of form ***A*** (red), form ***B*** (green), form ***C*** (blue), and form ***D*** (yellow) and (b−d) conformers $\boldsymbol{A}_i$, $\boldsymbol{B}_i$, $\boldsymbol{B}_{ii}$, etc., and C−H···O helix and dimer synthons ***I***−***III*** mediate different crystal packing arrangements in polymorphs ***A***, ***B***, and ***D*** ($Z' = 1$, 4, and 2) of molecule **1**. Form **C** (not shown, $Z' = 12$) is similar to ***B***.

sulfonamide moiety, so E_{conf} was computed as a function of τ_1. The observed conformers of **3** in crystal structures are within 10° torsion angle (~5 kcal mol^{-1}) of the minimum energy at $\tau_1 = 60°$. Thermodynamic form ***A*** is more stable

TABLE 1. Polymorphs with ≥3 Forms and High $Z' > 4$ in Organic Crystals

CSD Refcode	no. of polymorphs	Z' value
BENZIE	4	4.5
DUVZOJ	3	6
HEYHUO	4	12
IFULUQ	5	8
THIOUR	3	4.5
ZZZVTY	3	5

TABLE 2. Conformer Energy (E_{conf}, Spartan 04) and Lattice Energy (U_{latt}, Cerius^2) of Molecule **1**[a]

polymorph	U_{latt}, COMPASS	E_{conf},[b] HF/6-31G**	$E_{total} = U_{latt} + E_{conf}$
A	0.00	1.22	1.22
B	1.03	0.46	1.49
D	0.82	1.16	1.98

[a] Energy is reported in kcal mol^{-1} per molecule. Form **C** is excluded because of high *R*-factor (0.112). E_{conf} = 2.8−8.9 kcal mol^{-1}. [b] Mean energy of multiple conformers relative to the gas-phase minimum.

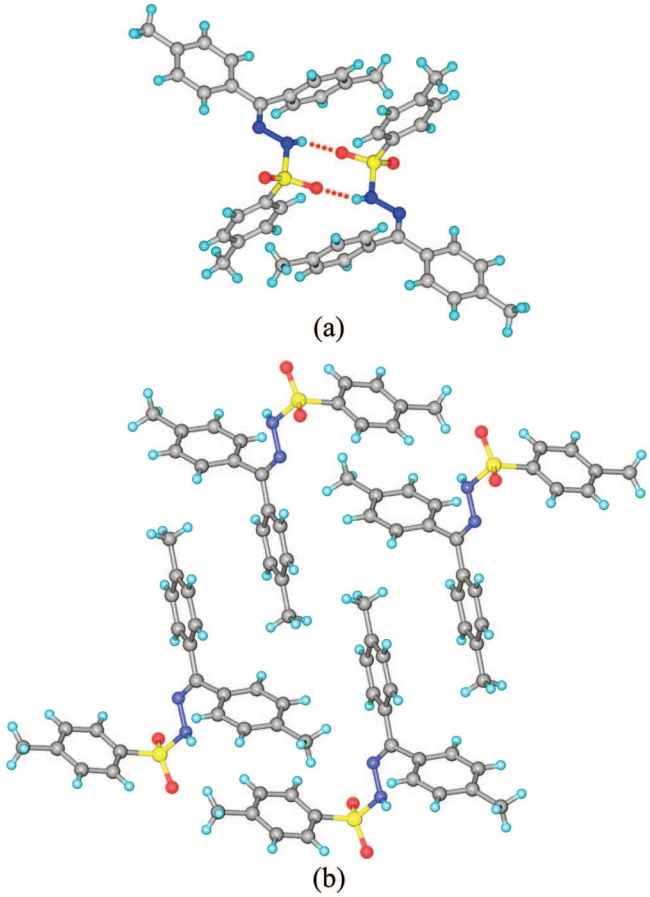

FIGURE 4. (a) N−H···O=S dimer in form ***1*** of tosylhydrazone **3**, (b) interdigitation of tolyl rings in form ***3***. There are no N−H···O hydrogen bonds in structures ***2*** and ***3***. Crystal packing in form ***2*** (not shown) is similar to that in form ***3***.

than form ***B*** (molecule **1**) and form ***3*** is more stable than form ***1*** (molecule **3**) based on DSC, HSM, and powder X-ray diffraction.[29,35] These experimental observations are consistent with E_{total} ($U_{latt} + E_{conf}$) rankings but not U_{latt} values (Tables 2 and 3). Notably, the transient, disappearing nature of forms ***C*** and ***2*** (of compounds **1** and **3**, respectively) is rationalized by their highly strained conformers. All this reinforces the importance of accounting for the E_{conf} contribution. The gain or penalty from E_{conf} must be added or subtracted to U_{latt} before validating computed energies with experimental polymorph stabilities.

TABLE 3. E_{conf} (Gaussian 03, B3LYP/6-31G(d,p)), U_{latt} (Cerius^2, COMPASS), and E_{total} of Molecule **3** (in kcal mol^{-1}) Relative to the Minimum Crystal Conformer and Lattice Energy

polymorph	τ_1	U_{latt}	E_{conf}	E_{total}
form ***1***	65.9	3.39	0.00	3.39
form ***2***	70.3	2.42	6.29	8.71
form ***3***	62.4	0.00	0.85	0.85

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (**4**), or ROY, is the archetype conformational polymorph with its red, orange, and yellow crystal colors arising from different molecular conformations in different structures.[36] Polymorphs of **1** and **2** have multiple molecular conformers in the asymmetric unit (conformational isomorphs), whereas **3**, **4**, and methacrylamide[37] polymorphs have one symmetry-independent molecule but in different conformations (conformational polymorphs).

Multiple Z' in Polymorphic Sets

High Z' is an uncommon and enigmatic event. Z' is ≤1 (usually 1 or 0.5) in 87% of structures; less than 12% of "organic" crystal structures have $Z' > 1$.[38] Steed's[39] seminal review on high Z' in crystal structures and Brock's[40] crystallographic studies on alcohols led us to summarize some of the reasons for multiple molecules in crystals.[29] (1) The "packing problem" of awkwardly shaped molecules is resolved through the presence of multiple molecules or conformers, for example, biphenyls in twisted conformation have $Z' > 1$. (2) Alcohols and phenols often aggregate as O−H···O bonded clusters of σ-cooperative chains and helices. A conflict or frustration between the demands of directional hydrogen bonding and isotropic space filling is reconciled through pseudosymmetric $Z' > 1$ packing, for example, cholesterol $Z' = 8$, 16. (3) There are several low-lying, interconverting conformers in solution and more than one may crystallize simultaneously because of kinetic factors. The third reason usually applies to multiple Z' in conformational polymorphs.

We analyzed the factors responsible for high Z' in polymorphic sets[41] because of the simplifying factor that the molecular species is the same. A distance−angle scatter plot of C−H···O hydrogen bonds in polymorphs ***A***−***D*** of **1**

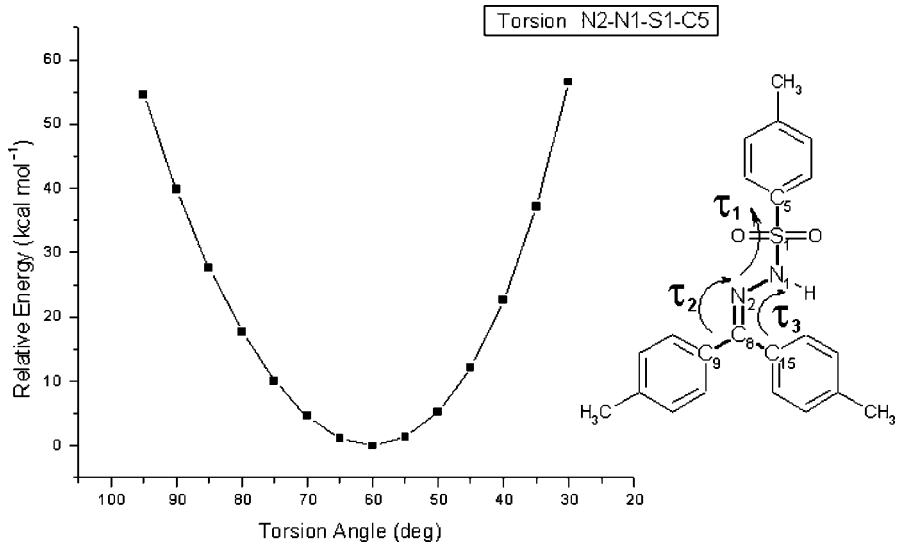

FIGURE 5. Potential energy curve of molecule **3** as a function of τ_1 computed in Gaussian 03, B3LYP/6-31G(d,p). The shallow curve near the minimum at $\tau_1 = 60°$ affords conformational diversity ($\Delta\tau_1 = \pm 10°$) at a small energy penalty ($\Delta E = 5$ kcal mol^{-1}). τ_2 and τ_3 variation in crystalline conformers is <4°.

showed that the more significant near-linear interactions (θ = 150−180°) are shorter (stronger) in the higher Z' polymorph. The shortest C−H···O in form ***C*** = 2.30 Å, ***B*** = 2.33 Å, ***D*** = 2.47 Å, and ***A*** = 2.54 Å (Figure S2, Supporting Information).[29] Our solitary observation in a tetramorph set was confirmed in crystal structures published about the same time.[42,43]

Data mining to extract new structural trends is an important research goal in chemical crystallography.[28] Even though the CSD contains over 415 000 entries, the number of accurate crystal structures that satisfy the requisite criteria could be small. There are 38 neutral organic polymorph sets having $Z' \geq 1$ in molecules without competing OH/NH groups.[44] Strong hydrogen-bonding groups were excluded from the polymorph subdatabase to minimize structural interference in weakly bonded crystals. Geometric data in C−H···O distance−angle scatter plots were classified into two categories: the higher Z' polymorph has shorter C−H···O interactions in 26 cases, while the reverse situation is true in 12 examples. The more significant short and linear interactions (<2.3 Å and >150°) are more frequent in high Z' polymorphs. There are 13/194 red dots (high Z') compared with 3/77 blue dots (low Z') in the upper left quadrant of the scatter plot (Figure 6). That the high Z'−strong C−H···O correlation is followed in 26 out of 38 polymorph sets, or in 68% of cases, is quite good given the relatively diffuse geometry and moderate strength−length relation of weak C−H···O interactions.[5,6] The accepted notion that high Z' in alcohol/ phenol crystal structures is due to H bond stabilization[40] was evaluated statistically. Now the higher Z' structure has shorter O−H···O bond distances in 22/32 sets (40/116 red interactions compared with 14/47 blue dots at <1.8 Å, >160° cutoff), while the converse is true in 7 cases (69% positive correlation; 3 pairs were excluded because crystal structures were determined at different temperatures or the distance difference is too small). The interaction geometry in all 70 crystal structure sets of high and low Z' is given in the Supporting Information to ref 44. There is evidence of a connection between hydrogen bond strength and multiple molecules in the asymmetric unit. However, the trend is derived from a small subset of hits in the current database. About 150 polymorph sets of variable Z' would make a statistically robust subset. The H bond strength−high Z' relation will surely refine over the years as additional polymorphs and new systems are deposited (see growth in Table S1, Supporting Information). We note that that the behavior of N−H···N interactions[30,45] (Figure S3, Supporting Information) is similar to that of C−H···O and O−H···O bonds.

Analysis of the interaction geometry in polymorph sets suggests that enthalpy is important in bringing together multiple molecules during crystal nucleation because high Z' crystal structures have shorter (stronger) hydrogen bonds than the low Z' polymorphs.[44] We postulate that clusters of molecules sustained by stronger interactions carry over from solution to the solid state without achieving identical conformation or symmetry adjustment, leading to multiple molecules and pseudosymmetry in the crystal lattice, that is, $Z' > 1$. Whereas this has been noted in crystal structures sustained by O−H···O chains and helices[46−48] and those crystallized from the melt,[49] our database results generalize these arguments and extend them to exclusively C−H···O bonded molecular crystals.[29,44]

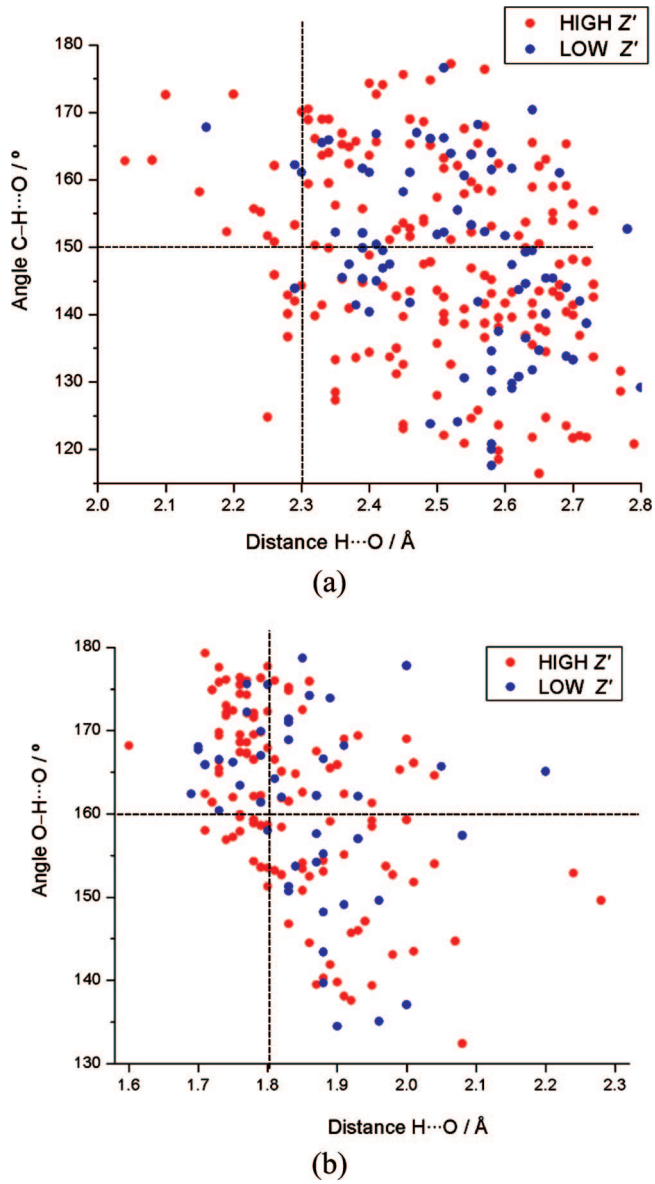

FIGURE 6. (a) Short C−H···O interactions are more numerous in high *Z*′ (red) compared with low *Z*′ (blue) polymorphs and (b) H bond strength−high *Z*′ correlation for O−H···O hydrogen bonds is presented. The percentage population of red dots (high *Z*′ crystal structures) is higher in the short−linear quadrant (stronger H bonds). The cutoffs of 2.30 Å/150° for short C−H···O and 1.80 Å/160° for short O−H···O hydrogen bonds are based on the accepted criteria.[3−6] The higher frequency of red dots in the upper left quadrant persists even when the threshold is increased by 0.1 Å.

Conformational Flexibility and Polymorph Promiscuity

Two views have been expressed on whether conformationally flexible molecules are more likely to be polymorphic. Yu et al.[50] argued that when different conformers lead to different crystal structures, the effective concentration of the conformer that leads to the observed form(s) is lowered in the Boltzmann population, which reduces the degree of supersaturation, for example, crystallization of carbohydrates and alditols is affected by the relative energies of anomers in solution. Bernal[51] analyzed conformationally flexible molecules in the CSD and concluded that the likelihood of similar or different conformers in polymorphic crystals is comparable; that is, conformational flexibility neither hinders nor favors polymorph frequency. We analyze this issue from an energetic viewpoint.

How common are systematic effects, or conformer and lattice energy balance, in polymorphs? Polymorphic structures of flexible organic molecules published during the past decade to good crystallographic accuracy (*R*-factor < 0.08, 3D coordinates determined, no disorder) were culled from the literature, and their conformer and lattice energies were recalculated[52] to compare on a uniform scale. Since observed conformers in crystal structures can have different torsion angles compared with the gas-phase minimized state and are of often higher in energy, "constrained optimization" of the crystal conformer was performed. The main torsion angles were held fixed, but bond distances of all atoms were allowed to relax at the nearest local minimum. This $E_{confopt}$ value is a better match to the experimental conformer energy than the E_{conf} parameter of Tables 2 and 3 (heavy atoms fixed, only X−H bonds were optimized)[29,35] because even small deviations in bond distances amount to a heavy energy contribution.[16] For crystal structure energy (U_{latt}), small variations in cell parameters were permitted but not gross differences between the calculated and experimental lattice parameters. Such computational practices are well established.[2,29,35,53]

Energy values on 23 conformational polymorph sets (Figure 7) recomputed for this Account (Table S2, Supporting Information) vary slightly from those calculated in the original papers, because of different constraints or minimization methods or basis set or force field used, but the ranking order remains largely unchanged. What is pertinent to the present discussion is not the absolute U_{latt} and $E_{confopt}$ values, but the fact that $\Delta U_{latt} \approx \Delta E_{confopt}$. Notably, conformer and lattice energy are compensatory in 16 polymorph systems. Typical ΔU_{latt} values are small (∼1−4 kcal mol^{-1}), and they become smaller when $E_{confopt}$ destabilization is accounted ($\Delta E_{total} \approx 0.2-2$ kcal mol^{-1}). For example, the α and β polymorphs of *N*,*N*′-bis(*m*-nitrophenyl)urea (SILTOW, Figure 7) typify conformer and synthon energy compensation[54] to give polymorphs of very similar total energy. The planar, stable diphenyl urea conformer makes N−H···O$_{urea}$ and N−H···O$_{nitro}$ H bonds in the thermodynamic α form, whereas a twisted, strained conformer builds up the energetically favored N−H···O$_{urea}$ tape in the metastable β polymorph.

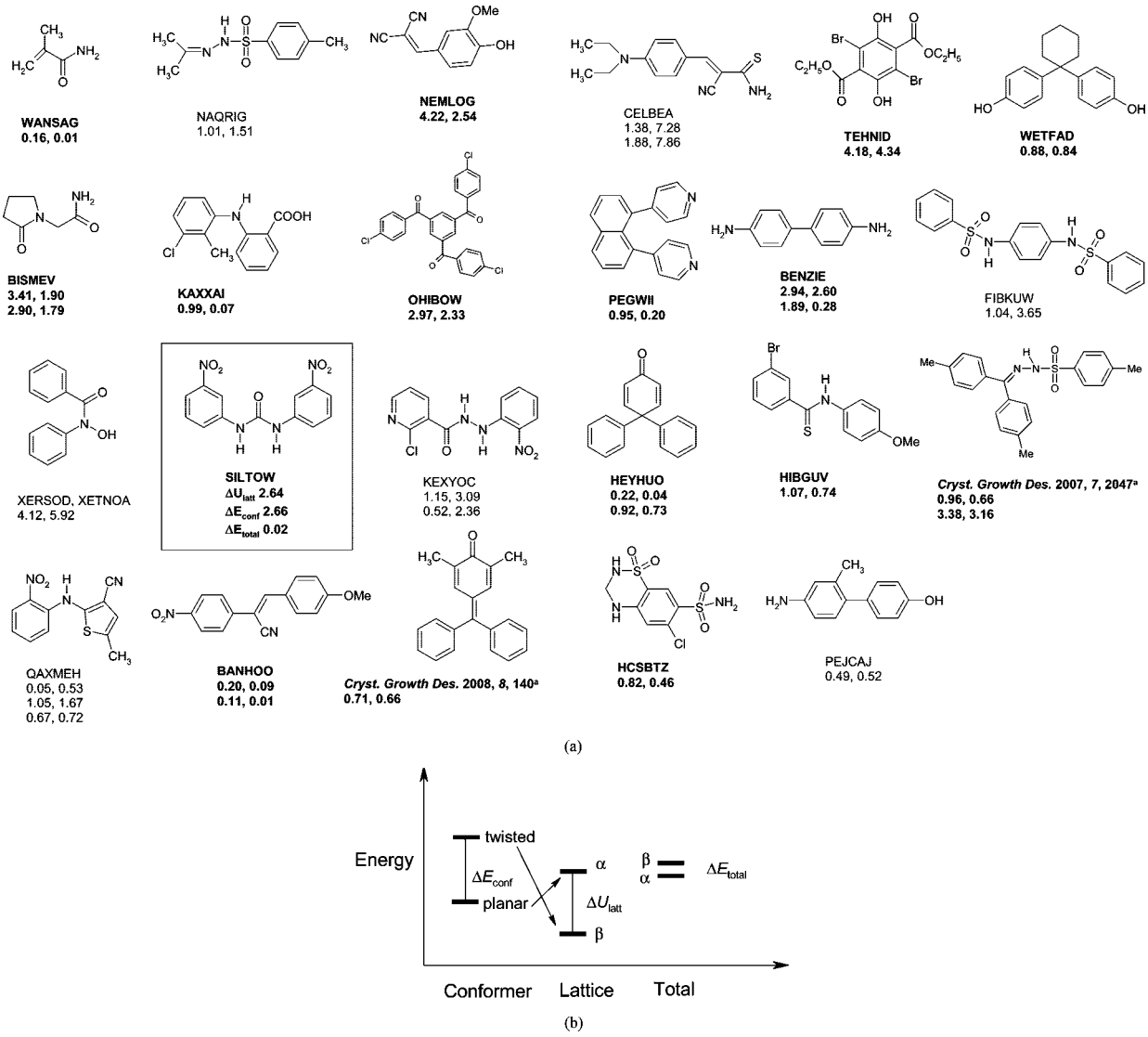

FIGURE 7. (a) Polymorph sets analyzed for conformer ($E_{confopt}$) and lattice (U_{latt}) energy compensation. ΔU_{latt} and ΔE_{total} values (kcal mol^{-1}, Table S2, Supporting Information) are mentioned below the CSD REFCODE. Systematic effects (16/23 cases) are shown in bold. (b) Qualitative energy diagram of *N*,*N*′-bis(*m*-nitrophenyl)urea (SILTOW) concomitant polymorphs based on values from Table S2. The total energies are very close due to intra- and intermolecular compensation. The "a" indicates that the data are too recent for inclusion in the CSD.

The phenylene rotor-linked gyroscope molecule **5** (Figure 2) with an almost flat conformer energy landscape has at least seven solid-state forms, of which four are polymorphs (***B***−***E***) and three are solvates (***A***, ***F***, ***G***).[55] A test system to evaluate the above-mentioned hypothesis is fuchsones or 4-(α,α-diphenylmethylene)-1,4-benzoquinone, **6**, which are conformationally labile at the *exo*-methylene-diphenyl moiety (see Figure 2). Four compounds are polymorphic among the seven 2,6-disubstituted fuchsones synthesized and screened using solution and melt crystallization methods.[56] Fuchsones are the first instance of a polymorphic family discovered by a molecular engineering approach. To summarize, since conformer strain and barrier to rotation are about 2−3 kcal mol^{-1} or lower, interconversion will be relatively facile to restock the reactive conformer via a Curtin−Hammett-like energy profile.[35] Sufficient concentration of the right conformer will be available in the liquid phase to give a particular polymorph in molecular systems at fast pre-equilibrium. We conclude that conformational flexibility in organic molecules increases the likelihood of polymorphism. (1) Several conformers are available in the crystallization milieu (solution or melt phase) to form different hydrogen bond synthons and close-packing motifs. (2) The intra- and intermolecular energy compensation reduces total crystal energy differences, which increases the likelihood of polymorphism. In this physical organic approach to understanding conformational polymorphism, we take gas-phase conformer values for molecules present in solid-state structures. The role of solvent in conformer stabiliza-

tion and crystal nucleation[57] is surely important but beyond the scope of this Account.

Conclusions and Future Directions

Systematic effects wherein high-energy conformers are stabilized by stronger hydrogen bonds or more efficient close packing in crystal structures are not a one-off occurrence. They are frequently observed in polymorphic crystal structures. The compensation of conformer destabilization by the crystal environment increases the likelihood of polymorphism in molecules with flexible torsions. This observation is of significant relevance in pharmaceutical polymorphism because typical drug molecules represent a confluence of conformational mobility and functional complexity.[18,19] Accounting for the energetic tradeoff in the equation $\Delta E_{total} = \Delta U_{latt} + \Delta E_{conf}$ is a necessary step in the experimental validation and crystal structure prediction of conformationally flexible molecules.[53] Cocrystals and their practical applications in pharmaceuticals[58] could not be covered due to space limitation. Starting with the unexpected discovery of aspirin form II in an attempted 1:1 cocrystallization with levetiracetam,[59] new polymorphs of one of the components were obtained in cocrystallizations.[30,44,60] Apart from pure organic systems, conformational isomerism in organic ligands amplify polymorphism opportunities in coordination polymers and hybrid solids.[20,21] Polymorphism is a fascinating research topic spanning the interests of physical, organic, inorganic, metal−organic, supramolecular, computational, and pharmaceutical chemists.

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Supporting Information Available. Symmetry-independent molecules, C−H···O and N−H···N scatter plots, growth of polymorph systems, and crystallographic and computational details on conformational polymorphs. This material is available free of charge via the Internet at http://pubs.acs.org.

BIOGRAPHICAL INFORMATION

Ashwini Nangia is Professor of Chemistry at the University of Hyderabad. After completing a M.Sc. from IIT Kanpur in 1983 he earned a Ph.D. degree from Yale University in 1988. Subsequent to graduate training and early research at Hyderabad in natural product synthesis (1989−1996), he has worked for the past decade on crystal engineering, polymorphism, and host−guest inclusion compounds and has published over 120 papers on these topics. He is an Associate Editor for *Crystal Growth & Design*.

FOOTNOTES

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REFERENCES

1 Corradini, P. X-ray Studies of Conformation: Observation of Different Geometries of the Same Molecule. *Chem. Ind. (Milan)* **1973**, *55*, 122–129.

2 (a) Buttar, D.; Charlton, M. H.; Docherty, R.; Starbuck, J. Theoretical Investigations of Conformational Aspects of Polymorphism. Part 1: o-Acetamidobenzamide. *J. Chem. Soc., Perkin Trans. 2* **1998**, 763–772. (b) Starbuck, J.; Docherty, R.; Charlton, M. H.; Buttar, D. A. Theoretical Investigation of Conformational Aspects of Polymorphism. Part 2. Diarylamides. *J. Chem. Soc., Perkin Trans. 2* **1999**, 677–691. (c) Bashkirava, A.; Andrews, P. C.; Junk, P. C.; Robertson, E. G.; Spiccia, L.; Vanderhoek, N. Conformational Polymorphism in N-(4′-methoxyphenyl)-3-bromothiobenzamide. *Chem.—Asian J.* **2007**, *2*, 530–538.

3 Steiner, T. The Hydrogen Bond in the Solid State. *Angew. Chem., Int. Ed.* **2002**, *41*, 48–76.

4 (a) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, 1991. (b) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.

5 Desiraju, G. R. Hydrogen Bridges in Crystal Engineering: Interactions without Borders. *Acc. Chem. Res.* **2002**, *35*, 565–573.

6 Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, U.K., 1999.

7 Almenningengen, A.; Bastiansen, O.; Fernholt, L.; Cyvin, N. N.; Cyvin, S. J.; Sandal, S. Structure and Barrier of Internal Rotation of Biphenyl Derivatives in the Gaseous State: Part 1. The Molecular Structure and Normal Coordinate Analysis of Normal Biphenyl and Perdeuterated Biphenyl. *J. Mol. Struct.* **1985**, *128*, 59–76.

8 Brock, C. P.; Minton, R. P. Systematic Effects of Crystal Packing Forces: Biphenyl Fragments with H atoms in All Four Ortho Positions. *J. Am. Chem. Soc.* **1989**, *111*, 4586–4593.

9 Dunitz, J. D.; Gavezzotti, A. Molecular Recognition in Organic Crystals: Directed Intermolecular Bonds or Nonlocalized Bonding. *Angew. Chem., Int. Ed.* **2005**, *44*, 1766–1787.

10 Rodríguez-Spong, B.; Price, C. P.; Jayashankar, A.; Matzger, A. J.; Rodríguez-Hornedo, N. General Principles of Pharmaceutical Solid Polymorphism: A Supramolecular Perspective. *Adv. Drug Delivery Rev.* **2004**, *56*, 241–274.

11 Bernstein, J. *Polymorphism in Molecular Crystals*,; Clarendon: Oxford, U.K., 2002.

12 Threlfall, T. L. Analysis of Organic Polymorphs. A Review. *Analyst* **1995**, *120*, 2435–2460.

13 Ostwald, W. The Formation and Changes of Solids. *Z. Phys. Chem.* **1897**, *22*, 289–330.

14 Desiraju, G. R. Cryptic Crystallography. *Nat. Mater.* **2002**, *1*, 77–79.

15 (a) McCrone, W. C. Polymorphism. In *Physics and Chemistry of the Organic Solid State*; Fox, D.; Labes, M. M.; Weissberger A., Eds.; Wiley-Interscience: New York, 1965, Vol. 2, pp 725−767. (b) McCrone's definition is the most widely accepted one but the meaning of the term polymorphism is an active topic even today. Desiraju, G. R. Polymorphism: The Same and Not Quite the Same. *Cryst. Growth Des.* **2008**, *8*, 3–5.

16 Bernstein, J. Conformational Polymorphism. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987, pp 471−518.

17 See http://www.dur.ac.uk/zprime for updates on Z'.

18 Hilfiker, R., Ed. *Polymorphism in the Pharmaceutical Industry*; Wiley-VCH: Weinheim, Germany, 2006.

19 Brittain, H. G. Polymorphism and Solvatomorphism 2005. *J. Pharm. Sci.* **2007**, *96*, 705–728.

20 Moulton, B.; Zaworotko, M. J. From Molecules to Crystal Engineering: Supramolecular Isomerism and Polymorphism in Network Solids. *Chem. Rev.* **2001**, *101*, 1629–1658.

21 Steed, J. W. Interplay of Non-covalent Bonds: Effect of Crystal Structure on Molecular Structure. In *Frontiers in Crystal Engineering*; Tiekink, E. R. T.; Vittal, J. J., Eds.; Wiley: Chichester, U.K., 2006, pp 67−90.

22 Zimmerman, H. E.; Schuster, D. I. The Photochemical Rearrangement of 4,4-Diphenylcyclohexadienone. Paper I on a General Theory of Photochemical Reactions. *J. Am. Chem. Soc.* **1961**, *83*, 4486–4488.

23 Anthony, A.; Desiraju, G. R.; Jetti, R. K. R.; Kuduva, S. S.; Madhavi, N. N. L.; Nangia, A.; Thaimattam, R.; Thalladi, V. R. Crystal Engineering. Some Further Strategies. *Cryst. Eng.* **1998**, *1*, 1–18.

24 The target C−H···O tape motif was realized not in **1** but in its *p*-phenyl derivative. Kumar, V. S. S.; Nangia, A. Inclusion Adducts of 4,4-Bis(4′-biphenylyl)-2,5-cyclohexadienone: A Clay Mimic Organic Host. *Chem. Commun.* **2001**, 2392–2393.

25 Bernstein, J.; Davey, J.; Henck, J.-O. Concomitant Polymorphs. *Angew. Chem., Int. Ed.* **1999**, *38*, 3440–3461.

26 Kumar, V. S. S.; Addlagatta, A.; Nangia, A.; Robinson, W. T.; Broder, C. K. R.; Mondal, R.; Evans, I. R.; Howard, J. A. K.; Allen, F. H. 4,4-Diphenyl-2,5-cyclohexadienone: Four Polymorphs and Nineteen Crystallographically Independent Molecular Conformations. *Angew. Chem., Int. Ed.* **2002**, *41*, 3848–3851.

27 Dunitz, J. D.; Bernstein, J. Disappearing Polymorphs. *Acc. Chem. Res.* **1995**, *28*, 193–200.

28 (a) Allen, F. H. The Cambridge Structural Database: A Quarter of a Million Crystal Structures and Rising. *Acta Crystallogr.* **2002**, *B58*, 380–388. (b) Nangia, A. Database Research in Crystal Engineering. *CrystEngComm* **2002**, *4*, 93–101. (c) Chisholm, J.; Pidcock, E.; van de Streek, J.; Infantes, L.; Motherwell, S.; Allen, F. H. Knowledge-Based Approaches to Crystal Design. *CrystEngComm* **2006**, *8*, 11–28. (d) The November 2006 release of the CSD (ConQuest, May 2007 update, >415 000 entries) was used to extract structural data on polymorphs reported in this Account. Polymorphs have the same six-letter REFCODE.

29 Roy, S.; Banerjee, R.; Nangia, A.; Kruger, G. J. Conformational, Concomitant Polymorphs of 4,4-Diphenyl-2,5-cyclohexadienone. Conformation and Lattice Energy Compensation in Kinetic and Thermodynamic Forms. *Chem.—Eur. J.* **2006**, *12*, 3777–3788.

30 Rafilovich, M.; Bernstein, J. Serendipity and Four Polymorphic Structures of Benzidine, $C_{12}H_{12}N_2$. *J. Am. Chem. Soc.* **2006**, *128*, 12185–12191.

31 Burger, A. Ramberger, R. On the Polymorphism of Pharmaceuticals and Other Molecular Crystals. I. Theory of Thermodynamic Rules. *Mikrochim. Acta* **1979**, *II*, 259–272. Several phase transition rules go as Burger and Ramberger Rules for monotropic and enantiotropic systems (see refs 11 and 25).

32 Etter, M. C. Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds. *Acc. Chem. Res.* **1990**, *23*, 120–126.

33 (a) Senju, T.; Hoki, T.; Mizuguchi, J. 2,9-Dichloro-5,12-dihydroquino[2,3-b]acridine-7,14-dione. *Acta Crystallogr.* **2005**, *E61*, o1061–o1063. (b) Senju, T.; Nishimura, N.; Hoki, T.; Mizuguchi, J. 2,9-dichloro-5,12-dihydroquino[2,3-b]acridine-7,14-dione (red phase). *Acta Crystallogr.* **2005**, *E61*, o2569–o2598.

34 Bacchi, A.; Bosetti, E.; Carcelli, M.; Pelagatti, P.; Pelizzi, G.; Rogolino, D. Triarylcarbinol Derivatives Barter Intermolecular Interactions to Accommodate Substituents and Create polymorphs. *CrystEngComm* **2006**, 233–244.

35 Roy, S.; Nangia, A. Kinetic and Thermodynamic Conformational Polymorphs of Bis(*p*-Tolyl) Ketone *p*-Tosylhydrazone. The Curtin—Hammett Principle in Crystallization. *Cryst. Growth Des.* **2007**, *7*, 2047–2058.

36 (a) Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. Thermochemistry and Conformational Polymorphism of a Hexamorphic Crystal System. *J. Am. Chem. Soc.* **2000**, *122*, 585–591. (b) Chen, S.; Guzei, I. A.; Yu, L. New Polymorphs of ROY and New Record for Coexisting Polymorphs of Solved Structures. *J. Am. Chem. Soc.* **2005**, *127*, 9881–9885.

37 Guo, C.; Hickey, M. B.; Guggenheim, E. R.; Enkelmann, V.; Foxman, B. M. Conformational Polymorphism of Methacrylamide. *Chem. Commun.* **2005**, 2220–2222.

38 Steiner, T. Frequency of Z′ Values in Organic and Organometallic Crystal Structures. *Acta Crystallogr.* **2000**, *B56*, 673–676.

39 Steed, J. W. Should Solid-state Molecular Packing Have to Obey the Rules of Crystallographic Symmetry? *CrystEngComm* **2003**, *5*, 169–179.

40 (a) Brock, C. P.; Duncan, L. L. Anomalous Space-Group Frequencies for Monoalcohols C_nH_mOH. *Chem. Mater.* **1994**, *6*, 1307–1312. (b) Lehmler, H.-J.; Robertson, L. W.; Parkin, S.; Brock, C. P. $Z' = 4$ Structure without Obvious Pseudosymmetry: Implications for the Formation of Solid-State Compounds. *Acta Crystallogr.* **2002**, *B58*, 140–147. (c) Brock, C. P. Crystal Packing in Vicinal Diols $C_nH_m(OH)_2$. *Acta Crystallogr.* **2002**, *B58*, 1025–1031. (d) Patrick, B. O.; Brock, C. P. S,S-1,2-Dicyclohexylethane-1,2-diol and Its Racemic Compound. A Striking Exception to Wallach's Rule. *Acta Crystallogr.* **2006**, *B62*, 488–497.

41 Gavezzotti, A.; Filippini, G. Polymorphic Forms of Organic Crystals at Room Conditions. Thermodynamic and Structural Implications. *J. Am. Chem. Soc.* **1995**, *117*, 12299–12305.

42 Chandran, S. K.; Nangia, A. Modulated Crystal Structure ($Z' = 2$) of α-D-Glucofuranose-1,2:3,5-bis(p-tolyl)boronate. *CrystEngComm* **2006**, *8*, 581–586.

43 Nichol, G. S.; Clegg, W. The Importance of Weak C—H···O Bonds and $\pi\cdots\pi$ Stacking Interactions in the Formation of Organic 1,8-Bis(dimethylamino) naphthalene Complexes with $Z' > 1$. *Cryst. Growth Des.* **2006**, *6*, 451–460.

44 Babu, N. J.; Nangia, A. High Z′ Polymorphs Have Shorter C-H···O Interactions and O-H···O Hydrogen Bonds. *CrystEngComm* **2007**, *9*, 980–983.

45 Zhang, Z.-Q.; Njus, J. M.; Sandman, D. J.; Guo, C.; Foxman, B. M.; Erk, P.; van Gelder, R. Diiminoisoindoline: Tautomerism, Conformations, and Polymorphism. *Chem. Commun.* **2004**, 886–887.

46 Das, D.; Banerjee, R.; Mondal, R.; Howard, J. A. K.; Boese, R.; Desiraju, G. R. Synthon Evolution and Unit Cell Evolution During Crystallization. A Study of Symmetry-Independent Molecules ($Z' > 1$) in Crystals of Some Hydroxy Compounds. *Chem. Commun.* **2006**, 555–557.

47 Gdaniec, M. On the Polymorphs of Pentafluorophenol and its 2:1 Cocrystal with Pentafluoroaniline. *CrystEngComm* **2007**, *9*, 286–288.

48 Aitipamula, S.; Nangia, A. Guest-Induced Supramolecular Isomerism in Inclusion Complexes of T-Shaped Host 4,4-Bis(4′-hydroxyphenyl)cyclohexanone. *Chem.—Eur. J.* **2005**, *11*, 6727–6742.

49 Sarma, B.; Roy, S.; Nangia, A. Polymorphs of Bis(4-hydroxyphenyl)cyclohexane and Multiple Z′ Structures by Melt and Sublimation Crystallization. *Chem. Commun.* **2006**, 4918–4920.

50 Yu, L.; Reutzel-Edens, S. M.; Mitchell, C. A. Crystallization and Polymorphism of Conformationally Flexible Molecules: Problems, Patterns, and Strategies. *Org. Process Res. Dev.* **2000**, *4*, 396–402.

51 Bernal, I. Is Polymorphism Caused by Molecular Conformational Changes? In *Models, Mysteries and Magic of Molecules*; Boeyens, J. C. A., Ogilvie, J. F., Eds.; Springer: New York, 2007; pp 137—165.

52 (a) Gaussian 03, DFT, B3LYP/6-31G (d,p) level, www.gaussian.com. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. Gaussian 03, Revision C.02; Gaussian, Inc., Wallingford, CT, 2004. (b) Cerius^2, COMPASS force field, www.accelrys.com.

53 (a) Nowell, H.; Price, S. L. Validation of a Search Technique for Crystal Structure Prediction of Flexible Molecules by Application to Piracetam. *Acta Crystallogr.* **2002**, *B61*, 558–568. (b) Nagel, N.; Bock, H.; Eller, P. Dimorphism and Inclusion Compounds of N,N′-Di(benzenesulfonyl)-p-phenylenediamine. *Acta Crystallogr.* **2000**, *B56*, 234–244. (c) Timofeeva, T. V.; Kinnibrugh, T.; Borbulevych, O. Y.; Averkiev, B. B.; Nesterov, V. N.; Sloan, A.; Antipin, M. Y. Vanishing Polymorphism of (2E)-2-cyano-3-[4-(diethylamino) phenyl]prop-2-enethioamide: X-ray Structural Study and Polymorph Prediction. *Cryst. Growth Des.* **2004**, *4*, 1265–1276. (d) Mitchell-Koch, K. R.; Matzger, A. Evaluating Computational Predictions of the Relative Stabilities of Polymorphic Pharmaceuticals. *J. Pharm. Sci.* **2007**, *96*, DOI: 10.1002/jps.21127.

54 Reddy, L. S.; Chandran, S. K.; George, S.; Babu, N. J.; Nangia, A. Crystal Structures of N-Aryl-N′—4-Nitrophenyl Ureas: Molecular Conformation and Weak Interactions Direct the Strong Hydrogen Bond Synthon. *Cryst. Growth Des.* **2007**, *7*, 2675–2690.

55 Nuñez, J. E.; Khuong, T.-F. V.; Campos, A. M.; Farfán, N.; Dang, H.; Karlen, S. D.; Garcia-Garibay, M. A. Crystal Phases and Phase Transitions in a Highly Polymorphogenic Solid-State Molecular Gyroscope with meta-Methoxytrityl Frames. *Cryst. Growth Des.* **2006**, *6*, 866–873.

56 Chandran, S. K.; Nath, N. K.; Roy, S.; Nangia, A. Polymorphism in Fuchsones. *Cryst. Growth Des.* **2008**, *8*, 140–154.

57 Baker, C. M.; Grant, G. H. A Solvent Induced Mechanism for Conformational Change. *Chem. Commun.* **2006**, 1387–1389.

58 Rodríguez-Hornedo, N., Ed. Special Section on Pharmaceutical Cocrystals. *Mol. Pharmaceutics* **2007**, *4*, 299—434.

59 (a) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. Z. The Predictably Elusive Form II of Aspirin. *J. Am. Chem. Soc.* **2005**, *127*, 16802–16803. (b) Bond, A. D.; Boese, R.; Desiraju, G. R. On the Polymorphism of Aspirin: Crystalline Aspirin as Intergrowths of Two "Polymorphic" Domains. *Angew. Chem., Int. Ed.* **2007**, *46*, 618–622.

60 Day, G. M.; Trask, A. V.; Motherwell, W. D. S.; Jones, W. Investigating the Latent Polymorphism in Maleic Acid. *Chem. Commun.* **2006**, 54–56.