# Conformational Polymorphs, Multiple Z′ Crystal Structures and Phase Transformations

*Ashwini Nangia*

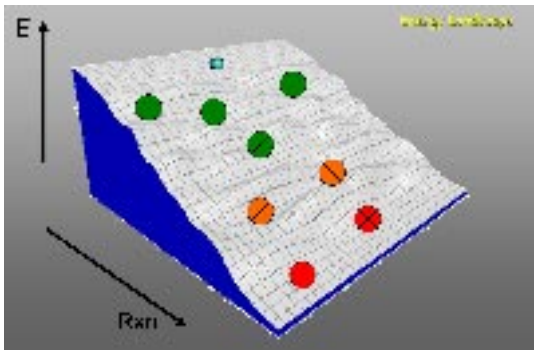
Abstract | Molecular conformer ($E_{conf}$) and crystal lattice energy ($U_{latt}$) contributions are of comparable magnitude in crystal structures of flexible molecules. Bond torsion variations about C–C single bonds are worth 1–3 kcal $mol^{-1}$ and hydrogen bonds, intermolecular interactions have energy of 1–10 kcal $mol^{-1}$. Both these energy factors should be considered in calculating the total crystal energy ($E_{total}$) of organic crystalline solids. Intra- and intermolecular contributions may be additive or cancel one another. Polymorphism is likely in molecular systems wherein molecular conformer and crystal energy effects compensate one other, i.e. a metastable conformer resides in a stable packing arrangement or a stable rotamer is present in a metastable crystal environment. Organic conformational polymorphs are found to be promiscuous in a small energy window of $<3$ kcal $mol^{-1}$. Polymorph clusters having different number of symmetry-independent molecules in the unit cell are discussed and their phase transformations monitored by variable temperature powder X-ray diffraction and differential scanning calorimetry. The final section deals with polymorphism in pharmaceuticals and the need to know the most stable polymorph of drug molecules.

## 1. Introduction

McCrone[1] 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' over 40 years ago. This broad definition is widely accepted in crystal engineering, materials science and pharmaceutical development.[2] The existence of polymorphs implies that free energy differences between various forms are small (0.5–4 kcal $mol^{-1}$, occasionally $<8$ kcal $mol^{-1}$) and that kinetic factors are important during crystal nucleation and growth. The importance of kinetics in crystallization was stated by Ostwald[3] over a century ago in his 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.' Thus when molecular aggregates or crystal nuclei proceed along the crystallization pathway, more often than not, one of the several crystal structures lying in metastable minima are isolated instead of the thermodynamic crystal structure (Figure 1). Molecular conformations, hydrogen bonding, packing arrangements, and lattice energies of the same molecule in different supramolecular environments may be compared in polymorphic structures. Polymorphs are ideal systems to study molecular structure—crystal structure–crystal energy relationships with a minimum number of variables, because differences arise due to molecular conformations, hydrogen

*School of Chemistry, University of Hyderabad, Hyderabad 500 046*
*ashwini_nangia@rediffmail.com*

Figure 1: As the high-energy species (blue) cascades down the energy landscape, it settles in metastable crystal structures (green), more stable ones (orange), and finally the thermodynamic form (red). Polymorphs occur when the same molecules crystallizes in more than one minima.




bonding, and crystal packing effects but not due to a different chemical species. There is keen interest in understanding polymorphism, the mechanism of crystal nucleation from solution, growing new crystal forms, controlling the selective growth of one form, transformations between polymorphs, and high-throughput crystallization of drugs.[4] Polymorphism is more widespread in pharmaceutical solids, with estimates of 30–50% in drug-like molecules,[5] compared to 4–5% polymorphic crystals in the Cambridge Structural Database (CSD).[6] Table 1 gives a historical overview of some important milestones in the development of polymorphism as a fully grown subject.

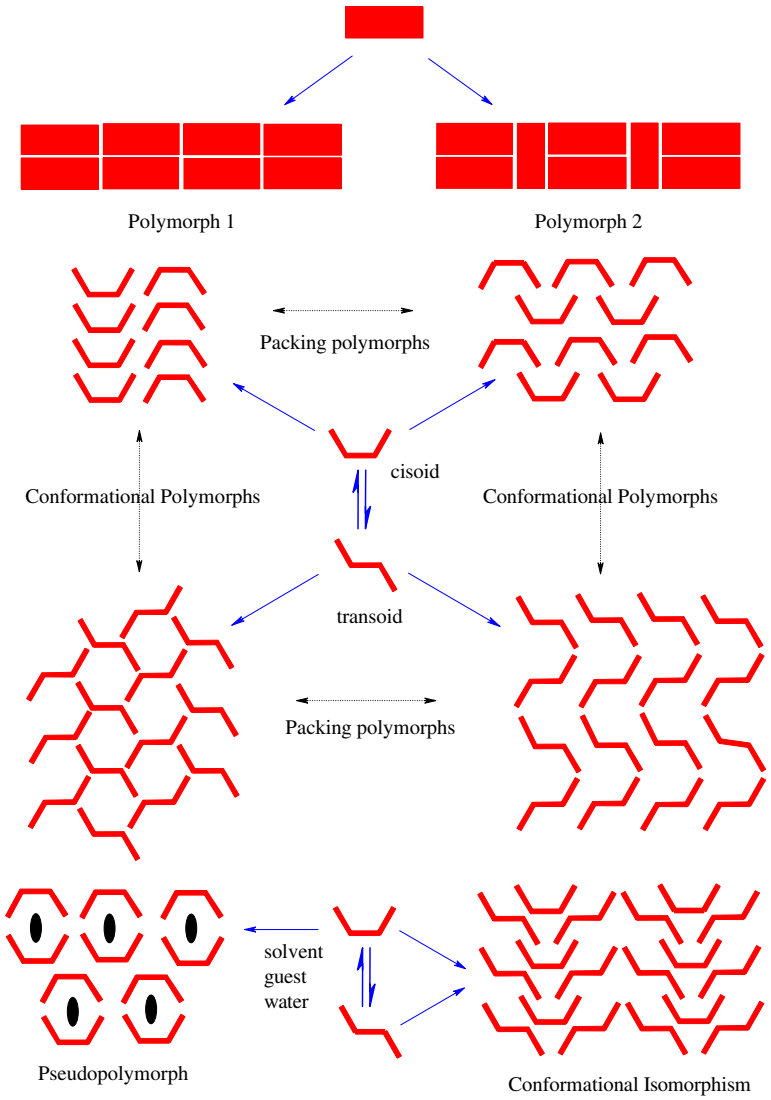
Among organic crystal structures, there is one example of a compound with nine polymorphs, 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (**1**), common name ROY[7] because of its red, orange and yellow colored polymorphic forms. Single crystal X-ray structures are reported for seven of these forms (QAXMEH), followed by 3 pentamorphs, 20 tetramorph clusters, and 124 trimorphic systems (Table 2). Interest in polymorphism is growing because different solid-state modifications can have different physical, chemical and functional properties such as melting point, stability, color, bioavailability, toxicity, pharmacological activity, nonlinear optical response, etc. Polymorph screening is a necessary, important step in the development of specialty chemicals, drugs and pharmaceuticals. The number of polymorphs reported is growing rapidly in the current decade (Table 3).

Polymorphs are classified according to the following terminologies. Concomitant polymorphs crystallize simultaneously from the same solvent and crystallization flask under identical crystal growth conditions. They may be viewed as supramolecular isomers in a chemical reaction. Conformational polymorphs occur for flexible molecules, i.e. those molecules that can adopt more than one conformation under the crystallization conditions (typically −10 to 150 °C). When different conformers of the same molecule are present in the same crystal structure the situation represents conformational isomorphs. Conformational isomorphism, the existence of multiple conformations in the same crystal structure, is closely related to the presence of more than one molecule/ion in the asymmetric unit, i.e.

Table 1: Important milestones in polymorphism during the last 200 years.

| | |
|---|---|
| 1798 | Klaproth concluded that calcite and aragonite have the same chemical composition $CaCO_3$ |
| 1822 | Mitscherlich identified different crystal forms of arsenate and phosphate |
| 1844 | Amici discovered polarizing microscope for visual characterization of solids |
| 1876 | Millard considered geometrical and structural basis in growing different forms of the same substance |
| 1891 | Lahman observed phase transformation in crystal forms |
| 1897 | Ostwald's famous 'Rule of Steps' on relative stability of polymorphs |
| 1906–19 | Organic crystal polymorphism in Groth's five volume collection |
| 1926 | Tamman's work on thermodynamic stability and relationships of polymorphs |
| 1937 | Bloom and Buerger's fundamental property changes in polymorphs |
| 1956–69 | McCrone's work on pharmaceutical and drug polymorphism |
| 1973 | Corradini coined the term conformational polymorphism |
| 1996 | Glaxo vs. Novopharm litigation on form I and II of ranitidine hydrochloride (Zantac) |
| 1998 | Unexpected appearance of stable, less soluble form II of ritonavir (Norvir) at Abbott |
| 2000–present | Several books, monographs, and reviews on polymorphism. Special issues of journals on crystallization, polymorphism and its industrial significance |

Figure 2: Polymorphs of rigid molecules and conformationally flexible molecules. Molecular conformation changes lead to diverse supramolecular arrangements in the solid state. Inclusion of solvent/guest/ water in the crystal lattice is pseudopolymorphism.




$Z' > 1$. The number of formula units (Z) divided by the number of independent general positions for that space group is Z′. Pseudopolymorphism[8] is the occurrence of the same molecule with different type or stoichiometry of solvent in the crystal lattice. These different situations in solid state forms are shown in Figure 2 and some molecular solids that exhibit conformational polymorphism are listed in Figure 3.

## Conformer and Lattice Energy Compensation

A molecule is defined by three parameters: bond distances, bond angles and torsion angles. Bond stretching and compression is insignificant to cause structural changes because of the high bond energies of covalent bonds (80–200 kcal $mol^{-1}$). The distortion of a single bond by 0.03 Å is worth 0.3 kcal $mol^{-1}$ while the values for double and triple bonds are proportionately higher (0.6–1.0 kcal $mol^{-1}$). Distortion of bond angle by 6–10 ° has the same energy penalty as bond distance changes of 0.03–0.05 Å. Rotation about C–C single bonds, or single bond torsions have energy requirement of 0.5–3.0 kcal $mol^{-1}$, which can be as high as 8-10 kcal $mol^{-1}$ due to steric factors and hindered rotation.[9] Bond angle and bond torsion deviations are approximately one and two orders of magnitude less energy expensive than bond stretching.

Table 2: CSD refcodes of organic polymorph clusters up to the recent update of the Cambridge Structural Database (May 2007 update).

| | | | | | |
|---|---|---|---|---|---|
| **Heptamorph (one)** | | | | | |
| QAXMEH | | | | | |
| **Pentamorph (three)** | | | | | |
| GLYCIN | IFULUQ | SUTHAZ | | | |
| **Tetramorphs (20)** | | | | | |
| ADULEQ | BISMEV | MABZNA | VIPKIO | | |
| AMBACO | CBMZPN | PYRZIN | VISKAJ | | |
| BENZIE | CILHIO | RUWYIR | WUWTOX | | |
| BEWKUJ | HEYHUO | STARAC | KELGEO | | |
| BIXGIY | KAXHAS | SLFNMB | TPEPHO | | |
| **Trimorphs[a] (124)** | | | | | |
| AMNTPY | DIYJUQ | GEHBAX | MBYINO | PHTHCY | UDAYUT |
| AWAKIS | DLABUT | GISRIJ | MBZYAN | PUBMUU | UJORIU |
| AZADAG | DLMSUC | HADKIG | MCHTEP | PUPBAD | UNEWUF |
| BALWEQ | DMANTL | HIMWIJ | METHOL | QOGNEF | WEFKIC |
| BANHOO | DMFUSC | HNIABZ | MEZKEH | RBTCNQ | WIRXAW |
| BIMYAX | DMMTCN | HYQUIN | MNIAAN | SAMPYM | WUWTIR |
| BIYSEH | DOBTUJ | IJETOG | NADQAL | SIFLOI | XINBEB |
| BOPKOG | DPYRAM | IMDIAC | NAGHOT | SIKLIH | YACTEC |
| BZCHOL | DUCKOB | IVADUE | NAPYMA | SILTOW | YERRUI |
| CENRIW | DUVFUV | JATFUF | NAZLAC | SLFNMA | YUYHIJ |
| COMXAD | DUVZOJ | JIBCIG | NIMFOE | SOBPEE | ZEPFAB |
| DATREV | ESTRON | JUSBUU | NOJHEZ | SULAMD | ZEXREZ |
| DBEZLM | FACRIK | KTCYQM | OCHTET | TAWRIT | ZOGQAN |
| DCBFRO | FAFWIS | LAURAC | PARQUI | TELYAK | ZZZHWI |
| DCLANT | FAWFOY | LAVMOK | PATSEJ | TEPHTH | ZZZIYE |
| DCLBEN | FOMNEB | LCYSTN | PATVEM | THIOUR | ZZZVTY |
| DEGGEB | FEGWAP | LILXIN | PCBZAM | TNBENZ | KEXYOC |
| DETBAA | FESKAP | MACCID | PDABZA | TORSEM | PETNEI |
| DHNAPH | FIDYIA | MALEHY | PEFTIE | TUHBAZ | QNACRD |
| DIMETH | FILGEM | MALOAM | PHBARB | TURPYB | |
| DIWWEL | GADSIO | MBPHOL | PNEOSI | UCECAG | |

[a] A recent report of conformational trimorph not yet included in the CSD update. N-(4′-methoxyphenyl)-3-bromothiobenzamide: A. Bashkirava, P. C. Andrews, P.C. Junk, E. G. Robertson,L. Spiccia and N. Vanderhoek, Chem. Asian J. 2 530 (2007).

Table 3: Statistics on the number of polymorph clusters for trimorphs and higher number of forms extracted from the CSD.

| | Gavezotti & Filipini[a] 1995 | Yu et. al.[b] 2000 | Kumar[c] 2002 | Yu et. al.[d] 2005 | As of June 2007[e] |
|---|---|---|---|---|---|
| three forms | 13 | 27 | 42 | 102 | 124 |
| four forms | 3 | 3 | 3 | 14 | 20 |
| five forms | none | none | one | one | 3 |
| six forms | none | none | one | one | none |
| seven forms | none | none | none | none | one |

[a] A. Gavezzotti, G. Filippini, J. Am. Chem. Soc.**117** 12299 (1995).
[b] L. Yu, G. A. Stephenson, C. A. Mitchell, C. A. Bunnell, S. V. Snorek, J. J. Bowyer, T. B. Borchardt, J. G. Stowell, S. R. Byrn, J. Am. Chem. Soc. **122** 585 (2000).
[c] V. S. S. Kumar, PhD thesis, University of Hyderabad (2002).
[d] S. Chen, I.A. Guzei, L. Yu, J. Am. Chem. Soc. **127** 9881 (2005).
[e] S. Roy, PhD thesis, University of Hyderabad (2007).

Figure 3: Chemical structures of some conformational polymorph systems.

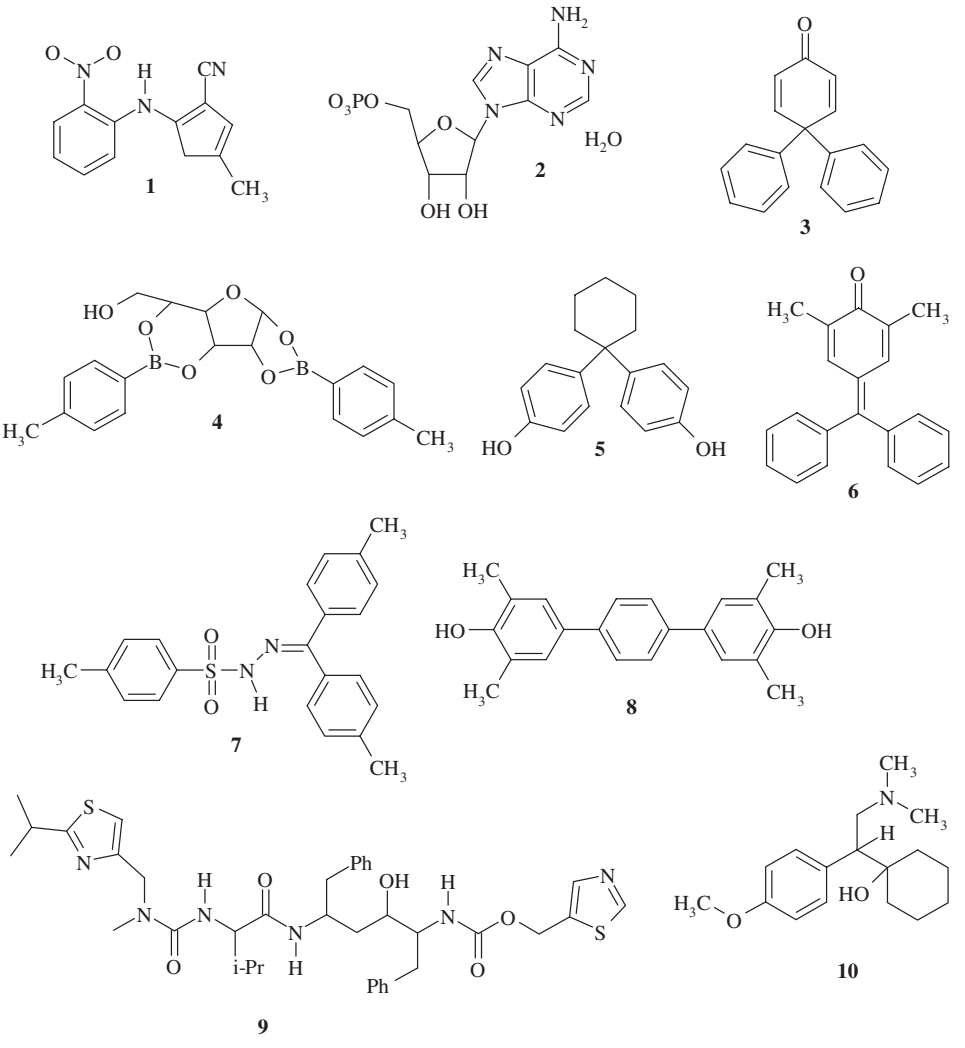
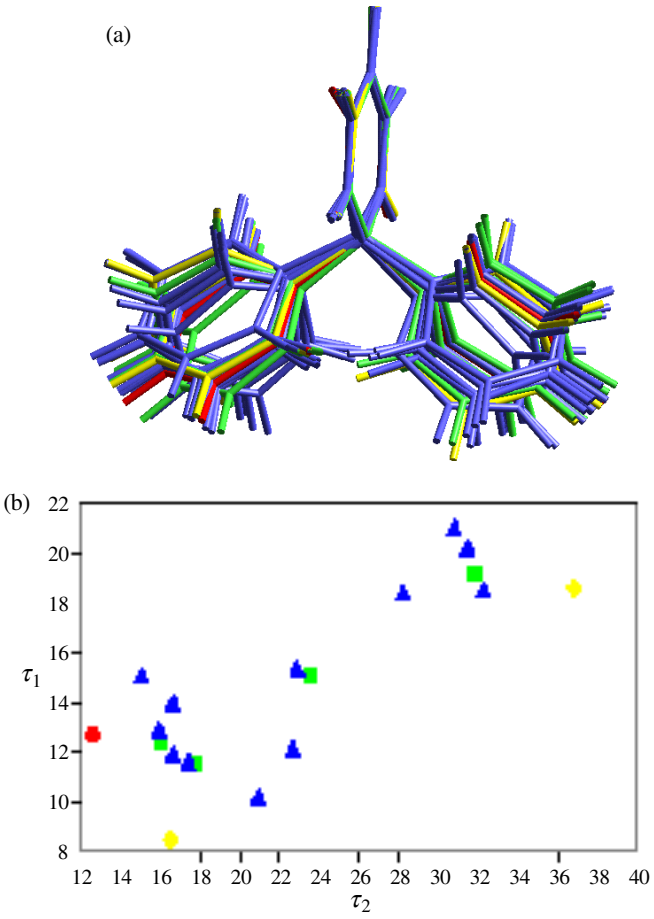



Table 4: Crystallographic data on polymorphs A–D of diphenyl quinone **3**.

| | Form A | Form B | Form C | Form D |
|---|---|---|---|---|
| CSD refcode | HEYHUO | HEYHUO01 | HEYHUO02 | HEYHUO03 |
| Space group | $P2_1$ | $P\bar{1}$ | $P\bar{1}$ | *Pbca* |
| Z′, Z | 1, 2 | 4, 8 | 12, 24 | 2, 16 |
| a / Å | 7.9170(6) | 10.0939(2) | 18.3788(4) | 10.7921(6) |
| b / Å | 8.4455(6) | 16.2592(3) | 19.9701(4) | 17.4749(12) |
| c / Å | 10.3086(9) | 16.2921(4) | 24.4423(5) | 27.9344(19) |
| $\alpha$/deg | 90 | 88.2570(10) | 95.008(1) | 90 |
| $\beta$/deg | 105.758(2) | 85.3380(10) | 111.688(1) | 90 |
| $\gamma$/deg | 90 | 83.6450(10) | 105.218(1) | 90 |
| V / Å$^3$ | 663.36(9) | 2648.00(10) | 7871.8(3) | 5268.2(6) |
| R-factor | 0.050 | 0.068 | 0.112 | 0.059 |

Figure 4: Overlay diagram of 19 molecules (a) and $\tau_1$–$\tau_2$ scatter plot (b) of conformational diversity in polymorphs of **3**. Red = form A (Z′ = 1), Green = form B (Z′ = 4), Blue = form C (Z′ = 12), yellow) = form D (Z′ = 2).




Hydrogen bond and intermolecular interactions have the energy scale: O–H···O, N–H···O hydrogen bonds = 4.0–10.0 kcal mol$^{-1}$, C–H···O interactions = 1.0–4.0 kcal mol$^{-1}$, and lastly weak van der Waals interactions = 0.5–1.0 kcal mol$^{-1}$ ~ *R*T at ambient temperature.[10] This means that a torsion angle deformation is about the energy of a weak C–H···O or van der Waals interaction and several deformations may add up to the energy of a strong H bond. This leads to the situation that bond torsion changes, which determine molecular shape, are of comparable energy to intermolecular interactions that direct crystal packing. Thus, it is possible that stronger interactions and better crystal packing stabilize a metastable molecular conformation whereas the stable conformation engages in weaker hydrogen bonds and/ or inefficient packing. For example, the most important torsion angle in adenosine-5′-mono-phosphate monohydrate **2** is rotation of the phosphate group with respect to the furanose ring. The *gg* conformation observed in the monoclinic crystal structure is ~4 kcal/mol higher in energy that the stable *tg* conformer. The torsion angle differs about the base–sugar bond by 47 ° and the furanose ring pucker and 3′, 4′-OH donor groups are oriented differently in the two polymorphs of **2** (space group $P2_1$ and $P2_12_12_1$, CSD refcodes ADPOSM, ADPOSM01). The metastable conformer makes good O–H···O and O–H···N H bonds (1.90, 2.05 Å) to make up for the energy penalty in the monoclinic crystal structure. Hydrogen bonding is weak in the orthorhombic structure of the stable rotamer. Only one of the diol OH groups acts as N–H···O bond acceptor (1.91 Å) and the other OH is free; both OH donors are unused in H bonding.

Molecular conformer ($E_{conf}$) and crystal lattice energy ($U_{latt}$) compensation in polymorph clusters was nicely illustrated in diphenyl quinone **3**. Molecular conformer energies were calculated in

Figure 5: (a) Powder XRD of a typical crystallization batch of **3** from EtOAC–*n*-hexane is matched with the simulated profile form X-ray crystal structures of form A, B and D. The percentages were calculated by the least-squares refinement method in Powder Cell 2.3. (b) PXRD at 70 °C in VT-PXRD experiment (black line) matches with the calculated powder pattern of polymorph A (dotted line). (c) Experimental PXRD by melt crystallization at 115 °C (black line) matches with the calculated PXRD of polymorph B (dotted line). The starting solid was a mixture of forms A–D as shown in (a).

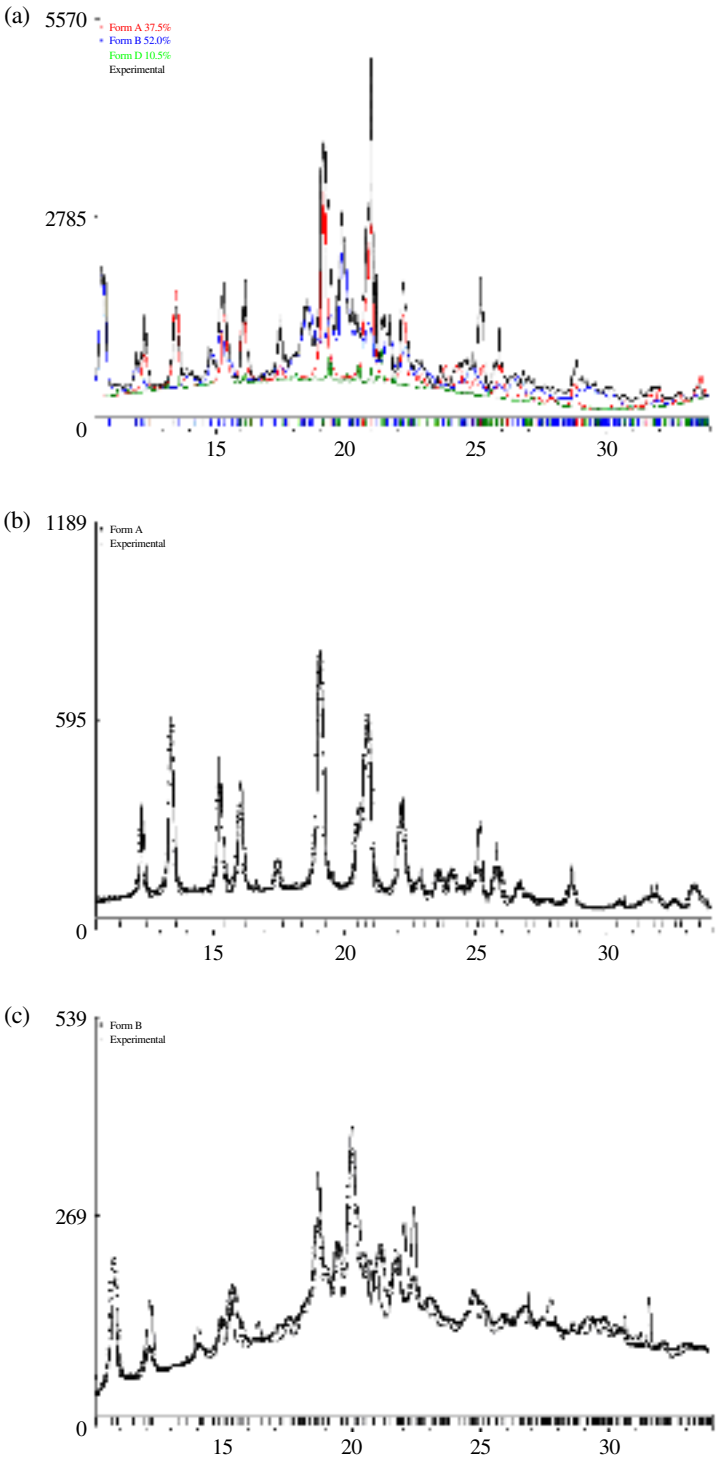


Table 5: Data on polymorphs (≥3 forms)[a] in organic crystal structures with multiple molecules in the asymmetric unit.

| Entry | CSD refcode | No. of polymorphs | Highest Z′ |
|---|---|---|---|
| | Conformational polymorphs (≥4 forms)[a] | | |
| 1 | QAXMEH | 7 | 1 |
| 2 | SUTHAZ | 5 | 2 |
| 3 | BEWKUJ | 4 | 2 |
| 4 | BIXGIY | 4 | 1 |
| 5 | HEYHUO[b] | 4 | 12 |
| 6 | KAXHAS | 4 | 1 |
| 7 | MABZNA | 4 | 4 |
| 8 | RUWYIR | 4 | 2 |
| | Multiple molecules in asymmetric unit (Z′ >4)[a] | | |
| 9 | PUBMUU[b] | 3 | 16 |
| 10 | IFULUQ | 5 | 8 |
| 11 | DUVZOJ | 3 | 6 |
| 12 | ZZZVTY | 3 | 5 |
| 13 | THIOUR | 3 | 4.5 |

[a] Cut-offs were made to limit the number of structures analyzed.
[b] Compound has high number of polymorphs and high Z′.

Figure 6: Overlay of conformer in sublimed polymorph **5**s, and symmetry-independent molecules A and B in melt phase **5**m. The diol OH groups are syn in **5**s and A molecule whereas they are anti in B molecule. Form **5**s = magenta, form **5**m (A) = blue, From **5**m (B) = green.

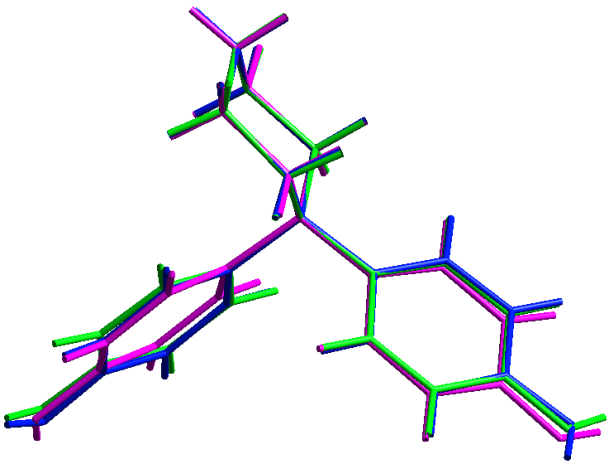
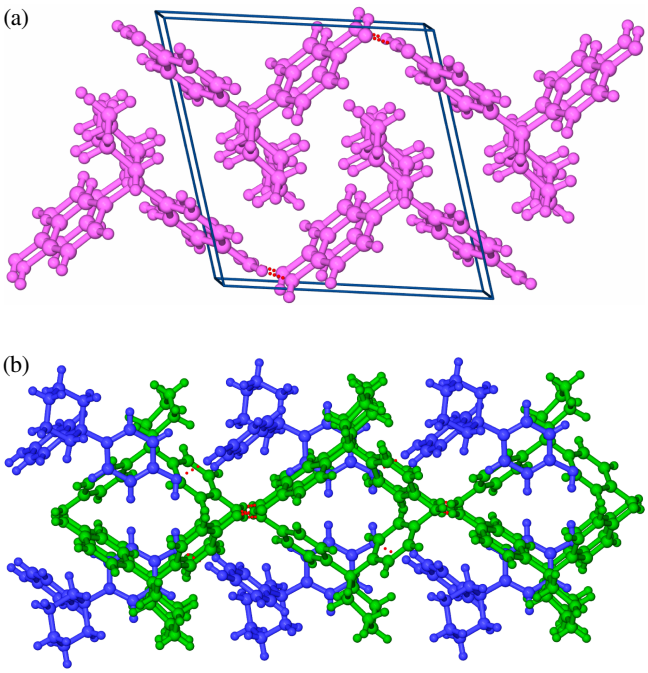


Table 6: Relative energies(per molecule, kcal mol$^{-1}$) of crystal forms A, B and D of **3**. Lattice energies, $U_{latt}$, were calculated in both COMPASS and DREIDING force field of Cerius$^2$ but only COMPASS numbers are discussed in text. Molecular conformer energies were computed in Spartan (HF/6-31G**).

| Polymorph | $U_{latt}$ | | $E_{conf}$ of each conformer | $E_{conf}$ av. | $E_{total} = U_{latt} + E_{conf}$ | |
|---|---|---|---|---|---|---|
| | COMPASS | DREIDING | | | COMPASS | DREIDING |
| A | 0.00 | 0.30 | 1.22 | 1.22 | 1.22 | 1.52 |
| B | 1.03 | 2.76 | 0.00, 0.06, 0.66, 1.12 | 0.46 | 1.49 | 3.22 |
| D | 0.82 | 0.00 | 1.08, 1.25 | 1.16 | 1.98 | 1.16 |

Figure 7: (a) O–H···O H bond chain along [010] in triclinic polymorph 5s (OH groups of diol are syn). (b) The rectangular voids in the molecular ladders along [010] of green B molecules (OH groups are anti) have a cross-section of 3.6 × 2.2 Å. Blue A molecules have similar H bonding to 5s.




Gaussian 03 or Spartan 04 and crystal lattice energies were computed in Cerius[2] software suites[11] in the examples discussed.

4,4-Diphenyl-2,5-cyclohexadienone **3** crystallized as four concomitant polymorphs, A–D, upon crystallization from EtOAc–*n*-hexane.[12] Manual selection of single crystals and X-ray data collection revealed different packing arrangements in different unit cells. Chiral form A crystallized in space group $P2_1$ ($Z' = 1$), forms B and C in triclinic space group $P\bar{1}$ ($Z' = 4, 12$), and form D in orthorhombic space group *Pbca* ($Z' = 2$, see Table 4 for crystallographic data). A total of 19 crystallographic unique molecular conformations (Figure 4) is a record of sorts in polymorph clusters (Table 5). The main difference between these conformations is torsion angles about the $C_{quinone}$–$C_{phenyl}$ single bonds, $\tau_1$ and $\tau_2$. Polymorphs A–D are conformational and concomitant polymorphs whereas B–D are conformational isomorphs. Conformational polymorphs may have $Z' = 1$ or higher but conformational isomorphs must have $Z' > 1$. Here we refer to molecules residing on general positions in the unit cell only. If the molecule occupies a special position, say the inversion center, two-fold axis or mirror plane, 1 is replaced by 0.5.

Concomitant crystallization of forms A–D was evident from the powder X-ray diffraction pattern of a typical crystallization batch which contained form A 38%, forms B + C 52% and form D 10% (Figure 5). Heating the mixture to 70 °C on the diffractometer pan gave essentially pure form A, indicating that polymorph A is the thermodynamic (stable) modification in the enantiotropic cluster A–D between 30–70 °C. On the other hand, melt crystallization by rapid cooling at 115 °C gave form B (kinetic modification) in pure yield.[13] The observed powder diffractions patterns were matched with the calculated profiles from the respective single crystal structures in Powder Cell 2.3.[14]

Conformer energies ($E_{conf}$) of the 19 rotamers and the most stable conformer in the gas phase have the energy order: gas phase (−2.78 kcal mol$^{-1}$) < form B < form D < form A. Crystal lattice energies ($U_{latt}$, COMPASS force field, Cerius[2]) follow the order form A < form D < form B. The most stable gas phase rotamer is not observed in any crystal structure so far. Notably, conformer and lattice energies follow a different ranking and their energy differences are comparable. A consideration of both the lattice energy and the conformer energy takes into account energy penalty from a metastable rotamer in a stable crystal structure and vice versa. The total energy ($E_{total}$) order A < B < D (COMPASS values) is consistent with phase transformation experiments. However, consideration of $U_{latt}$ alone, whether in COMPASS or DREIDING force field, did not agree with experiments. COMPASS force field generally gives superior results for typical organic molecules. The observed phase relationships match with calculations only when both the conformer penalty and the lattice energy stabilization are considered together under the $E_{total}$ column of Table 6. The energy difference of 0.3 kcal mol$^{-1}$ between forms A and B (1.22 vs. 1.49 kcal mol$^{-1}$) not only serves as benchmark to calibrate available force fields used but also shows that it is possible to arrive at experimental conditions for the selective crystallization of pure polymorphs with <0.5 kcal mol$^{-1}$ energy difference.

Table 7: Relative energies of the molecular conformation ($E_{conf}$), crystal lattice ($U_{latt}$) and total energy ($E_{total}$, kcal mol$^{-1}$) of the six polymorphs of ROY **1**.

| Polymorph | $U_{latt}$ | $E_{conf}$ | $E_{total}$ | Torsion $\phi$ |
|---|---|---|---|---|
| Y | 0.00 | 0.00 | 0.00 | 75 |
| R | 2.86 | –1.19 | 1.67 | 22 |
| ON | 1.90 | 0.00 | 1.90 | 53 |
| OP | 2.86 | 0.95 | 3.81 | 46 |
| YN | 2.86 | 1.43 | 4.29 | 76 |
| ORP | 3.09 | 2.14 | 5.23 | 39 |

Figure 8: DSC of **5**m and **5**s polymorphs. Metastable phase **5**m shows phase transition to sublimation polymorph **5**s and transformation to the thermodynamic form upon heating up to 200 °C. Polymorph **5**s does not show phase changes under similar conditions except the sublimation endotherm. The reheating cycle endotherm is shifted to ~5 °C lower T than the first heating cycle due to better contact of the melted solids with the sample holder.

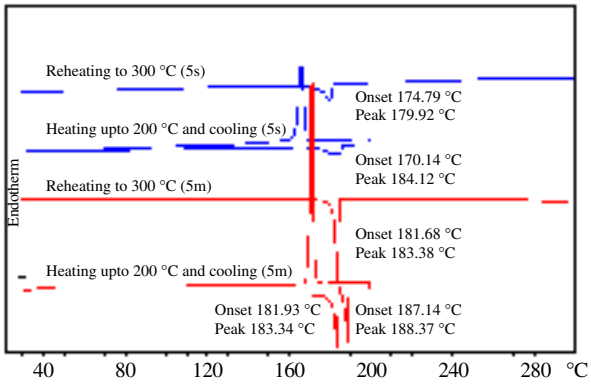



Table 8: Relative energies (per molecule, kcal mol$^{-1}$) of melt and sublimed phases **5**m and **5**s. $U_{latt}$ were calculated using COMPASS force field in Cerius$^2$ and $E_{conf}$ was computed in Gaussian 03 at the DFT, B3LYP/6-31G level.

| Polymorph | $U_{latt}$ | $E_{conf}$ | $E_{conf}$ av. | $E_{total} = U_{latt} + E_{conf}$ |
|---|---|---|---|---|
| **5**s ($Z' = 1$) | –37.11 | 0.00 | 0.00 | –37.11 |
| **5**m ($Z' = 2$) | –36.23 | 0.23, 0.29 | 0.26 | –35.97 |

ROY **1** is an archetype of conformation polymorphs with a record nine forms as of date.[7] Single crystal X-ray structures are reported for 7 forms. However, ROY is a classic example of a conformational polymorph cluster wherein conformer and lattice energy compensation is absent (Table 7, $Z' = 1$ in all structures).[15] As a matter of fact, the two effects are additive. The most stable crystal structure, Y, also has the stable rotamer of this flexible molecule. The difference between the lowest and highest energy polymorphs, Y and ORP, is 5.2 kcal mol$^{-1}$ when both molecular and crystal energies are considered together. The absence of energy balance and the relatively large energy difference between polymorphs leads to the thought: will metastable polymorphs of ROY one day transform to the win-win thermodynamic state of the stable molecule and crystal lattice in the thermodynamic form?

Figure 9: (a) Originally marketed form I of ritonavir **9** (trans carbamate). (b) Appearance of cyclic carbamate as degradation product in impurity profile. (c) Nucleation of stable form II (cis carbamate) due to seeded crystallization.

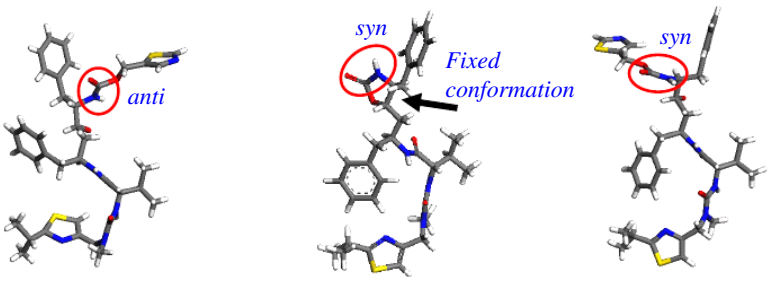
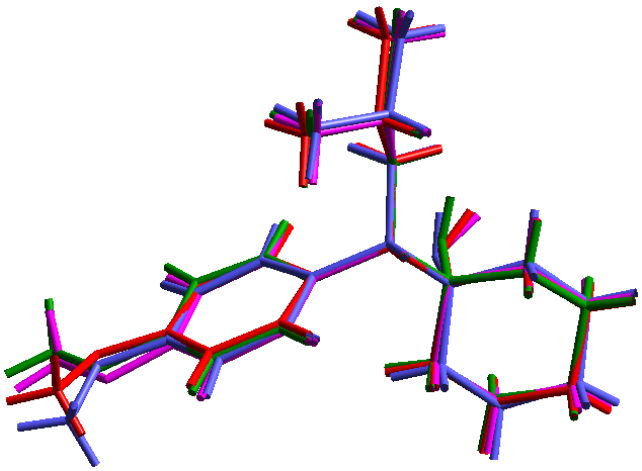


Table 9: Occurrence of Z′ in organic crystals crystallized 'from the melt' (83 hits), 'by sublimation' (334 hits), and 'overall statistics' in the CSD. Overall percentages are values from 160 850 organic crystal structures in the CSD.

| Z′ | Sublimation % (# hits) | From melt % (# hits) | Overall Organic %age | S + M ÷ 2 × O %age values |
|---|---|---|---|---|
| <1 | 29.04 (97) | 22.89 (19) | 17.64 | 1.47 |
| 1 | 53.89 (180) | 59.04 (49) | 71.88 | 0.78 |
| > 1 | 17.06 (57) | 18.07 (15) | 11.54 | 1.52 |
| 2 | 12.28 (41) | 10.84 (9) | 10.04 | 1.15 |
| ≥ 3 | 3.89 (13) | 7.23 (6) | 1.24 | 4.48 |
| > 3 | 2.99 (10) | 3.61 (3) | 0.69 | 4.78 |
| 4 | 2.69 (9) | 2.40 (2) | 0.45 | 5.65 |

Figure 10: Overlay of symmetry-independent venlafaxine molecules. Form 1 (red), form 2 (magenta), form 6: molecule i (blue), molecule ii (green). The only difference in these conformers is orientation of OMe group in the crystal structure. Chloride counter ion is omitted for clarity.



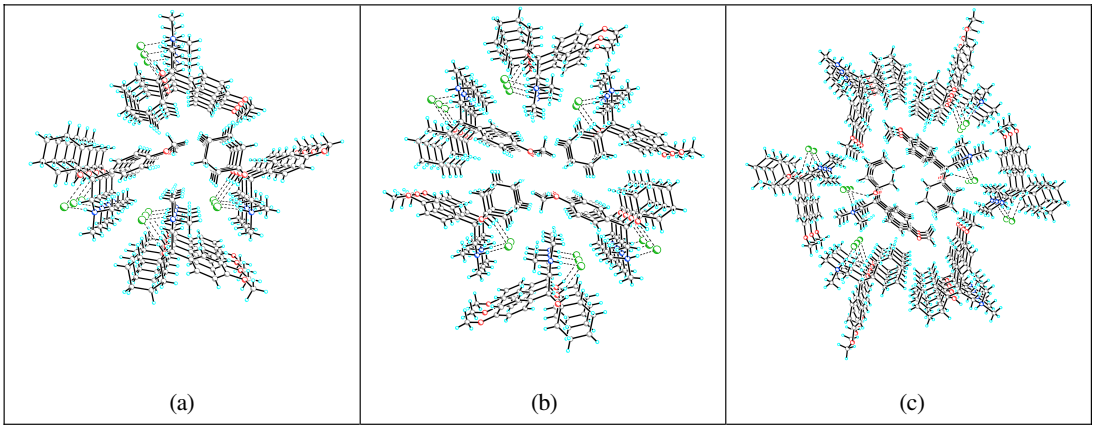
## Multiple Z′ in Crystal Structures

Several research groups are currently working to understand why certain crystal structures have multiple molecules in the asymmetric unit. Less than 12% crystal structures have Z′ > 1. Typical values of Z′ are 0.5 or 1. Jon Steed[16] critically reviewed the reasons for high Z′ crystal structures. (1) The molecule has a packing problem because of its awkward shape, which is reconciled by having two or more molecules in different conformations. Carol Brock[17] refers to this situation as the 'packing problem.' (2) The molecules organize in stable clusters prior to reaching the highest symmetry arrangement in strong O–H···O hydrogen-bonded structures because of enthalpic advantage from $\sigma$-cooperative chains, e.g. as in alcohols, phenols, steroids, nucleotides, nucleosides. (3) There are several low-lying molecular conformations interconverting in solution and more than one molecule may crystallize simultaneously because of kinetic factors. The last of these situations is present in conformational polymorphs of **3**, which also provides a unique opportunity to study multiple Z′ in polymorphic structures. High Z′ polymorph

Table 10: Unit cell parameters of forms 1, 2 and 6 of venlafaxine hydrochloride (**10**). The drug is currently marketed in forms 1 and 2 as well as hydrate form 4.

| | |
|---|---|
| From 1 | *Pca*2$_1$, a = 26.230(5) Å, b = 5.881(1) Å, c = 11.448(2) Å, V = 1765 Å$^3$, Z′ = 1, Z = 4, $\rho_{calc}$ = 1.180 g cm$^{-3}$, m.p. 208–210 °C. |
| Form 2 | $P2_1/n$, a = 5.797(6) Å, b = 26.074(7) Å, c = 11.722(3) Å, $\beta$ = 100.72(5) °, V = 1740 Å$^3$, Z′ = 1, Z = 4, $\rho_{calc}$ = 1.197 g cm$^{-3}$, m.p. 208–210 °C. |
| Form 6 | $P2_1/n$, a = 5.887(10) Å, b = 19.37(3) Å, c = 31.41(5) Å, $\beta$ = 92.16(3) °, V = 3579 Å$^3$, Z′ = 2, Z = 8, $\rho_{calc}$ = 1.165 g cm$^{-3}$, m.p. 218–220 °C |

Figure 11: Close packing of helical chains of molecules organized via the V-shaped O–H···$Cl^-$ and $N^+$–H···$Cl^-$ hydrogen bond synthon in crystal structures of **10**. (a) Form 1 down [010], (b) Form 2 down [100], and (c) Form 6 down [100].



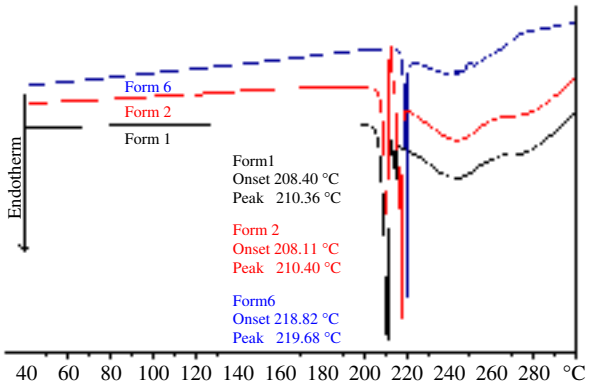

structures have been variously referred to as 'fossil relic'[16] and 'snapshot picture of crystallization',[18] particularly when a lower Z′ form also exists. According to Desiraju,[19] these different reasons are simply different ways of saying the same thing. The proportion of $Z' > 1$ crystal structures is relatively constant at ∼12% in the period 1970 to 2006 even as the CSD has grown 43 times in the same period. The fundamental physical basis for multiple Z′ is the difference between $\Delta G^z_T$ and $\Delta G^z_K$ ($T$ = thermodynamic, K = kinetic) for the crystallization of a given molecule. These energy differences are related to the modest energy of intermolecular interactions in organic crystals (0.5–8 kcal $mol^{-1}$) and so the appearance of high Z′ will depend on the temperature of crystallization. Since most crystallization experiments are carried out between 10–30 °C, the proportion of high Z′ crystal structures will stay the same. His argument is that chemical or geometric or symmetry factors are different manifestations of the constancy of temperature range for crystallization and the energy range of intermolecular interactions in organic solids.[20]

We recently crystallized two polymorphs of the pure host compound 1,1-bis(4-hydroxyphenyl)cyclohexane **5** by melt crystallization and sublimation.[21] The experimental conditions for each polymorph were slightly different. Sublimation of pure **5** at 150–175 °C gave thin plate and fine needle shaped crystals on the cold finger. When the same starting material was heated up to 180–190 °C and the melt liquid flash-cooled, crystals of plate and block morphology appeared. These crystals, designated as melt and sublimed forms, respectively, were confirmed to be polymorphs by single crystal X-ray diffraction (**5**s: $P\bar{1}$, $Z' = 1$; **5**m, *Pbca*, $Z' = 2$). The OH group orientations qualify them to be referred to as conformational polymorphs because the remaining carbon framework superposes nicely (Figure 6). In triclinic form **5**s, one of the OH groups engages in O–H···O H bonds along [010] and the second OH is bonded in an O–H···$\pi$ interaction. In orthorhombic form **5**m, the syn diol molecule A has identical H bonding to the above polymorph but the anti diol B uses both its OH groups in making O–H···O H bonds in cooperative chains along [100] (Figure 7). Z′ of 2 in **5**m is ascribed to stronger H bonding in oligomers crystallized from the neat liquid under fast cooling (kinetic) conditions. A closely related molecule exhibiting host–guest behavior is again a case of $Z' = 2$ in phenol crystal structures.[22]

There is no rotamer and lattice energy compensation here but crystal energy differences are very small and surely indicative of polymorphism (Table 8). Melting point, crystal density and packing fraction of kinetic phase **5**m are lower than that of the thermodynamic form **5**s (**5**m 1.261 g/$cm^3$, 69.9%; **5**s 1.275 g/$cm^3$; 71.1%). Differential scanning calorimetry (Figure 8) showed that these conformational polymorphs do not undergo phase transition up to 160 °C (monotropic cluster) but the metastable form **5**m transforms to the stable phase **5**s between 180–200 °C (enantiotropic system).

Solvent-free melt and sublimation methods for crystallization and frequency of Z′ in such crystal structures was surveyed in the CSD (Table 9). There is a dramatic increase in the occurrence of $Z' \geq 3$ crystal structures when melt or

Figure 12: DSC of form 1, form 2 and form 6 at heating rate of 5 °C $min^{-1}$. Form 6 has the highest melting point of 219–220 °C compared to form 1 and 2 of 210–211 °C (first endotherm). There is no phase transition of form 6 but both forms 1 and 2 undergo transformation to forms 3 and 5 between 210–220 °C.




sublimation crystallization conditions are used.[21] The occurrence of high Z′ in melt crystallization and sublimation methods is ascribed to the rapid cooling of the hot liquid or vapor (100–300 °C) in the open flask or on the cold finger (kinetic phase), conditions under which hydrogen-bonded clusters are likely to condense in a pseudo-symmetric crystalline arrangement. On the other hand, the slower nucleation process of solution crystallization gives the frequent situation of $Z' \leq 1$ (88% hits).

## Polymorphism in drugs

Polymorphs have different crystal structures and dissolution rates. Several recent patent battles between innovator and generic drug companies center on different polymorphs or hydrate forms of the same API (active pharmaceutical ingredient). Therefore it is to the benefit of innovator companies to patent all possible forms before somebody else finds a non-infringing polymorph or hydrate showing bio-equivalence with the parent drug form. Blockbuster drugs such as ranitidine hydrochloride (Zantac, Glaxo vs. Novopharm) and paroxetine hydrochloride (Paxil, GSK vs. Apotex) were the subject of litigation because of different solid forms in the market. Another reason for exhaustive polymorph search of drugs is phase transformation to stable, less soluble forms after it hits the market. This was the case in atrovastatin (Lipitor, Pfizer) and ritonavir (Norvir, Abbott).

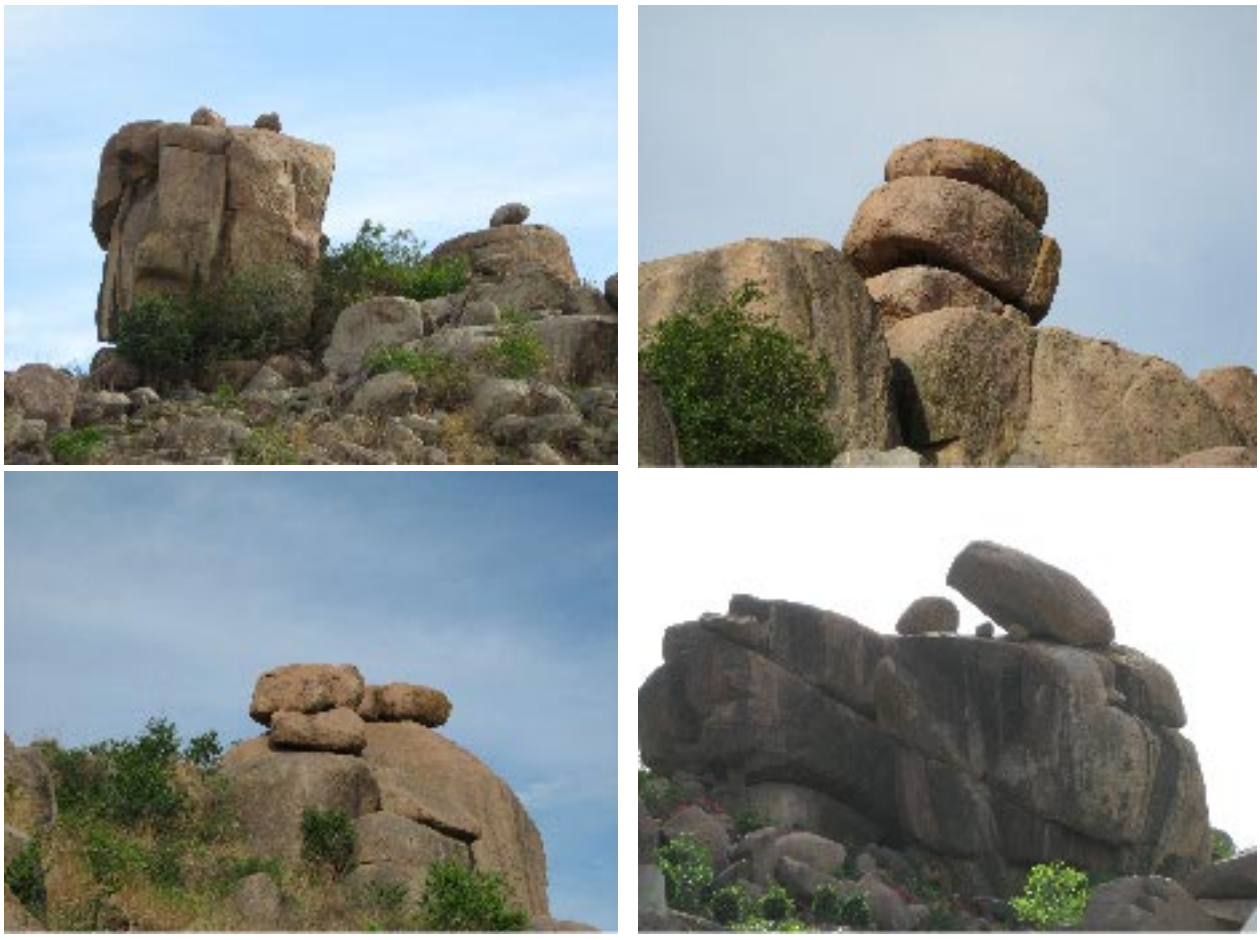
The Norvir accident occurred at Abbott laboratories in 1998, two years after the launch of this HIV-1 protease inhibitor. Only one form of the drug (**9**) was known until 1995 (form I) and marketed as oral solution or soft gelatin capsules. In early 1998, some batches of ritonavir capsules failed the dissolution test because a new less-soluble crystalline modification had precipitated. The drug product was forced to be withdrawn, a new formulation was developed, and the drug re-introduced into the market. New form II had cis NHC=O compared to trans orientation in form I (conformational polymorphs). The cause of accidental crystallization of form II was traced to heterogeneous nucleation by a cyclic carbamate degradation product behaving as seeds. Base-catalyzed hydrolysis of carbamate linkage in **9** gave hydroxy-acid intermediate which cyclized readily. The syn orientation of NHC=O group in cyclic carbamate mimics the cis conformation of form II (Figure 9).[23] The latter appearing modification is more stable (and less soluble) consistent with Ostwald's law of stages.[3] This accident warned the pharmaceutical industry to know the complete physical landscape of the drug by phase II clinical trials.

The last example is on the discovery of the stable polymorph of an API. Venlafaxine **10** is a serotonin–norepinephrine reuptake inhibitor drug (SNRI) for treating anxiety and depression, and marketed as the hydrochloride salt in forms 1 and/or 2. Form 3 (melt phase), form 4 (hydrate/ solvate) and form 5 (sublimed phase)[4i] were characterized by powder XRD, DSC, TGA and FT-IR but their X-ray crystal structures are know known. We recently crystallized a novel polymorph, designated form 6, having unit cell parameters significantly different from both forms 1 and 2 (Table 10). Forms 1, 2 and 6 of venlafaxine are conformational polymorphs (Figure 10) and form 6 with multiple conformers exhibits conformational isomorphism. Form 1 rotamer is more stable than form 2 conformer by 0.2 kcal $mol^{-1}$ at the B3LYP/6-31G (d,p) level in Gaussian 03. Crystal packing of form 6 is similar to forms 1 and 2 (Figure 11) but its melting point is 10 °C higher than that of forms 1 and 2. A single endotherm for form 6 in DSC at higher temperature compared to two endotherms for forms 1 and 2 (Figure 12) means that the last appearing polymorph is most stable. This new form was discovered by solid-to-solid phase transition of form 2 at high temperature and this transformation was visualized in thermal microscopy.[24]

## Conclusions

The theme that polymorphs represent metastable states on the crystallization energy landscape is exemplified in this review. The occurrence of polymorphs in crystallization is not surprising if one views the natural formation of rocks by solidification of lava (magmatism, volcanism) due to pressure

Figure 13: An example of kinetically locked metastable state in Nature on geological time scale is the rock formations in and around the University Gachibowli campus. Geologists date these rocks to 2500 million years back, amongst the oldest and hardest rocks on planet Earth. The rocks perched on top may be viewed as green and orange circles (kinetic polymorphs) in local minima of Figure 1. These pictures were taken by the author for writing this article. Interested readers may browse http://www.saverocks.org for more images.



and temperature (metamorphism, weathering) as a phenomenon on geological time scale. Some rock formations shown in Figure 13 are not in their lowest energy state and yet stable over millions of years. Similarly polymorphs are kinetic products in crystallization.

New experimental techniques, crystallization methods and automated protocols are being developed to carry out crystallization screens for the discovery of new polymorphs using solution crystallization, solid-state grinding, solvent-drop grinding, cocrystal former, crystal structure prediction, functionalized polymer support, and cross-nucleation.[25] A proper understanding of polymorphism and crystallization should surely evolve from ongoing studies in the coming years. Despite the extensive work on polymorphism and advances in computer simulation of crystal structures, we still have no reliable way of predicting whether a given molecule will be polymorphic, how many forms will it have, how the crystal packing will look, when polymorphism will strike an API manufacturing process, does one have the most stable polymorph, and so on. What is certain however is that McCrone's[1] dictum is truer today than ever before, '…that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.'

We show in this article that polymorphism is likely when there is balance of intramolecular and intermolecular energies in conformationally flexible molecules. Conformational polymorphism and multiple $Z'$ are related issues and we offer explanations, at least after crystal structure determination and analysis, as to why some

polymorphs crystallize with multiple molecules in the unit cell. High Z′ polymorphs are generally metastable relative to their low Z′ structures but there are exceptions.

## Acknowledgment

I thank the Department of Science and Technology, Government of India for financial support through Project No. SR/S5/OC-02/2002 and Ramanna Fellowship No. SR/S1/RFOC-01/2007.

Received 20 June 2007; revised 20 July 2007.

## References

1. W. C. McCrone, in Physics and Chemistry of the Organic Solid State, Vol. 2, D. Fox, M. M. Labes and A. Weissberger (Eds.), Wiley Interscience, New York (1965) pp. 725–767.
2. (a) J. Bernstein, Polymorphism in Molecular Crystals, Clarendon, Oxford (2002).
(b) A. R. Verma and P. Krishna, Polymorphism and Polytypism in Crystals, Wiley, New York (1966).
3. W. Ostwald, Z. Phys. Chem. 22, 289 (1897).
4. (a) R. J. Davey, Chem. Commun. 1463 (2003).
(b) N. Blagden and R. J. Davey, Cryst. Growth Des. **3** 873 (2003).
(c) P. Erk, H. Hengelsberg, M. F. Haddow and R. van Gelder, CrystEngComm **6** 474 (2004).
(d) J. Bernstein, Chem. Commun. 5007 (2005).
(e) L. Yu, J. Am. Chem. Soc. **125** 6380 (2003).
(f) P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson and M. J. Zaworotko, J. Am. Chem. Soc. **127** 16802 (2005).
(g) C. P. Price, A. L. Grzesiak and A. J. Matzger, J. Am. Chem. Soc. **127** 5512 (2005).
(h) R. J. Davey, G. Dent, R. K. Mughal and S. Praveen, Cryst. Growth Des. **6** 1788 (2006).
(i) S. Roy, S. Aitipamula and A. Nangia, Cryst. Growth Des. **5** 2268 (2005).
(j) P. M. Bhatt and G. R. Desiraju, Chem. Commun. 2057 (2007).
5. R. Hilfiker, F. Blatter and M. von Raumer, in Polymorphism in the Pharmaceutical Industry, R, Hilfiker (Ed.), Wiley–VCH, Weinheim, 2006, 1–19.
6. J. van de Streek and S. Motherwell, Acta Crystallogr. B61 504 (2005).
7. (a) L. Yu, G. A. Stephenson, C. A. Mitchell, C. A. Bunnell, S. V. Snorek, J. J. Bowyer, T. B. Borchardt, J. G. Stowell, S. R. Byrn, J. Am. Chem. Soc. **122**, 585 (2000).
(b) S. Chen, I. A. Guzei and L. Yu, J. Am. Chem. Soc. **127** 9881 (2005).
8. A. Nangia, Cryst. Growth Des. **6** 2 (2006).
9. (a) D. Buttar, M. H. Charlton, R. Docherty and J. Starbuck, J. Chem. Soc., Perkin Trans. 2 763 (1998).
(b) J. Starbuck, R. Docherty, M. H. Charlton and D. Buttar, J. Chem. Soc., Perkin Trans. 2 677 (1999).
10. (a) G. R. Desiraju and T. Steiner, The Weak Hydrogen Bond in Structural Chemistry and Biology, IUCR Monograph, Oxford University Press, Oxford (1999).
(b) G. A. Jeffrey, An Introduction to Hydrogen Bonding, Oxford University Press, Oxford (1999).
11. (a) Gaussian 03: www.gaussian.com.
(b) Spartan 04: www.wavefun.com.
(c) Cerius$^2$: www.accelrys.com.
12. V. S. S. Kumar, A. Addlagatta, A. Nangia, W. T. Robinson, C. K. Broder, R. Mondal, I. R. Evans, J. A. K. Howard and F. H. Allen, Angew. Chem. Int. Ed. **41** 3848 (2002).
13. S. Roy, R. Banerjee, A. Nangia and G. J. Kruger, Chem. Eur. J. **12** 3777 (2006).
14. N. Krauss and G. Nolze, Federal Institute for Materials Research and Testing, Berlin, Germany (2000).
15. J. D. Dunitz and A. Gavezzotti, Cryst. Growth Des. **5** 2180 (2005).
16. J. W. Steed, CrystEngComm 5 169 (2003).
17. (a) C. P. Brock and L. L. Duncan, Chem. Mater., 6 1307 (1994).
(b) X. Hao, J. Chen, A. Cammers, S. Perkin and C. P. Brock, Acta Crystallogr. **B61** 218 (2005).
18. D. Das, R. Banerjee, R. Mondal, J. A. K. Howard, R. Boese and G. R. Desiraju, Chem. Commun. 555 (2006).
19. G. R. Desiraju, CrystEngComm **9** 91 (2007).
20. Read counterpoint. (a) K. M. Anderson and J. W. Steed, CrystEngComm 9 328 (2007).
(b) G. S. Nichol and W. Clegg, CrystEngComm Advance Article DOI: 10.1039/b709051j (2007).
21. B. Sarma, S. Roy and A. Nangia, Chem. Commun. 4918 (2006).
22. S. Aitipamula and A. Nangia, Chem. Eur. J. **11** 6727 (2005).
23. J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter and J. Morris, Pharma. Res. **18** 859 (2001).
24. S. Roy, P. M. Bhatt, A. Nangia and G. J. Kruger, Cryst. Growth Des. **7** 476 (2007).
25. (a) B. Rodríguez-Spong, C. P. Price, A. Jayashankar, A. J. Matzger and N. Rodríguez-Hornendo, Adv. Drug. Del. Rev. **56** 241 (2004).
(b) A.V. Trask and W. Jones, Top. Curr. Chem. **254** 41 (2005).

**Ashwini Nangia** is Professor of Chemistry at the University of Hyderabad. He did his MSc from IIT Kanpur (1983) and earned PhD degree from Yale University (1988). His graduate training and early research projects at UoH (1989–1995) were in the area of natural product synthesis, enzyme inhibitors and medicinal molecules. Starting with structure-based drug design he gradually shifted research focus towards crystal engineering and supramolecular chemistry (1996–2000). His current research interests are in host-guest inclusion compounds, crystal design via hydrogen bonds and halogen bonds, and polymorphism. He has published over 140 research publications and is a co-author on four patents. He is Editorial Board member of RSC journal *CrystEngComm* and ACS journal *Crystal Growth & Design*.