Polymorphic Packing Arrangements in a Class of Engineered Organic Crystals

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Polymorphism occurs in the family of engineered cocrystals that form from *N*,*N*′-bis(*p*-X-phenyl)melamines (X = H, F, Cl, Br, I, CH_3, and CF_3) and barbital. X-ray powder diffraction indicates that only one crystalline phase formed for X = Cl, F, and CH_3, that primarily one phase occurred for X = H and I, but that a small contribution from an alternative phase or phases was possibly also present, and that at least two different polymorphs exist for both X = Br and CF_3. Agreement of *positions* of peaks in experimental XPD traces and reflections calculated from single-crystal data is good, while agreement in *intensities* is good in some cases but only fair in others. Reasons for this disagreement are likely to include the physical design of the diffractometer and preferred orientation of crystallites in the sample. Two of the polymorphic forms of X = Br are converted to a third on annealing at 140 °C. Steric effects seem the most probable origin of the polymorphism: the bromine-substituted diphenylmelamine crystallizes in several polymorphs, and the bromine substituent is intermediate in size for the family of substituents examined. This cocrystal forms one polymorph that is formed by cocrystals having larger substituents (I and CH_3) and one that packs similarly to a cocrystal having a smaller substituent (Cl).

Introduction

Successful design of crystalline organic solids requires control over molecular packing. As part of our studies of the engineering (that is, the design and preparation) of organic molecular crystals,[1−4] we are concerned with the occurrence of multiple patterns of packing—polymorphism—for compounds of interest. The widespread occurrence of polymorphism in organic crystals makes the packing of organic molecules especially difficult to rationalize and predict. As Desiraju has rhetorically asked in his important overview of organic solids, "does the existence of polymorphism negate ... the very concept of crystal engineering?".[5]

Truly rational solid-state design will not be possible until polymorphism is understood and controlled.[6] Almost all approaches to understanding the structure of crystals focuses on their thermodynamics: the first question is always "what is the most stable crystal form?" The occurrence of polymorphs often reflects the kinetic factors that determine the rates of nucleation and growth of crystals and is even more difficult to understand than the thermodynamics of the most stable crystal.[7] Since the crystal that forms in some circumstances is not necessarily the most stable crystal, it is especially difficult to work out structure−stability relations of the sort on which physical-organic chemistry is based.[8] Complicating this issue is the fact that many polymorphs differ in energy only slightly (for example, by less than 10 or 12 kJ/mol, according to compilations of heats of transition between polymorphs).[9,10]

A further difficulty is that conformational polymorphism[11] will always be a theoretical possibility for molecules that have multiple conformational isomers accessible energetically: every different conformation is a different molecular shape and can, in principle, form its own crystalline polymorph (or polymorphs). Even molecules constrained to pack in geometrically simple aggregates through the use of directional intermolecular forces—the class of interest in our work—can show conformational isomerism and polymorphism. Evidence of the present difficulty in rationalizing and controlling polymorphism is the fact that an experimental examination for polymorphs usually involves an almost undirected, empirical search across the many parameters—solvent, temperature, mass transport, nucleation—that influence crystallization.[12]

The study of polymorphism can be valuable for several reasons.[13] It can yield information about the interplay between molecular conformation and intermolecular interactions. It will contribute to the determination of the stable thermodynamic form of a molecular crystal. It also has technological ramifications: polymorphism is an important consideration in the design of acentric

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[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

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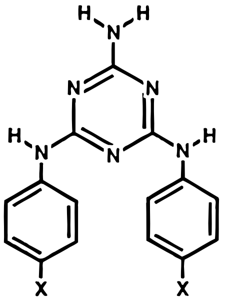
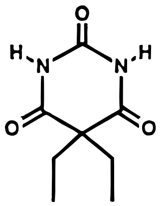
phases for nonlinear optical materials,[14] in explaining solid-state reactivity,[15] in stabilizing bioavailability in pharmaceutical applications where rates of dissolution of a drug can differ among polymorphs,[16] and in controlling the physical properties (packing, pourability, triboelectrical effects) of crystalline solids.[17−19]

We have previously demonstrated that 1:1 cocrystals of melamines and barbiturates serve as a model system for the study of packing in organic molecular crystals in which molecular structure can be correlated with crystal structure (at least to some extent).[1−4] One class of this system, composed of *N*,*N*′-bis(*p*-X-phenyl)-melamines and barbital (where X = H, F, Cl, Br, I, CH_3, and CF_3), clearly exhibited polymorphism (see ref 1 for the crystal structures of this series of complexes). Here we present a study of the polymorphism of this family of complexes, using X-ray powder diffraction and solid-state NMR spectroscopy. Although techniques such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), solid-state IR spectroscopy, and optical microscopy have been used to study polymorphism, we have focused on XPD since this technique provides information about the packing of molecules in crystal lattices. We have not attempted to address the use of XPD as a method for ab initio determination of crystalline structure. Rather, a major objective of this work was to demonstrate, on a representative class of designed crystals, that XPD is the most convenient tool to use for rapid yet comprehensive screening for polymorphism in organic solids and that a survey for this phenomenon is crucial to rational crystal engineering.



N,N'-bis(para-X-phenyl)melamine
X = H, F, Cl, Br, I, CH_3, CF_3



barbital

Results and Discussion

Detection of Polymorphs using X-ray Powder Diffraction (XPD). We rely upon XPD for information about polymorphism in polycrystalline samples. This technique provides qualitative results quickly, and it characterizes the average structure of a sample of crystals generated by a given set of crystallization conditions, not just the structure of a few selected single crystals suitable for single-crystal X-ray diffraction. In contrast to spectroscopic methods, which characterize the local environment of individual atoms or functional groups, XPD provides a fingerprint, or diagnostic pattern, of any crystalline lattice that is present in a polycrystalline sample; that is, it characterizes the three-dimensional organization of molecules in a solid, not just the environment of single molecules.

For these studies, we have examined only the influence of solvent on crystallization;[20] all crystallizations were carried out at room temperature. Figures 1−3 show XPD traces for complexes containing the seven substituents used to construct this family. Each set of traces includes a calculated trace, generated using the Siemens program XPOW or the MSI program Cerius•2 from the data obtained from single-crystal diffraction studies. These calculated traces consider only the intensities of the reflections, the unit-cell dimensions, and the lattice symmetry; no explicit allowance is made for disorder of the molecules in the crystalline lattice, crystal morphology, or X-ray absorbance.[21] Experimental traces were obtained from crystals that had been ground for several minutes with a mortar and pestle. Crystals were grown from several solvents, not just the solvent used to obtain single crystals for diffraction.

Comparison of the experimental traces to the calculated trace suggests that these seven complexes can be separated into three classes. The first class (X = Cl, CH_3, and F) has, in our opinion, satisfactory agreement between experimental and calculated traces. By this judgment, we mean that the positions of the observed peaks (their 2θ values) do not deviate, within the experimental error of the technique (approximately $\pm 0.2°$), from the calculated values. Furthermore, the relative intensities are also in general agreement with calculations, although some peaks clearly are weaker or stronger than calculations predict. We discuss our investigation of potential causes for disagreement between calculated and experimental diffraction traces below.

The second class (X = H and I) is intermediate in agreement between experiment and calculation. The positions of peaks, especially the most intense ones, are in satisfactory agreement, but in some traces the relative intensities of experimental peaks agree less well with the relative intensities of calculated peaks than they do in the first class (X = Cl, F, and CH_3). Additional low-intensity peaks may appear, suggesting that other polymorphs may be present. Alternatively, some peaks expected from calculation may be weak or virtually absent. This diminution is most apparent in several traces of X = H that have only broad, ill-defined peaks, which may be indicative of poor crystallinity.

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(16) (a) Byrn, S. R.; Pfeiffer, R. R.; Stephenson, G.; Grant, D. J. W.; Gleason, W. B. *Chem. Mater.* **1994**, *6*, 1148. (b) Byrn, S. R. *Solid-State Chemistry of Drugs*; Academic Press: New York, 1982.

(17) For food behavior, see: (a) Walstra, P. In *Food Structure and Behavior*; Blanshard, J. M. V., Lillford, P., Eds.; Academic Press: London; 1987. (b) Craig, S. R.; Roberts, K. J.; Sherwood, J. N.; Sato, K.; Hayashi, Y.; Iwahashi, M.; Cernik, R. J. *J. Cryst. Growth* **1993**, *128*, 1263. (c) Davey, R. J.; Richards, J. *J. Cryst. Growth* **1985**, *71*, 597.

(18) For polymorphism of clathrate lattices, see: Weber, E.; Skobridis, K.; Wierig, A.; Nassimbeni, L. R.; Johnson, L. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2123.

(19) For polymorphism in organic conductors, see: Shibaeva, R. P.; Kaminskii, V. F.; Yagubskii, E. B. *Mol. Cryst. Liq. Cryst.* **1985**, *119*, 361.

(20) A number of techniques can be employed, such as vapor diffusion, sublimation, or melt crystallization. Experimental conditions such as temperature or rate of evaporation of the solvent can also be varied. Historically, attempts to crystallize neutral organic compounds have relied most frequently on changes of solvent. Ellern, A.; Bernstein, J.; Becker, J. Y.; Zamir, S.; Shahal, L.; Cohen, S. *Chem. Mater.* **1994**, *6*, 1378.

(21) Inasmuch as these factors do affect the observed reflection data in single-crystal studies, they will also make a contribution to a calculated powder trace based on those data. It is unknown, however, whether they would affect experimental powder diffraction data to the same extent.

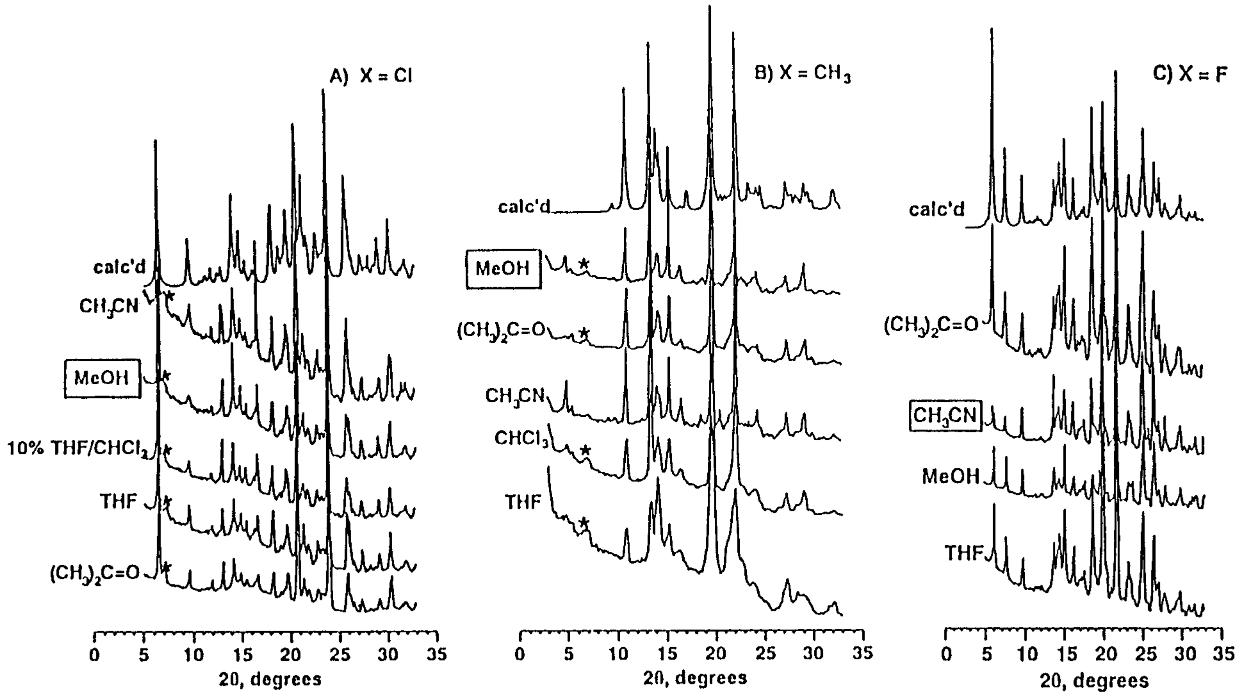

Figure 1. Experimental X-ray powder diffraction traces for X = Cl, CH_3, and F, and comparison with traces calculated from single-crystal coordinates. Agreement between experimental and calculated patterns is considered good. The boxed solvent is that used to grow the crystal studied by single-crystal diffraction. The starred peak that appears in many of the traces may be due to the fiberboard sample holder[23] or to an unknown contaminant; it is neither barbital nor the substituted diphenylmelamine in uncomplexed form.

The third class (X = Br and CF_3) obviously lacks even partial agreement between observed and calculated traces. We conclude that the single crystals used for structure determination were a different polymorph from the powdered bulk samples investigated by XPD. We will label the single-crystal phase as polymorph I, and the new phase detected as polymorph II.

After detecting the presence of polymorphs of X = Br and X = CF_3 by XPD, we made repeated attempts at crystallization, varying experimental conditions such as solvent and rate of evaporation and were able to grow single crystals of polymorph II for X = Br. For X = CF_3, however, we could not obtain single crystals of polymorph II or a powder sample consisting predominantly of polymorph I, as judged by XPD.[22] Figure 4 shows comparisons between calculated and observed XPD traces for the X = Br polymorphs (calculated traces for both polymorphs are based on single-crystal data); agreement is satisfactory, especially between the 2θ values of the calculated and experimental peaks, as it was for the X = Cl, CH_3, and F complexes described above.

In addition to these first two polymorphs for X = Br, we obtained a third polymorph, no single crystal of which could be grown (Table 1 lists the conditions that yielded each polymorph). The XPD result for this third polymorph (Figure 4) is unusual: only one dominant diffraction peak appears, with few separate small peaks. The presence of one very intense reflection may indicate that the constituent molecules pack in flat, parallel layers in this phase. In fact, the value of 2θ of this reflection, 21.9°, corresponds to a spacing of lattice planes of 4.05 Å, a reasonable value for the distance between adjacent molecular layers.

Table 1. Crystallization Parameters and Crystal Data for X = Br Polymorphs I–III

polymorph	solvent(s)[a]	crystal morphology	density[b] (g/cm^3)
I	MeOH THF 1:1 CH_3CN/THF	plates	1.636
II	$(CH_3)_2C{=}O$ EtOAc MeOH CH_3CN 5:95 THF/$CHCl_3$	needles	1.602
III	THF (fast evap)[c] 2:5 CH_3CN/THF 1:1 $CHCl_3$/THF	prisms	

[a] All evaporations of solvent took several days from a closed vessel unless otherwise noted. The underlined solvent was the one used to grow single crystals. [b] Calculated from single-crystal results. [c] Evaporation was complete in several hours from an uncovered beaker.

This third polymorph of the X = Br complex is unlikely to be a partially amorphous solid, where poor crystallinity could be caused by desolvation of a lattice with trapped solvent, leading to a comparatively featureless XPD trace of this sort. First, there is no evidence of even trace amounts of residual solvent in an NMR spectrum of the redissolved solid. Second, a decrease in crystallinity should be accompanied by broadening of the diffraction peaks, whereas the major peak of polymorph III is no broader than intense peaks in the other polymorphs. Similarly, resonances in the solid-state ^{13}C NMR are not broadened relative to resonances for the other polymorphs (see below). Finally, heating polymorph III transforms it to one of the polymorphs with known structure (see below).

Influence of Sample Preparation on XPD Traces. There are significant differences in the intensities of observed and calculated peaks in the data summarized in Figures 1–3; the peaks at 2θ = 6° in Figure 1c and

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(22) For an overview of "disappearing polymorphs", see: Dunitz, J. D.; Bernstein, J. *Acc. Chem. Res* **1995**, *28*, 193.

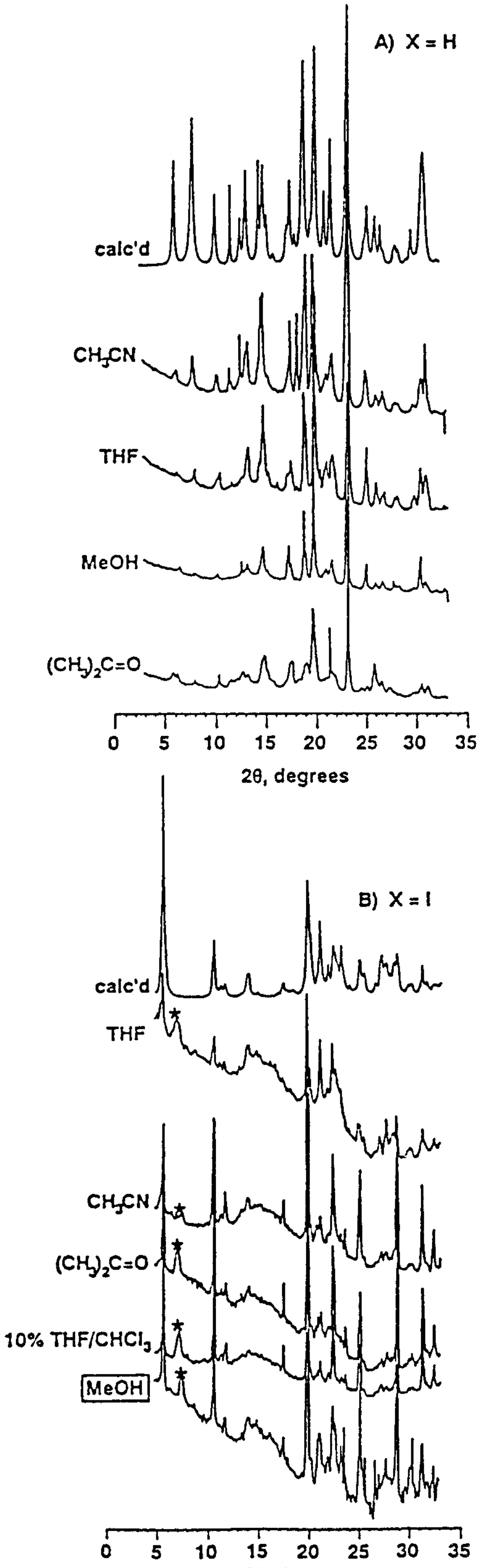

Figure 2. Experimental X-ray powder diffraction traces for X = H and I. Agreement with the calculated traces is only fair: although the peaks in the calculated trace are present in the observed traces, additional peaks are also observed and the agreement in intensities is poor. The boxed solvent is that used to grow the crystal studied by single-crystal diffraction (for X = H, the solvent for growth of single crystals was dichloromethane). The starred peak may be due to the sample holder or to a contaminant as in Figure 1.

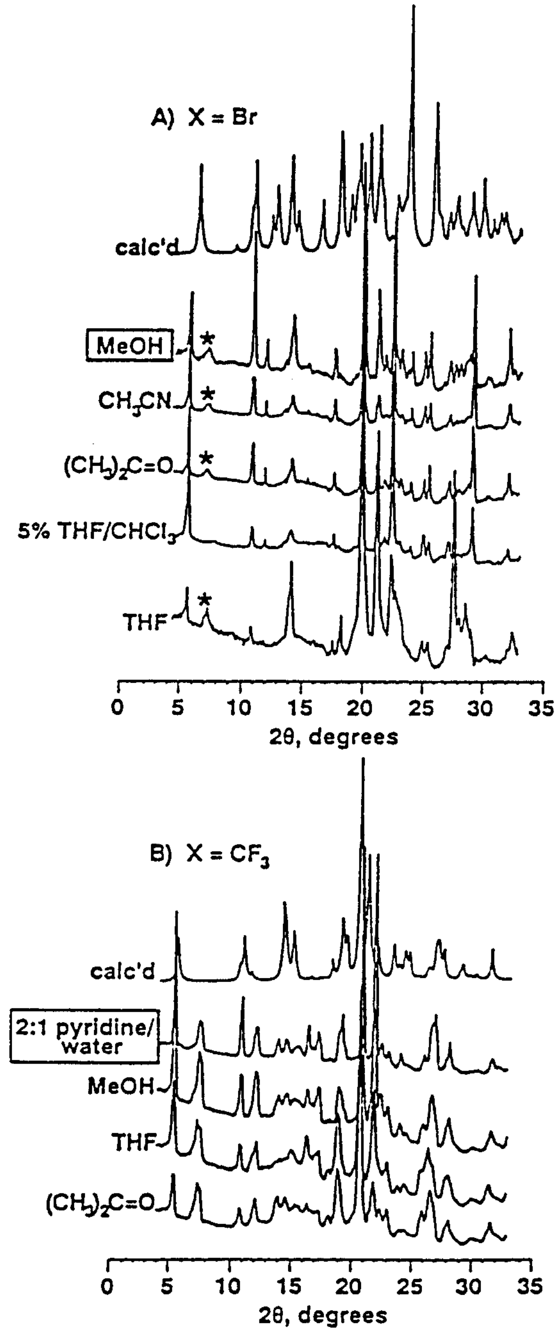

Figure 3. Experimental X-ray powder diffraction traces for X = Br and CF_3; the disagreement between experimental and calculated traces indicates that the single-crystal and powder data were obtained on different polymorphs. The boxed solvent is that used to grow the crystal studied by single-crystal diffraction. The starred peak may be due to the sample holder or to a contaminant as in Figure 1.

2θ = 31° in Figure 2a provide examples. Effects associated with the geometry of the diffractometer are likely to be responsible for intensity differences at low values of 2θ.[23,24] In fact, attempts to solve crystal structures from powder data might discard from the calculations diffraction peaks at low angles[25] or at least apply a correction factor,[26] for this reason. The explanation is as follows: a divergence slit of fixed width (in our case, 0.5°) will bathe a wider area with X-rays at

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(23) *Modern Powder Diffraction*; Bish, D. L., Post, J. E., Eds.; Mineralogical Society of America: Washington, DC, 1989.

(24) Parrish, W.; Mack, M.; Taylor, J. *J. Sci. Instrum.* **1966**, *43*, 623.

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(26) Petit, S.; Coquerel, G.; Perez, G.; Louër, D.; Louër, M. *Chem. Mater.* **1994**, *6*, 116.

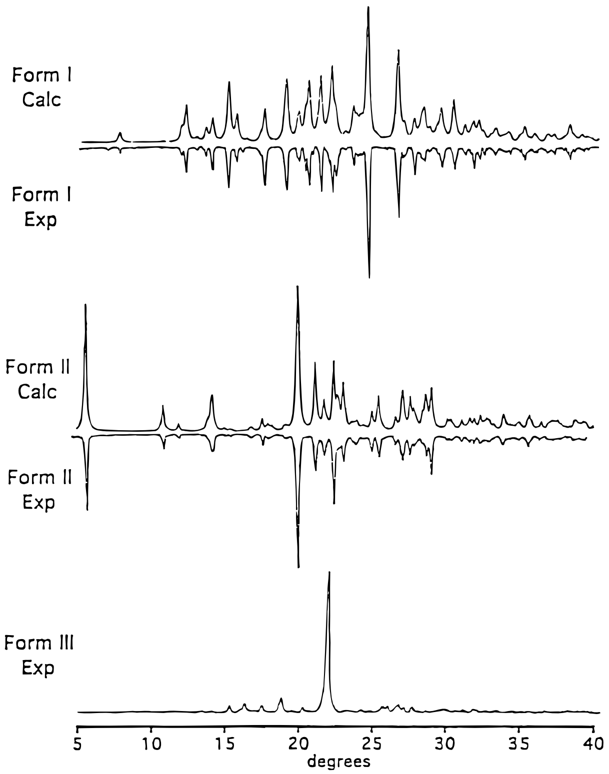

Figure 4. Comparison of experimental X-ray powder diffraction traces for three polymorphs of the X = Br complex with traces calculated from the solved crystal structures. There is no calculated trace for the third polymorph, since no single crystal suitable for X-ray diffraction could be grown.

low 2θ than at high 2θ. Equation 1, taken from ref 24,

$$L = R \tan \alpha / \sin \theta \quad (1)$$

details this relationship for a point X-ray source (an approximation that will serve for demonstration purposes). For example, with α, the angular slit width, equal to 0.5°, and R, the distance from the source to the sample, equal to 170 mm, the irradiated area L is 10 mm wide (the size of our sample) at $2\theta = 17°$. For $2\theta = 5°$, the area is 34 mm wide. In effect, the sample will then be sensing only a fraction of the total X-ray intensity of the beam, so diffraction from crystallite planes below about 17° in our experimental setup is correspondingly weaker. In addition, at low angles there will be a contribution from scattering due to the sample holder, which can give rise to a small peak at low 2θ.[23] We suspect that this background scattering is the origin of the small peaks that are starred in Figures 1−3, as well as the broad hump from approximately 13−18° in Figure 2b.

Effects associated with sample preparation could also be important. In general, we propose that some combination of two experimental features—preferred orientation and crystallite size—could produce powders that are not sufficiently isotropic to yield experimental XPD data in good agreement with idealized traces calculated only from unit-cell information and the molecular structure of the asymmetric unit.

We first considered preferred orientation, which is known to cause a weakening of some reflections experimentally.[27,28] Crystals composed of linear hydrogen-bonded tapes, when ground for XPD studies, probably afford crystallites with high aspect ratios due to the anisotropy of the intermolecular forces.[29] Fracture should thus be easier parallel, rather than perpendicular, to the tapes. Alignment of these microneedles with their long axes parallel seems likely, although we do not have independent experimental evidence (such as electron micrographs) for this effect.

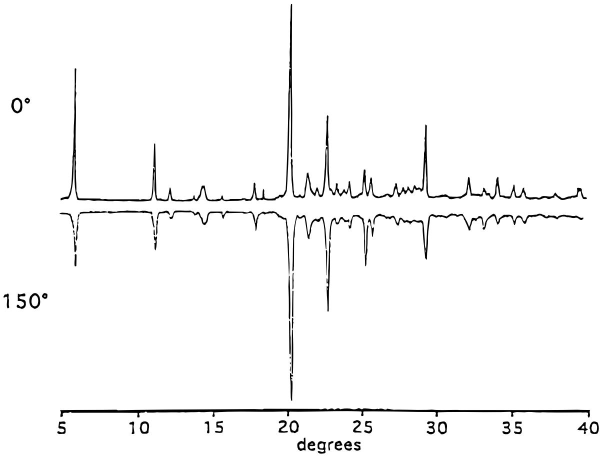

Figure 5. Comparison of two XPD traces performed on the same sample showing the effect of rotation of the sample holder in the diffractometer. The initial orientation is arbitrarily labeled 0°. The change in relative intensities of peaks, especially at low 2θ, could be an indication of preferred orientation of crystallites in the sample or of variations in the beam width due to the geometry of the diffractometer (see text).

We tested for preferred orientation by rotating a sample (polymorph II of the X = Br complex in all cases) in the diffractometer by 30° increments about the axis perpendicular to the horizontal sample holder.[30] Figure 5 shows the diffraction traces obtained at two such orientations; the biggest change occurs in the relative intensity of the peak at about 6°. These results suggest that preferred orientation might be occurring in these samples, although considering the small effects in relative intensity in primarily one region of the spectrum (at low 2θ, where the beam-width problems discussed above are also operative), it is probably not responsible for all the discrepancies between calculated and observed traces.[31]

A second factor could be incomplete grinding of the sample, leaving large crystallites; this situation could lead to a poorly isotropic distribution of crystal planes in the X-ray beam.[32,33] To test for the effects that a broad distribution of crystallite size might have, we ground samples for varying lengths of time. Grinding

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[27] Klug, H. P.; Alexander, L. E. *X-ray Diffraction Procedures for Polycrystalline and Amorphous Materials*, 2nd ed.; Wiley: New York, 1974.

[28] (a) Nakata, K.; Sugihara, H.; Mori, S.; Yamaguchi, H.; Takaki, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3395. (b) Nakata, K.; Takaki, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1168.

[29] Macroscopically, these complexes do frequently yield needle-shaped crystals. The plate morphology that also regularly occurs can also lead to orientation problems of crystallites.[28]

[30] The sample for this experiment was ground for 5−8 min in an agate mortar and pestle. This method was the one we commonly used to prepare all our powdered samples, so we believe that this search for preferred orientation is based on a representative class of powders.

[31] Note, however, that by rotating the sample and sample holder only around one axis, we would only be able to detect preferred orientation in one plane (the plane of the sample holder). Tilting the sample holder (which is essentially impossible in our diffractometer) should also be performed to test for a horizontal packing of needle-shaped crystallites.

[32] Large crystallites can give anomalously intense spikes for some reflections.[23] We speculate that some of the peaks in the X = I complex (Figure 2b) could arise in this manner.

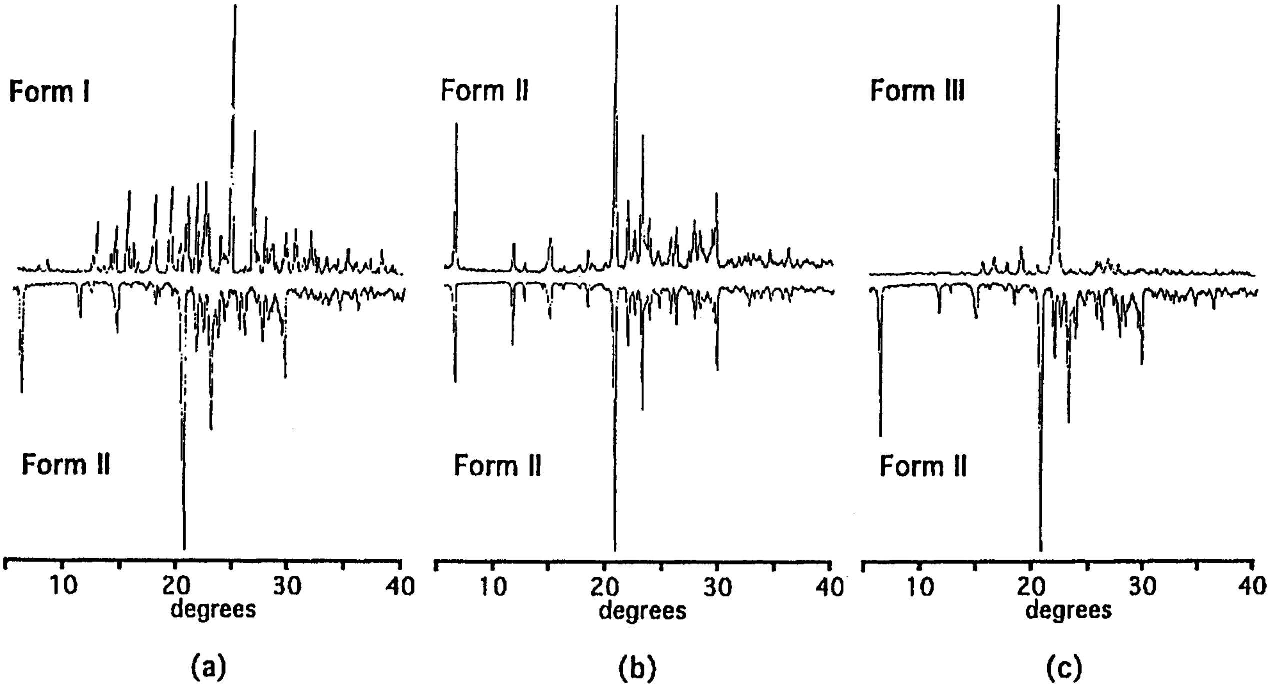

Figure 6. XPD traces of three polymorphs of the X = Br complex before (above) and after (below) thermal annealing at 140 °C for 6 days. Forms I and III have been converted to form II.

samples 10 min longer than usual (for a total of 15−18 min) led to small changes in the relative intensities of peaks at 6° and 11° (data not shown), on the order of magnitude of the changes seen above for rotating the sample. Visual inspection of crystalline samples showed that individual crystals did not become opaque or develop fractures with the passage of time (over a period of at least several days), indicating that they were not solvates. Grinding was therefore unlikely to be responsible for any changes in crystallinity associated with desolvation of the lattice (none of the members of this para series of complexes were ever found to contain solvent in the lattice).[1]

Our conclusion is that disagreement between calculated and observed traces, especially at low 2θ, are likely to be due primarily to the physical design of the diffractometer.[34] This contention is consistent with the fact that even for those complexes where agreement is satisfactory (X = Cl, CH_3, and F), agreement is *least* good at low 2θ. An auxilliary reason for the disagreement could be heterogeneity and anisotropy over the region probed by the diffractometer, caused by preferred orientation and/or crystallite size. The magnitudes of these effects associated with sample preparation, as determined by tests intended to check for their presence, seem too small to explain the discrepancies fully.[35]

Annealing of the X = Br Polymorphs. Annealing powders of the three polymorphs at 140 °C for 6 days demonstrated that both forms I and III convert to form II (see Figure 6). The relative intensities of the peaks in form II itself change slightly. These results indicate that form II is thermodynamically the most stable (at 140 °C) of these three polymorphs. We do not know which polymorph is the thermodynamically stable one *at room temperature*, although one rule of thumb holds that the denser polymorph (in this case polymorph I) will be the more stable.[36,37] Polymorph I also has a higher packing density, 0.72 vs 0.68 for polymorph II.[1]

Differential scanning calorimetry (DSC) was attempted on forms I−III. Separate runs were conducted for each sample during which the rate of heating was varied from 1 to 10 °C/min. In each case, the samples began to turn brown and decompose in the range 240−260 °C. Each sample showed a broad melting endotherm in the range 270−280 °C. None of the samples gave a detectable endotherm/exotherm prior to melting that indicated a phase transition under the conditions reported above. For melting points of the complexes, see ref 1.

Comparison of Packing in Single Crystals of Br Polymorphs I and II. Figures 7 and 8 show several views of the molecular packing in polymorphs I and II

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(33) For a demonstration that differences in crystallite size and shape can lead to powder diffraction traces that can be mistakenly interpreted as arising from different polymorphs, see: Potts, G. D.; Jones, W.; Bullock, J. F.; Andrews, S. J.; Maginn, S. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2565.

(34) Other problems associated with the setup of the diffractometer, e.g., inconsistent filling of the sample holder, could also make a contribution. Furthermore, the very act of grinding a sample could generate enough heat or mechanical stress to initiate a polymorphic phase transition. There seem to be few ways around this dilemma, except perhaps by employing a gradual increase in grinding time or vigor while remaining aware of the problems mentioned in footnotes 32 and 33.

(35) For studies that demonstrate the difficulty of reproducing peak intensities exactly, see: (a) Chrzanowski, F. A.; Fegely, B. J.; Sisco, W. R.; Newton, M. P. *J. Pharm. Sci* **1984**, *73*, 1448. (b) Kidd, W. C.; Varlashkin, P.; Li, C. *Powder Diffraction* **1993**, *8*, 180. (c) Davey, R. J.; Maginn, S. J.; Andrews, S. F.; Black, S. N.; Buckley, A. M.; Cottier, D.; Dempsey, P.; Plowman, R.; Rout, J. E.; Stanley, D. R.; Taylor, A. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1003. (d) Davey, R. J.; Maginn, S. J.; Andrews, S. F.; Black, S. N. *Mol. Cryst. Liq. Cryst.* **1994**, *242*, 79. These last two papers demonstrate an important but subtle point: different polymorphs may have XPD patterns that appear virtually indistinguishable from each other.

(36) Burger, A.; Ramberger, R. *Mikrochim. Acta (Wien) II* **1979**, 259.

(37) In the absence of calorimetric measurements, we cannot tell whether forms I and II are enantiotropic or monotropic.[36] The fact that the thermally produced samples of form II did not revert to their initial identity (forms I and III, respectively) is not proof that form II is the thermodynamically stable polymorph at room temperature. Metastable phases can be trapped well below the temperature of phase transition: (a) Yang, Q.-C.; Richardson, M. F.; Dunitz, J. D. *Acta Crystallogr.* **1989**, *B45*, 312. (b) Richardson, M. F.; Yang, Q.-C.; Novotny-Bregger, E.; Dunitz, J. D. *Acta Crystallogr.* **1990**, *B46*, 653.

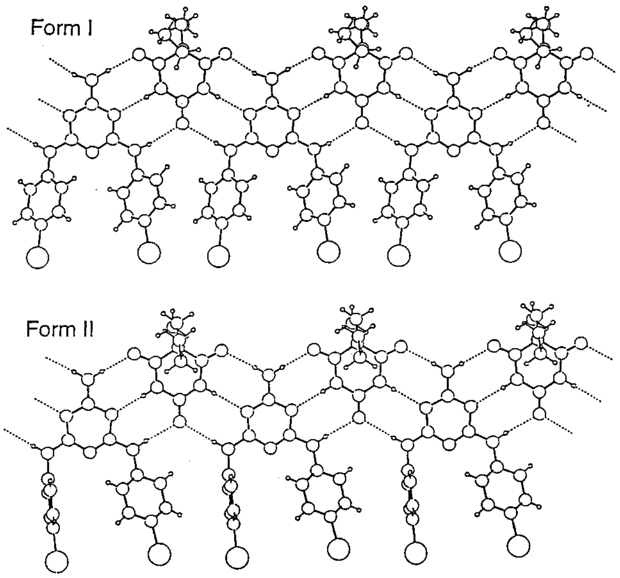

Figure 7. Comparison of tape geometry for two X = Br polymorphs. The disorder of the ethyl groups in form I is *not* shown in this figure; the torsion angles of one ethyl group cause it to appear skewed in this top-down view of the tapes.

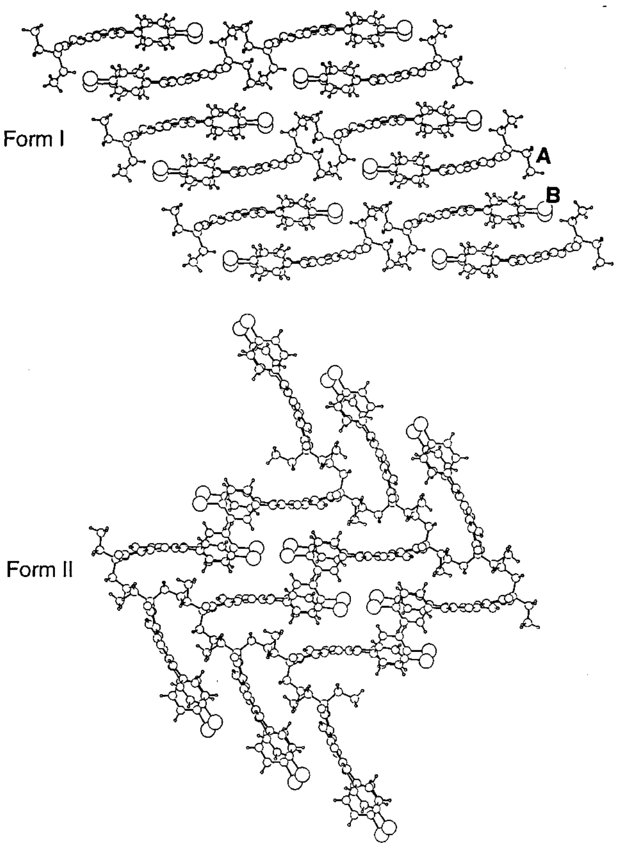

Figure 8. End-on packing views of two X = Br polymorphs.

of the X = Br complex (both of these structures were described in a previous paper on the family of complexes built from para-substituted diphenylmelamines).[1] Both polymorphs adopt the same kind of secondary architecture, namely, the linear tape motif. Differences arise instead at the tertiary level of architecture. Polymorph I exhibits dimer-based packing (illustrated by tapes A and B in Figure 8), while polymorph II adopts a sheetlike architecture. There are also differences in molecular conformation (Figure 9). The torsion angles of the phenyl groups differ: they are 42° and −136° in polymorph I, and 156° and −93° in polymorph II. Polymorph I is statistically disordered in the Et groups of barbital, and the torsion angles of these groups also differ: they are 38° (roughly a gauche conformation) and 178° in polymorph I, and −180° and −174° in polymorph II (both groups extended and trans).

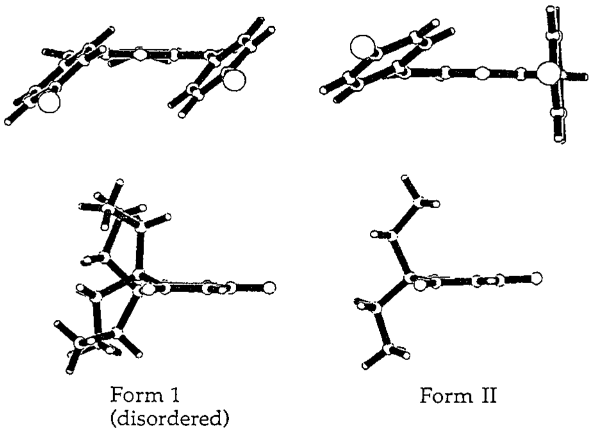

Figure 9. Comparison of the molecular geometry in two polymorphs of the X = Br complex. The ethyl groups in form I are statistically disordered in a ratio of about 2:1; the minor component has essentially the same torsion angles, but with trans and gauche conformations switched as though the molecule were flipped upside-down.

^{13}C Solid-State NMR of Br Polymorphs I, II, and III. We also used ^{13}C CP/MAS NMR to characterize the three polymorphs. Solid-state NMR should be useful for studies on polymorphism. The characteristics that define a molecule in alternative polymorphs, such as its conformation, thermal motion, and near-neighbor contacts, will also affect the isotropic chemical shifts of each carbon atom in the solid state.[38] In practice, however, routine one-dimensional spectra provide little specific information about three-dimensional packing.[39] We use the technique primarily in a fingerprinting sense to confirm the composition of the solid and to show that solvent is not included in the lattice.

Figure 10 shows solution and solid-state NMR spectra of all three polymorphs. The only significant statement we can make is that polymorph III is qualitatively different from the other two, especially in the aliphatic region, in that it has three methylene resonances. We cannot, however, determine what structural features might cause this spectroscopic result: for example, the ethyl groups could be crystallographically disordered, or there could be multiple molecules in the crystallographic asymmetric unit.

Conclusions

Figures 1−3 indicate that, considering only a limited range of crystallization conditions, polymorphism is not equally likely across this closely related family of complexes. Three complexes (X = Cl, CH_3, F) adopt only one packing arrangement, two (X = H, I) adopt primarily one arrangement but may have a small contribution from an alternative phase or phases, and two complexes

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(38) Changes in van der Waals contacts, charge-transfer interactions, ionic field effects, or dipolar interactions that arise from alternative packing arrangements can lead to differences between solution-phase and solid-phase chemical shift values of up to 3 ppm. Larger differences of up to 10 ppm are likely to be associated with changes in molecular conformation from solution to solid.

(39) For solid-state studies using sophisticated NMR techniques, see: Edwards, A. J.; Burke, N. J.; Dobson, C. M.; Prout, K.; Heyes, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4637.

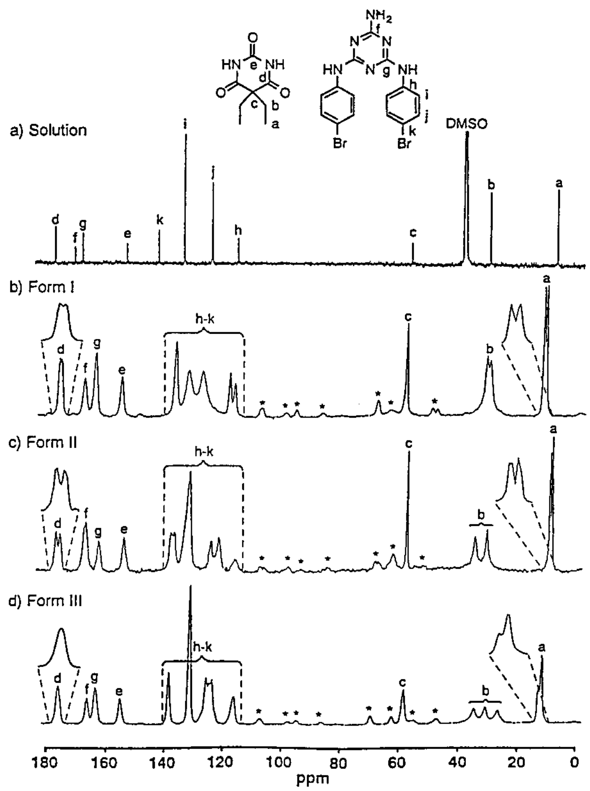

Figure 10. Solution and solid-state ^{13}C NMR spectra of X = Br polymorphs. Spinning sidebands are starred.

(X = Br, CF$_3$) adopt at least two packing arrangements. Given the polymorphism of the X = Br and CF$_3$ complexes, the single-crystal diffraction studies that we *initially* performed on those complexes only provided an incomplete picture of the packing preferences of these molecules.[1] In other words, the particular polymorph that was first described reflected a subjective choice of a crystallographer who simply selected the single crystals of diffraction quality. In the case of the X = Br complex, this choice amounts to a preference for polymorph I (plates) over polymorph II (needles; see Table 1). These studies reinforce the idea clearly stated by Desiraju,[5] Dunitz,[40] and Aakeroy and Seddon[41] that single-crystal studies should not form the basis for generalizations about molecular packing preferences in the absence of XPD studies (or other studies that explore polymorphism). Arguably, in studies directed toward crystal engineering, XPD studies that survey polymorphism should precede single-crystal studies.

In making connections to our previous work on crystalline architecture, we can draw only limited conclusions, since we have found only one complex that yields two polymorphs as single crystals. We note, however, that the differences between polymorphs occur at the levels of molecular conformation and tertiary packing, or aggregates of tapes; the secondary motif (linear tapes) is unchanged. This consistency in the secondary motif is expected considering our previous work: there are no steric or electronic reasons to force a change in the secondary motif, since the molecular composition has not changed.[1-3]

Furthermore, we speculate that the Br substituent, coming approximately at the midpoint of the size range spanned by these substituents (from H to CF$_3$), can crystallize in one of two alternative, polymorphic packing arrangements (see Figure 11). Phase II is isostructural to the packing adopted by the larger substituents X = I and CH$_3$, while phase I is isostructural to the packing of the smaller substituent X = Cl. We do not understand why the cocrystal with X = CF$_3$ has the structure it does. In other studies we have also found that fluorinated compounds show behavior that is anomalous based on steric arguments, but the origin of the anomalies remains undefined.[42] It remains to be seen whether the steric component to polymorphism turns out to be a general phenomenon that occurs in other families of organic crystals.

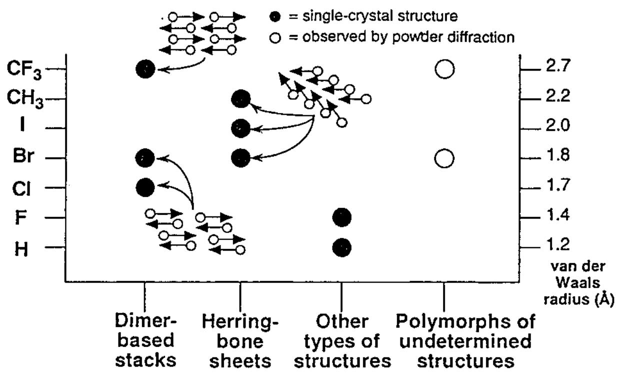

Figure 11. Relationship between the size of the substituent and the motif of tertiary crystalline architecture in complexes built from *N*,*N*′-bis(*p*-X-phenyl)melamines. Two varieties of dimer-based stacks and one of herringbone sheets are shown schematically. Arrows with circles attached represent end-on views of the tapes.

Experimental Section

General. Preparation of the complexes and single-crystal diffraction studies on them were described previously.[1]

X-ray Powder Diffraction Studies. Crystallizations to search for alternative polymorphs were performed by dissolving the complexes and placing the solution in a loosely closed vessel, such as a beaker or a crystallization dish covered with the lid of a crystallization dish. Evaporation proceeded at room temperature, usually over the course of several days. The crystalline solids obtained after evaporation was complete were ground by hand with an agate mortar and pestle, routinely for 5−8 min. The resulting powders were loaded into a fiberboard holder that had a 1 cm by 1 cm depression for the sample. The top of the powder was smoothed with a metal spatula to be flush with the top of the fiberboard holder. Thermal annealing of powder samples was performed in a drying oven.

Powder diffraction traces were obtained on both Phillips Model PW1010 and Scintag model XDS-2000 diffractometers with Cu Kα radiation (λ = 1.4506 Å). Scans were begun at 2θ = 3° and run to 33° or 43° in 0.1° step sizes with 40 s of counting at each step. Output files (intensity vs 2θ) were generated using the plotting program Kaleidagraph.

^{13}C CP/MAS NMR. Spectra of forms I−III of *N*,*N*′-bis(*p*-bromophenyl)melamine·barbital were collected at Eli Lilly Corp., Indianapolis, IN, on a Varian Unity 400 spectrometer operating at a carbon frequency of 100.577 MHz and equipped with a Varian solid-state NMR probe. Typical conditions for measurements utilized a 3.4 ms 90° proton radio frequency pulse, 1 ms contact time, 10 ms pulse-repetition time, 7 ± 0.2 kHz MAS frequency (rate of spinning), 50 kHz spectral width, and 50 ms acquisition time. The ^{13}C chemical shifts were referenced to the methyl resonance of hexamethylbenzene (δ = 17.3 ppm) by replacing the sample. Powders were prepared by grinding samples in an agate mortar and pestle for 5 min.

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(40) Dunitz, J. D. *X-ray Analysis and the Structure of Organic Molecules*; Cornell University Press: Ithaca, NY, 1979.

(41) Aakeroy, C. B.; Seddon, K. R. *Chem. Soc. Rev.* **1993**, *23*, 397.

(42) Schwiebert, K.; Chin, D.; Whitesides, G. M. Unpublished data.

Calculation of XPD Traces. The Siemens programs XPOW and XFOG in the SHELXTL-PLUS package of programs and the MSI package Cerius•2 were used to calculate XPD traces. XPOW (which uses observed single-crystal intensity data) and XFOG (which calculates intensity data based on an input molecular model and space group) gave identical calculated traces.

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Supporting Information Available: X-ray diffraction data (3 pages). Ordering information is given on any current masthead page.

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