Disappearing and Reappearing Polymorphs. The Benzocaine:Picric Acid System

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Abstract: The low-melting polymorphic modification of the 1:1 complex of benzocaine (**BC**) and picric acid (**PA**) had earlier been reported to be an example of a "disappearing polymorph". The **BC**:**PA** system has been reinvestigated by thermomicroscopy, calorimetry, solid-state NMR, and X-ray crystallography. The phase diagram has been derived, and robust procedures for the crystallization of the two 1:1 complexes, a hydrate of the 1:1 complex, and a 2:1 complex have been devised. The structures of all four phases have been determined and compared using graph set analysis to characterize the hydrogen-bonding patterns. It is shown that the thorough microscopic investigation of the thermal behavior, combined with calorimetric methods, can lead to the development of strategies to crystallize metastable polymorphic forms which may be difficult to obtain once their stable congeners have been obtained.

Introduction

Polymorphism, the ability of a substance to exist in several different crystal forms or modifications, is a frequently observed phenomenon in molecular compounds.[1] If a solid substance includes a solvent during crystallization, this structure is known as a pseudopolymorph, and in case of, e.g., water such crystal forms are generally called hydrates.[2] The polymorphic modifications of a compound are chemically identical but usually differ in their physical and chemical properties, such as density, vibrational spectra, and diffraction patterns.

Since a particular polymorph may have desirable properties, it may be useful to develop a robust method to obtain that polymorphic modification consistently and reproducibly. There are many documented cases of difficulties in obtaining crystals of a particular known modification.[3,4] Such difficulties may have serious practical consequences: a material designed to give a particular structure may exhibit an undesired polymorphic one;[5] a plant manufacturing a particular modification may have to close because it has been "poisoned" by an undesired polymorph;[6] a commercial drug formulation may no longer be available on the market due to the appearance of an undesired polymorphic modification.[7] We recently documented a number of representative cases in which it was difficult to obtain a given polymorphic form even though previously it had often been obtained routinely over long periods of time—so-called "disappearing polymorphs".[3] In the conclusion to that review, we stated our belief "that once a particular polymorph has been obtained, it is always possible to obtain it again; it is only a matter of finding the right experimental conditions". One of the challenges to those dealing with the preparation of solids is to be able to rationally develop those conditions and to control the polymorphic form obtained—in many instances to recover the disappeared polymorph. In this paper we present a case study of how such a challenge might be met.

One of the examples cited in the above-mentioned review was the case of benzocaine picrate (**BC**:**PA**). This binary system has been studied previously at least three separate times.[8−10] In 1972, Nielsen and Borka[8] reported the first preparation of the complex (now known as Mod. II) with a melting point of 130−132 °C. At the time, this modification was used as a pharmacopoeial standard for the identification of benzocaine (a topical anesthetic). Subsequently, the same authors prepared a high-melting modification (now known as Mod. I), mp 162−163 °C, whereupon they encountered severe difficulties in preparing and maintaining Mod. II for more than several hours before it transformed into Mod. I.[11] The low-melting modification is thermodynamically unstable at 20 °C.[8]

In 1974, Borka and Kuhnert-Brandstätter[9] reinvestigated the system using thermomicroscopy and found four modifica-

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(1) The April 1, 1998, release of the Cambridge Structural Database contains 181 309 entries, of which 5641 contain the qualifier "form", 163 the qualifier "polymorph", 172 the qualifier "modification", and 146 the qualifier "mod". Not all of these are entries for the structures of all polymorphs for a particular substance, but these numbers indicate that roughly 3% of the entries in the database are for polymorphic materials.

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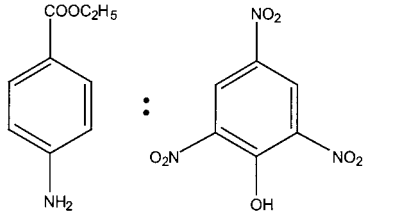

Benzocaine (**BA**) Picric acid (**PA**)

tions of **BC**:**PA**. They further identified two modifications of a (**BC**)$_2$:**PA** complex as well as a monohydrate. Apparently unaware of both of these earlier works, Togashi and Matsunaga also reported a (**BC**)$_2$:**PA** complex and an additional charge-transfer complex between the two compounds, observed by using differential scanning calorimetry (DSC).[10] No structural studies on any of the complexes were reported.

The aims of the work we report here were (1) to develop a general strategy and specific methods for controllably and reproducibly obtaining the "disappearing" modification II of **BC**:**PA**; (2) to develop methods for obtaining single crystals suitable for X-ray structure determination of as many as possible of the **BC**:**PA** species reported by earlier authors; and (3) to fully characterize the **BC**:**PA** phases by spectroscopic and structural techniques.

Experimental Strategy

Since the discovery of polymorphism in 1822,[12] one of the principal techniques for investigating the phenomenon has been optical microscopy and, in the latter part of the 20th century, thermomicroscopy.[13−16] These methods are particularly useful in detecting the existence of polymorphs and polymorphic transitions quickly and easily. In the last few decades, more sophisticated analytical techniques have supplanted the two classic ones,[17] but the net result of years of effort by a number of groups is that many polymorphic materials have been identified and characterized.[16,18−20] Despite the success of these methods, very few of these findings have been utilized as the starting point for structural studies.[21] The general problem apparently lies in the difficulty of translating the microscopic observations to the growth of single crystals that can be used for structure determination. In this work, we adopted a strategy for crystal growth experiments aimed at obtaining crystals for X-ray determination of the various phases of **BC**:**PA** based on the observations made using optical and thermomicroscopy and on the appearance and disappearance of those phases. We believe that this approach can be widely utilized and thus can provide the means for greatly expanding our understanding of the structural basis for polymorphic behavior.

Results

The Phase Diagram. The phase diagram can provide very useful information and guidelines for the preparation of a particular polymorphic modification. Much of the data for the preparation of the phase diagram may be readily obtained from thermomicroscopic studies. In fact, for a two-component system, such as **BC**:**PA**, Kuhnert-Brandstätter pointed out that "Kofler's contact method of thermal analysis offers the possibility of investigating organic two component systems qualitatively in the shortest possible time in the simplest possible manner."[16,22] More quantitative details may be added from DSC measurements.

Details on the preparation of the **BC**:**PA** contact sample and analysis are given in the Experimental Procedures section. Figure 1a shows the photomicrograph of the recrystallized contact preparation of **BC** and **PA** at 25 °C. The interference colors are due to the use of crossed polarizers. The pure compounds are at the extremities of the preparation, while in the region where the original compounds have merged, a number of different areas may be observed, due to the formation of different crystalline species combining the two components. Heating this preparation on the hot-stage microscope to a temperature of about 88 °C shows (Figure 1b) the eutectic melt of **BC** and the broad dark yellow crystals of a new compound. Due to the crossed polarizers, the isotropic melt appears black. As can be seen in Figure 1c, at about 120 °C on the left side of the preparation **BC** is melted, and on the right side the eutectic between **PA** and the remaining crystals of the **BC**:**PA** 1:1 complex melts. Figure 1d shows the situation which is observed at 122 °C. **PA** is almost melted, and in the middle of the preparation a eutectic melt appears. Thus, two chemically different kinds of complexes between **BC** and **PA** have been formed. The one on the right side is the 1:1 complex, while the small strip on the left side (the **BC** side) is a complex with composition (**BC**)$_2$:**PA**.[9] The former melts at 129 °C, while the latter shows a melting point at 124 °C.

The results obtained by means of thermomicroscopy and DSC experiments on different mixtures of benzocaine and picric acid led to the phase diagram (Figure 2). These investigations indicate the existence of two modifications of the 1:1 complex as well as of one modification of the 2:1 complex. The eutectic points of Mod. II of the 1:1 complex with benzocaine and picric acid are located at mole fractions of 0.07 (88 °C) and 0.85 (109 °C), respectively. The peritectic of Mod. II with the 2:1 complex appears at a mole fraction 0.33 and about 120 °C, and the eutectic between the 2:1 complex and benzocaine is located at 0.3 and at 110 °C.

Preparation of Single Crystals. The thermodynamic phase relationship between the two forms of **BC**:**PA** may be

(11) The authors reported the disappearing phenomenon and their attempts to overcome it as follows:[8] "As a matter of curiosity, it ought to be mentioned that once the stable modification was obtained, the metastable modification could no longer be isolated. It was first observed by one of us (TKN). This observation was later confirmed in a separate laboratory (LB). Further, it was found that after discarding all samples, washing the equipment and laboratory benches and waiting for 8−12 days, the low melting modification could be isolated again. This has now been repeated several times in our laboratories. Obviously the seeding effect during the formation of the primary crystals (or during the very procedure of determination of the melting point) is exceptionally strong."

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(14) Kofler, L.; Kofler, A. *Thermo-MikroMethoden zur Kennzeichnung organischer Stoffe und Stoffgemische*; Wagner: Innsbruck, 1954.

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(21) For a more detailed account of the use and decline of the use of the microscope in polymorphism research, see: Bernstein, J.; Henck, J.-O. *Cryst. Eng.* **1998**, *1*, 119−128.

(22) For a summary of the contact method, see also: Emons, H.-H.; Keune, H.; Seyfarth, H.-H. In *Chemical Microscopy*; Svehla, G., Ed.; Comprehensive Analytical Chemistry, Vol. XVI; Elsevier: Amsterdam, 1982; pp 180−184.

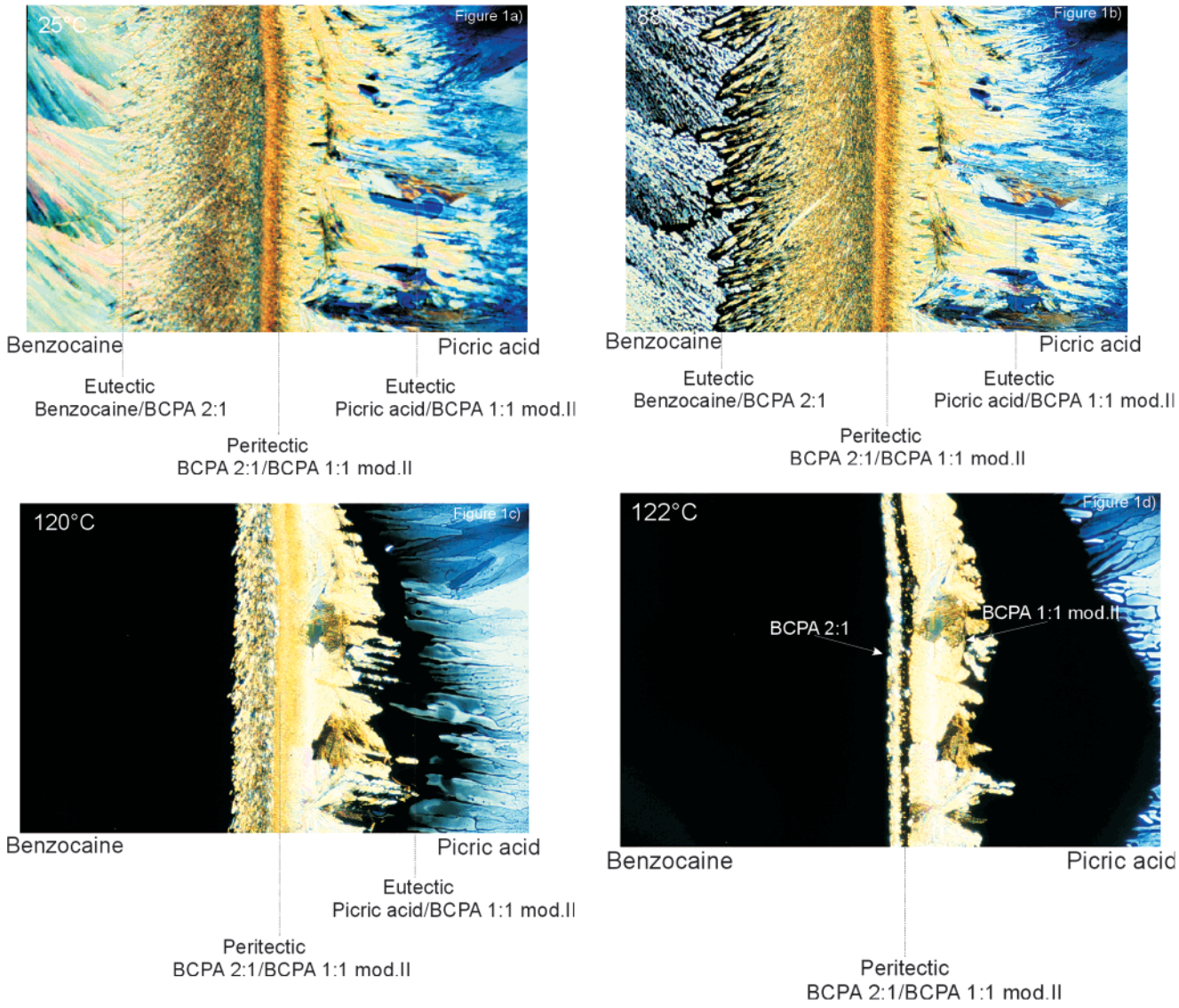

Figure 1. Photographs of the microscope slide Kofler preparations showing the various phases of the **BC**:**PA** binary system: (a) 25 °C, (b) 87 °C, (c) 120 °C, and (d) 123 °C (see text for explanation and discussion of details of the phenomena observed here).

enantiotropic or monotropic.[16] In the former case, the choice of crystallization conditions for one of the two polymorphs would be more facile, because thermodynamically controlled crystallization conditions could be chosen at temperatures below the thermodynamic transition point. To determine the monotropism/enantiotropism, we crystallized microcrystalline **BC**:**PA** Mod. II by means of thermomicroscopy and carried out DSC measurements on the resulting solid. The DSC trace shows an exothermic transition of Mod. II into Mod. I. We could then apply the empirical heat-of-transition rule[23] to conclude that these two crystal forms are monotropically related (Table 1). This means that Mod. I is the thermodynamically stable crystal form from absolute zero up to its melting point.

Since the lower melting Mod. II is thermodynamically less stable at all temperatures below the melting point, "kinetic" conditions must be created to attempt to crystallize this form. Therefore, a high-temperature (80 °C) crystallization was attempted, with water as the solvent, yielding single crystals up to 1 mm in maximum dimension. Since the prior work of Nielson and Borka[8] indicated that seeds of the stable form must be excluded, we obtained the less stable form prior to carrying out crystallization experiments aimed at obtaining the more stable one.

As Mod. I is the thermodynamically preferred form, an "equilibrium" crystallization is preferred over a "kinetic" one. Nielsen and Borka[8] obtained Mod. I by "excessive drying of [Mod. II] at 105 °C", conditions which are not particularly conducive to an "equilibrium" situation, nor to the growth of single crystals. Also, the existence of the hydrate (determined in the thermomicroscopic studies) suggests that the presence of water might be problematic in attempting to obtain nonhydrated phases. Hence, we resorted to a nonaqueous gel-diffusion crystallization,[24] using Sephadex as the gel medium, and obtained large single crystals (1−2 mm maximum dimension) after 3 days at 20 °C.

The rather drastic drying procedure described by Nielsen and Borka[8] to obtain Mod. I, Borka and Kuhnert-Brandstätter's report,[9] and our own observations on the hot-stage microscope indicated the existence of a hydrate of **BC**:**PA**. To obtain single crystals of this material, we attempted a crystallization from a

(23) According to the "heat-of-transition rule",[18] if the phase transition is exothermic, then there is no transition point below the experimentally observed transition temperature. This is generally observed if two transitions are monotropically related. As can be seen in Table 1, the phase transition has been determined by DSC measurements to be exothermic.

(24) Desiraju, G. R.; Curtin, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1977**, *99*, 6148−6149.

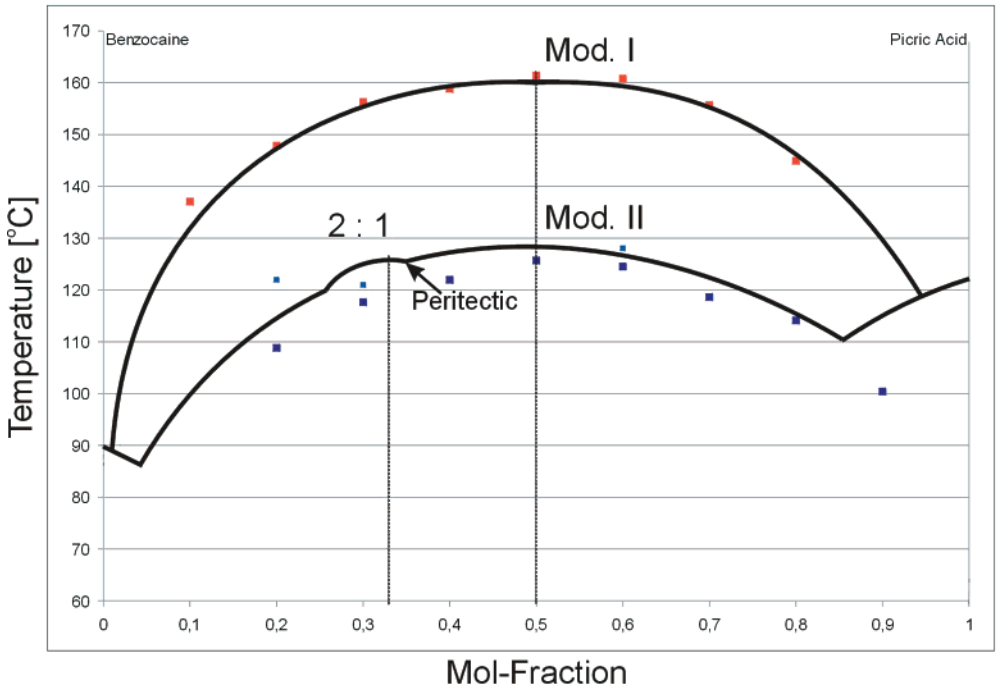

Figure 2. Phase diagram of the **BC**:**PA** system.

Table 1. Physicochemical Data of **BC**:**PA** Mod. I, **BC**:**PA** Mod. II, and (**BC**)$_2$:**PA**

	BC:**PA** Mod. I	**BC**:**PA** Mod. II	(**BC**)$_2$:**PA**
mp (°C), DSConset	161	129	119
thermomicroscopy	161	128	120
enthalpy of fusion (kJ mol^{-1})	63	56	
enthalpy of transition (kJ mol^{-1})		−9 → Mod. I	
entropy of fusion[a] (J mol^{-1} K^{-1})	145	118	

[a] Calculated by $\Delta S_f = \Delta H_f$ mp^{-1}.

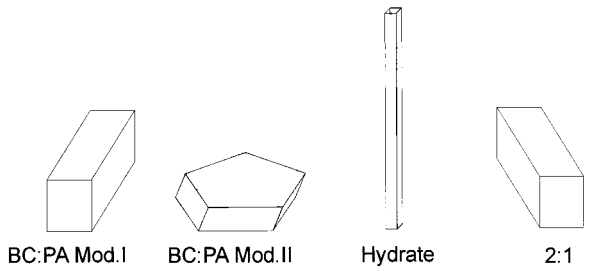

Figure 3. Line drawing representation of the morphologies of the four different crystalline materials obtained, as labeled.

saturated water solution in a sealed virgin flask (to prevent the unintentional incursion of seeds of any of the other forms) at 20 °C; needle-shaped crystals (up to 4 mm long) appeared after 48 h.

Crystals of the 2:1 complex were obtained by slow evaporation (ca. 4 weeks) of a 1:1 mixture of the components in 2-propanol at 4 °C. Admittedly, this was not an experiment designed to obtain the 2:1 complex, but the ample evidence to indicate its existence increased our interest in examining all the crystals obtained and motivated our attempts to obtain the crystals, using conditions different from those used for the other three species.

The crystals of all four complexes were yellow but were easily distinguished by their morphology (Figure 3) and, very clearly, by their melting points.

Crystal data for the four structures are given in Table 2; details of the structure determination are given in the Experimental Procedures section.

Crystal Structures. (a) General Features. All four structures are ionic picrates, the acidic hydrogen of the hydroxyl group on picric acid having been transferred to an amino group on benzocaine. The atomic numbering, given in a the ORTEP diagram (for (**BC**)$_2$:**PA**), is identical for all four structures

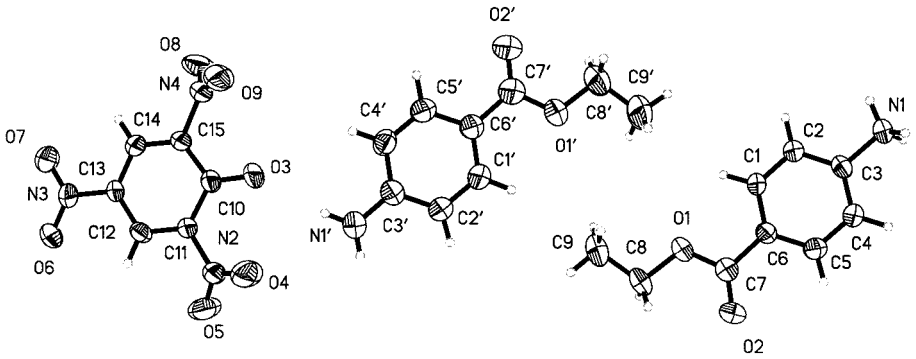

Figure 4. ORTEP diagram of the molecules in the (**BC**)$_2$:**PA** structure, showing the atomic numbering. Hydrogens are numbered according to the atoms to which they are attached. Numbering is identical for the other structures; the oxygen of the water molecule in **BC**:**PA**·H_2O is O01.

Table 2. Summary of Crystallographic Data for the Four Compounds Studied

	BC:**PA** Mod. I	**BC**:**PA** Mod. II	(**BC**)$_2$:**PA**	**BC**:**PA**·H$_2$O
formula	$C_{15}H_{14}N_4O_9$	$C_{15}H_{14}N_4O_9$	$C_{24}H_{25}N_5O_{11}$	$C_{15}H_{16}N_4O_{10}$
formula weight	394.3	394.3	559.5	412.3
crystal system	monoclinic	triclinic	triclinic	monoclinic
space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P2_1$
color of crystal	yellow	yellow	yellow	yellow
Z	4	2	2	2
a (Å)	7.149(3)	7.304(3)	8.190(2)	4.1478(8)
b (Å)	12.240(7)	8.231(2)	8.857(3)	12.732(3)
c (Å)	19.594(9)	15.361(5)	19.747(5)	17.518(4)
α (°)	90	99.91(2)	78.59(2)	90
β (°)	96.77(3)	99.53(2)	85.13(2)	93.84(3)
γ (°)	90	106.73(3)	67.93(2)	90
R-factor (%)	5.1	3.3	4.0	3.8
GOF (on F^2)	0.988	0.969	0.908	0.980

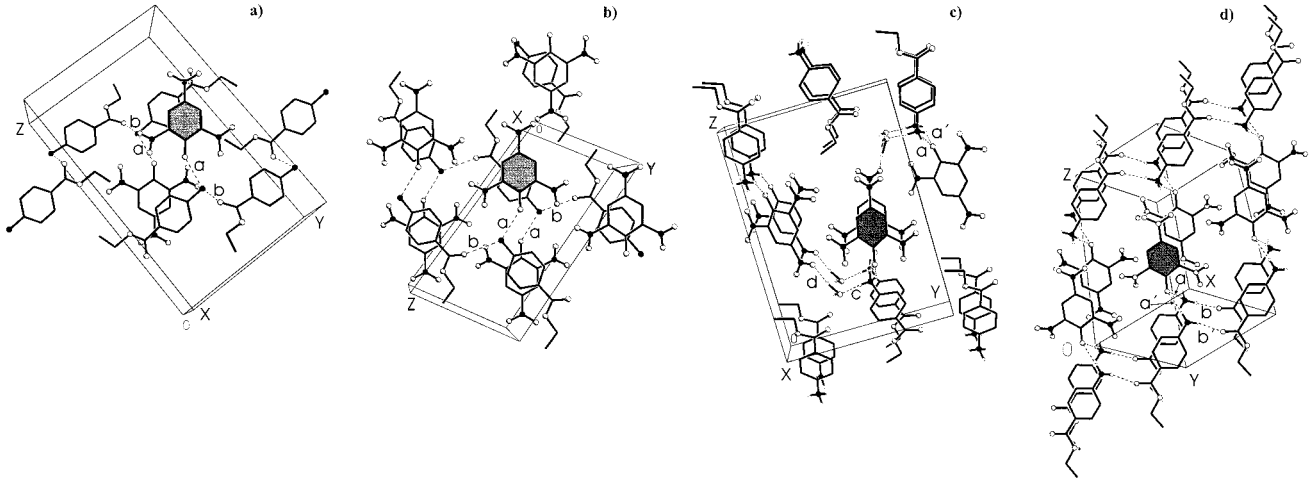

Figure 5. Packing diagrams the four crystal structures. For ease of comparison, in all cases the view is chosen on the best plane of the shaded picrate anion as a reference, with the C−O vector pointing down. Some slight rotational adjustments of the views have been made to facilitate better viewing of the packing and the hydrogen bonds. Carbon atoms are not explicitly drawn. Oxygens are represented by empty circles, and nitrogens are represented by filled circles. Hydrogens have been eliminated for clarity except where noted. The unit cell axes are marked as *X,Y,Z,* while hydrogen bonds are identified by lowercase letters (see text). (a) **BC**:**PA** Mod. I, (b) **BC**:**PA** Mod. II, (c) **BC**:**PA**·H$_2$O (hydrogens are included on the water molecule and on N1 of **BC**), and (d) (**BC**)$_2$:**PA** (hydrogens on N1 and N1′ are included).

Table 3. Rotation Angles (deg) of Nitro Groups in **PA** in the Four Crystal Structures

angle about C−N bond	**BC**:**PA** Mod. I	**BC**:**PA** Mod. II	**BC**:**PA**·H$_2$O	(**BC**)$_2$:**PA**
C11−N2	−176.0	−144.4	−168.5	−152.8
C13−N3	4.7	11.3	8.2	0
C15−N4	−37.9	147.4	19.2	−49.4

(Figure 4). There are no unusual bond lengths or angles. Only two of the torsion angle values for the ethyl ester chain of the **BC** moiety suggest some conformational variation, namely that for C5−C6−C7−O1 of **BC**:**PA** Mod. I (157.6°) and that for C7−O1−C8−C9 of **BC**:**PA** Mod. II (161.0°) compared to the others, which are all in the range 170−180°. These conformational differences were not investigated further.

The rotations of the nitro groups in **PA** are summarized in Table 3. That para to the phenolate oxygen is essentially coplanar with the benzene ring in all cases. The ortho nitro groups are rotated out of the phenyl plane, those about C11−N2 all in the same sense but to varying degrees, while those about C15−N4 are also rotated to approximately the same degree, but the rotation in the hydrate is opposite in sense from the other three instances.

BC:**PA** Mod. I in (Figure 5a) may be described as mixed stacks of ···**BC**$^+$··· **PA**$^-$··· with apparently $\pi-\pi$ plane-to-plane interactions along the [100] direction. The best planes of the BC$^+$ and PA$^-$ within a stack make an angle of 2.3° with each other, the distance between centers of rings being 4.04 Å. **BC**:**PA** Mod. II (Figure 5b) also crystallizes in mixed $\pi-\pi$ stacks of ···**BC**$^+$···**PA**$^-$···, again essentially along [100]. The mode of overlap along the stack is such that the four atom chain of the ester group is nearly parallel to the long (O--C···*p*-NO$_2$) axis of the molecule, while in Mod. I the chain of the ester group is nearly perpendicular to that axis. The angle between the phenyl rings (7.6°) is slightly larger, but the distance between centers is smaller (3.70 Å), indicating a greater degree of overlap between neighboring molecules in Mod. II.

In contrast to the two anhydrous complexes, in **BC**:**PA**·H$_2$O (Figure 5c) the cations and anions are arranged in segregated stacks ···**BC**$^+$···**BC**$^+$··· and ···**PA**$^-$···**PA**$^-$···. The perpendicular distance between planes in the **BC**$^+$ stack is 3.73 Å, while that in the **PA**$^-$ stack is 3.45 Å. Sheets of cations or anions are generated by the screw operation along the *b* axis, and in these sheets cations and anions alternate along the *c* axis. The angle between the phenyl rings of **BC**$^+$ and **PA**$^-$ is 35°. There are sheets of cations and sheets of anions, both parallel to the stacking direction, so that the structure is built up of parallel sheets of cations and anions, in a manner similar to zinc blende. Since the structure is polar, this means that, as drawn in Figure 5c, the (001) and (00$\bar{1}$) faces of the crystal should be oppositely

Table 4. Geometric Features of the Hydrogen Bonds Discussed in the Text (The Designations **a**, **a′...d** Correspond to the Hydrogen Bonds in Figure 4, and Are Defined for Each Section)

(**a**) N^+—H···$^-$O—C

	$N^+\cdots{}^-O$ (Å)	H···$^-$O (Å)
BC:**PA** Mod. I	2.681(4)	1.772(3)
BC:**PA** Mod. II	2.667(3)	1.716(3)
(**BC**)$_2$:**PA**	2.762(4)	1.792(4)
a′ [a]	3.024(4)	2.182(4)
BC:**PA**·H_2O	2.678(7)	1.709(8)
a′	2.791(7))	2.083(7)

(**b**) N^+—H···O═C

	$N^+\cdots$O (Å)	H···O (Å)
BC:**PA** Mod. I	2.834(4)	1.956(3)
BC:**PA** Mod. II	2.883(3)	2.279(3)
(**BC**)$_2$:**PA**	2.860(4)	1.945(4)
b′ [b]	2.994(4)	2.163(4)
BC:**PA**·H_2O	–	–

(**c**) N^+—H···O(w), (**d**) O(w)—H···O═N(nitro)

BC:**PA**·H_2O[c]	D···A (Å)	H···A (Å)
c[c]	2.803(8)	1.983(7)
d	2.948(7)	1.787(7)

[a] For this entry, **a′** is the hydrogen bond from the *neutral* **BC** to the **PA**$^-$ in the 2:1 complex. [b] For this entry, **b′** is the hydrogen bond from the *neutral* **BC** to the **PA**$^-$ in the 2:1 complex. [c] The generic notation (D—H···A) for the hydrogen bond is used here, since **c** and **d** are different hydrogen bonds.

charged as in zinc blende.[25] The (**BC**)$_2$:**PA** complex (Figure 5d) is composed of **BC**$^+$ cations, **PA**$^-$ anions, and an additional neutral **BC** molecule, confirming the conclusion of Togashi and Matsunaga from IR data.[10] The **PA**$^-$ anions are arranged across successive inversion centers at $^1/_2$, $^1/_2$, $^1/_2$, forming a stack in the *b* axis direction, with a perpendicular distance between atoms of one picrate ring and the plane of its centrosymmetric neighbor of 3.48−3.51 Å and a distance between ring centers of 5.90 Å. Translation of these stacks along the *a* crystallographic axis generates a sheet of picrate anions. The **BC** molecules are also stacked along the *b* crystallographic axis, with alternating neutral **BC** and **BC**$^+$ cations. The angle between the phenyl rings for the two species is 13.6°, with a center-to-center distance of 3.82 Å. Sheets of these **BC** moieties are then generated by the *a* axis translation.

(b) Hydrogen Bonding. There are clearly a number of possibilities for hydrogen bonding in these four structures, and a comparison of the hydrogen-bonding patterns facilitates recognizing the similarities and differences among them.

The hydrogen bonds are defined and their metrics are compared in Table 4. Hydrogen bond **a** appears in all structures and is remarkably constant, save for the bond to the neutral **BC** in (**BC**)$_2$:**PA** and for the second hydrogen bond of the type (noted as **a′**) in the hydrate. Hydrogen bond **b** appears in all but the hydrate, but the H···O distance is longer in **BC**:**PA** Mod. II and to the neutral **BC** in (**BC**)$_2$:**PA** than in the two other cases.

The two hydrogen bonds involving water (once as donor and once as acceptor) in the hydrate are denoted as **c** and **d** in Table 4. It is not clear if the long O−H and concomitantly short H···O distances for the latter are of significance or merely a result of the unconstrained refinement of the hydrogen atom position in the crystal structure analysis.

The most direct way of summarizing the hydrogen-bonding patterns and comparing them is through the use of graph sets.[26,27] The graph set assignments are conveniently summarized in (symmetric) matrix-type tables,[27] in which the diagonal elements are the first level graph set assignments and the off-diagonal elements are the second level assignments. Consistent ordering of the columns and rows with chemically identical hydrogen bonds through the four molecules (to the extent that it is possible) greatly facilitates comparison of hydrogen-bonding patterns among the structures. These graph set assignments are summarized in Figure 6.

BC:PA mod.I

	a	b
a	D	
b	$D_2^2(5)$	C(8)

BC:PA mod.II

	a	b
a	D	
b	$D_2^2(5)$	C(8)

BC:PA·H_2O

	a	a'	c	d
a	D			
a'	$D_2^1(3)$	D		
c	$D_2^2(5)$	$D_2^2(5)$	D	
d	$D_2^2(9)$	$D_2^2(9)$	$D_2^2(4)$	D

(BC)$_2$:PA

	a	a'	b	b'
a	D			
a'	$D_2^1(3)$	D		
b	$D_2^2(5)$	-	C(8)	
b'	-	$D_2^2(5)$	-	C(8)

Figure 6. Graph set assignments for the hydrogen bond patterns in the four structures studied. The hydrogen bonds are denoted by lowercase letters that correspond to the tabulation in Table 5 and the notation in Figure 6. As in ref 27, diagonal elements represent first level graph assignments, while off-diagonal ones represent second level graph sets composed of the two hydrogen bonds forming that element. A hyphen indicates that there is no connectivity between the hydrogen bonds at the second level.

The same two *individual* hydrogen bonds are present in **BC:PA** Mod. I and **BC:PA** Mod. II. The monotropic transformation from mod. II to mod. I is not accompanied by any overall pattern change. Also, the fact that the ∼7 Å axis is maintained suggests that the transformation takes place within the sheets nearly perpendicular to this axis. The transformation, observed by microscope, is seen to be a solid−solid transformation but involves extensive shattering of the crystalline material, indicating that quite drastic structural changes are, indeed, taking place. However, a careful visual examination and comparison of the two structures with all of these considerations did not reveal a simple geometric mechanism for the phase change.

Thermal Studies and Thermodynamic Relationships among the Structures Studied. The structural properties of Mod. I

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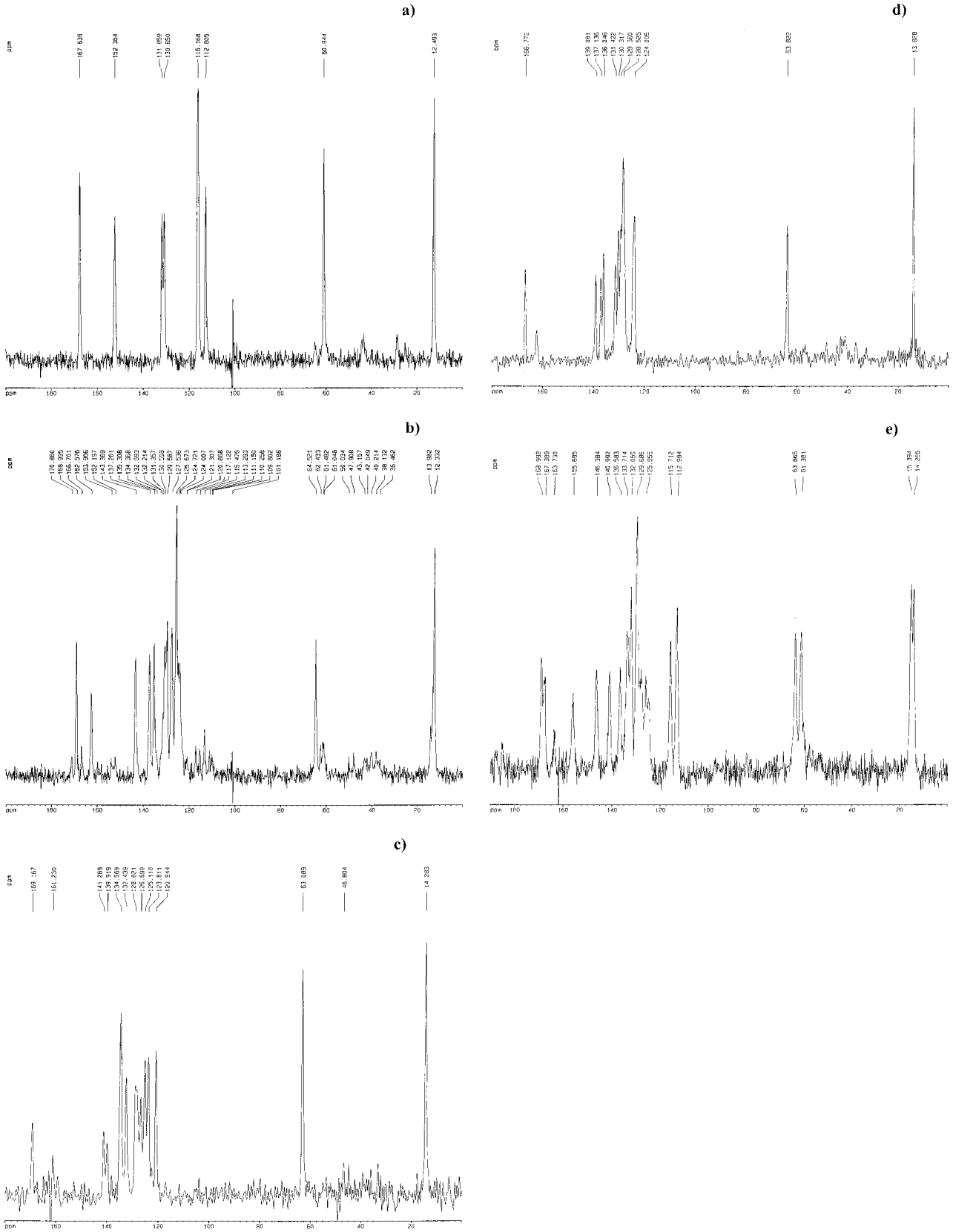

Figure 7. CP-MAS solid-state NMR spectra: (a) benzocaine, (b) **BC**:**PA** Mod. I, (c) **BC**:**PA** Mod. II, (d) **BC**:**PA**·H_2O, and (e) $(\mathbf{BC})_2$:**PA**.

and Mod. II are quite similar. Lacking the structural data, one might be tempted to suggest the 30 K difference in melting point as being due to extraordinary differences in the packing properties of the two modifications. The system studied here shows that it is questionable whether differences in melting can be used to try to relate thermodynamic properties of crystalline systems to structural features. It is the difference in entropy of fusion between the two forms which is the thermodynamic quantity for comparison here. The thermoanalytical results on **BC**:**PA** (Table 1) indicate that the entropy of fusion of the two crystal forms is also close. Since melting point, enthalpy of fusion, transition temperature, or enthalpy of transition can be

measured by "power compensation" DSC, the entropy of fusion is usually more readily available than the enthalpy of sublimation, which is a direct measure of the lattice energy.

Solid-State NMR Studies. The four crystalline complexes studied here (Figure 7) show different ^{13}C solid-state NMR spectra, which can be used as fingerprint identifiers. One of the most distinguishing signals is that for the methylene carbon atom of the ethyl group of benzocaine. For Mod. I, Mod. II, and the hydrate, this chemical shift appears at approximately 64 ppm, whereas the 2:1 complex shows two signals at 64 and 61 ppm, respectively, clearly reflecting two different kinds of benzocaine species. The chemical shift for this carbon atom in pure solid benzocaine is 61 ppm. Another observation reflecting the ionic and neutral nature of the two benzocaine molecules in the 2:1 complex is the fact that the chemical shift for the carbon atom which is connected to the amino group is at 152 ppm for pure solid benzocaine and 156 ppm in the 2:1 complex. This peak is not observed in the other crystal forms, in which all benzocaines are cationic.

Experimental Procedures

Kofler's Contact Method for Determination of the Binary Phase Diagram.[14,16] A few crystals of the lower melting substance picric acid (mp 122 °C) were placed on a microscope slide at the edge of a cover glass. The amount of substance is chosen in such a way that the melt, which is pulled by capillary forces between the microscope slide and cover glass, occupies about half of the space between them. The preparation is solidified by cooling, and benzocaine (mp 90 °C) is treated in the same manner. In the zone where the melts come into contact, the two compounds merge. The thermal behavior observed on the Kofler hot-stage microscope during heating of the resulting preparation was used to construct and confirm the phase diagram. DSC experiments were also performed to construct the isobar phase diagram (Figure 2) using the melting points and enthalpies of fusion of mixtures of benzocaine and picric acid, determined from DSC studies.

Production of Single Crystals of the Crystal Forms. Crystal growth experiments were carried out using commercially available benzocaine and picric acid (Sigma), and the solvents were of analytical grade. ***Note*: *Picric acid is potentially explosive*!**

The crystallization of Mod. II as described by Nielsen and Borka[8] leads to a microcrystalline precipitate, which is not suitable for single-crystal X-ray structure determination. However, a mixture of 50 mL of a room temperature saturated water solution of benzocaine and picric acid in a virgin one-neck 250-mL flask covered with Parafilm leads after 48 h at 20 °C to needlelike single crystals of benzocaine−picrate monohydrate. Another preparation of a solution maintained at 80 °C yields, by slow evaporation, platelike single crystals of Mod. II within 24 h. Mod. II resulted only if particular care was taken to exclude seeds of Mod. I. Therefore, it is preferable to perform the crystallization of Mod. II directly from of the synthesis of the compound.

Single crystals of Mod. I suitable for crystallographic analysis were obtained by means of nonaqeous gel diffusion.[24] In this procedure, 0.5 g of Sephadex LH-60-120 (Sigma) was placed in a sealable flask, and 0.5 g of benzocaine dissolved in 6 mL of a 3:1 mixture of chloroform: methanol was added. The gel sets immediately. A solution of 0.2 g of picric acid in 6 mL of the same solvent mixture was placed above the gel. Diffusion of the two solutions and a crystallization period of 3 days at 20 °C yielded yellow crystals of columnar habit with dimensions about $2.5 \times 1 \times 1$ mm^3.

Single crystals of (**BC**)$_2$:**PA** were obtained by slow evaporation (4 weeks) of a solution of a 1:1 mixture of **BA** and **PA** in 2-propanol at 4 °C. The procedure for obtaining the hydrate was described above.

Thermoanalytical Methods. Polarized microscopy was performed using a Kofler hot-stage microscope (Thermovar, Reichert, Vienna, Austria). DSC was carried out with a Perkin-Elmer DSC-7. The binary phase diagram was constructed from DSC data (heating rate of 5 K min^{-1}) on several ground mixtures of known composition.

(a) Single-Crystal X-ray Diffraction. Crystallographic Data. The X-ray data for **BC**:**PA** Mod. 1, **BC**:**PA** Mod. 2, and (**BC**)$_2$:**PA** were collected on a conventional Syntex $P\bar{1}$ diffractometer [λ(Mo Kα) = 0.711069 Å, graphite monochromator, $\omega/2\theta$ scan, T = 293 K]. The data for **BC**:**PA**·H_2O were collected on a Siemens SMART 1000 CCD diffractometer. All structures were solved by direct methods and refined by full-matrix least-squares for non-hydrogen atoms. All the hydrogen atoms were located from a difference Fourier map and were refined isotropically. The only exceptions were the H atoms of the $-NH_3^+$ group in the (**BC**)$_2$:**PA** structure, which were found as above, but refined as a "riding group". SHELXTL[29] was used for all calculations. All the metric parameters are collected in Table 2. Atomic coordinates, bond lengths, angles, and anisotropic parameters have been deposited at the Cambridge Crystallographic Data Center.

(b) Solid-State NMR. The solid-state ^{13}C CP-MAS NMR spectra were measured on a Bruker DMX-500 spectrometer, at a measurement frequency of 125.8 MHz and a rotation frequency of 11 000 Hz.

Conclusion

Careful consideration of the thermodynamics and phase diagram along with observation of crystallization phenomena can provide information about the relationship among phases and suggest conditions for growing different polymorphic forms and solvates. Although Mod. II of **BC**:**PA** has been reported to be a "disappearing polymorph", we have demonstrated a strategy for determining the conditions to consistently produce it. We believe that this strategy can be useful for the exploratory search for polymorphs, the development of robust procedures for selectively obtaining a particular polymorph, and the preparation of single crystals of polymorphs for single-crystal X-ray structure determination. The success of this strategy reinforces our earlier contention[3] that once a particular polymorph has been prepared, in principle it should always be possible to find the conditions to obtain it again.

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