Polymorphism

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On the Polymorphism of Aspirin: Crystalline Aspirin as Intergrowths of Two "Polymorphic" Domains**

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In the preceding paper, we highlighted the ambiguity that exists in the literature concerning the nature of crystalline aspirin.[1] In 2004, Ouvrard and Price demonstrated computationally that the long-established aspirin crystal structure[2–4] was amongst those predicted to be most stable, but they identified a slightly more stable structure as the thermodynamic minimum.[5] At the time, it was unclear whether the predicted minimum-energy structure was a remnant of inadequate energy assessment,[6] or whether it was a plausible structure that awaited discovery. This issue appeared to be resolved in 2005, when Peterson, Zaworotko, and co-workers (hereafter referred to as PZ) claimed to have obtained the predicted second polymorph,[7] following X-ray analysis of aspirin crystals obtained from hot acetonitrile solution in the presence of either levetiracetam or acetamide. The proposed new polymorph was labelled aspirin "form II", and the long-established aspirin crystal structure was thereby designated "form I".

The distinction between the proposed aspirin polymorphs is subtle. They contain identical arrangements of O–H···O hydrogen-bonded dimers lying in layers, but these layers are arranged differently with respect to each other in the two forms (Figure 1). In form I, the layers are arranged so that C–H···O interactions form centrosymmetric dimers (arrangement **A**, Figure 1). In the proposed form II, adjacent layers

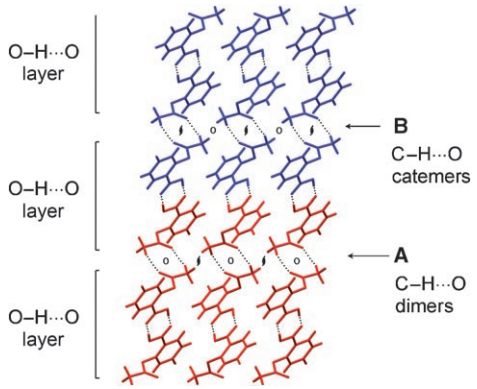

Figure 1. Illustration of the two interlayer arrangements within a representative aspirin crystal. Arrangement **A**, comprising centrosymmetric C–H···O dimers, exists between the layers that are colored red. Arrangement **B**, comprising C–H···O catemers extending along 2_1 screw axes, exists between the layers that are colored blue. The change in color within the central layer is for illustration only; all O–H···O hydrogen-bonded layers are identical.

are arranged so that C–H···O interactions generate catemers (arrangement **B**, Figure 1). Both interlayer arrangements are reasonable and acceptable in terms of the C–H···O interactions. Taken with the accord between the experimental and computational findings,[5] the PZ description of aspirin polymorphism appeared superficially to be plausible.[7] However, there are serious problems with their structure refinement. For the proposed form II, their crystallographic *R*-factors are unacceptable ($R1 = 0.162$, $wR2 = 0.327$), and several refined displacement parameters are close to or equal to zero, with anisotropic refinement being impossible. Combined with very close metric similarity between the unit cells of the form I and form II structures, this caused us to raise the question of whether the proposed form II might actually be an experimental artifact originating from erroneous handling of diffraction data collected from a form I crystal.[1] Indeed, we showed that form II of aspirin as reported by PZ may be derived, to the accuracy and precision reported by those workers, from experimental diffraction data collected on an aspirin crystal that was most certainly form I. Thus, we stressed that the PZ report did not establish the existence of aspirin form II to any acceptable level of scientific rigor.[1] In this report, we are able to resolve the issue fully. Aspirin exhibits a tendency to crystallize with an

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

intergrowth structure, in which layers of O–H···O hydrogen-bonded dimers form domains with arrangement **A** and domains with arrangement **B**, within the same single crystal. The distribution and total ratio of the domains is variable but appears to be limited. Aspirin form I, which comprises 100% arrangement **A**, is commonplace, but pure form II, which would comprise 100% arrangement **B**, has not been realized.

The crucial experimental result was first obtained after we freshly synthesized aspirin from salicylic acid (see the Supporting Information) and prepared single crystals by rapidly cooling a solution in hot acetonitrile (Table 1). Single-crystal X-ray diffraction analysis of these crystals (denoted **1a**, laths of typical dimension $0.20\times0.10\times0.05$ mm) proceeded apparently routinely to provide the form II structure, with $R1=0.071$ and $wR2=0.197$, against data measured to $2\theta=50°$ ($Mo_{K\alpha}$).[8] Unlike the PZ report, our refinement was anisotropic and entirely satisfactory, although we noted that our *R*-factors were a little higher than expected. These crystals were obtained without addition of levetiracetam or acetamide, demonstrating that the additive is not a significant factor. We obtained similar results by slow evaporation of an acetonitrile solution, indicating that the rapid cooling procedure also is not important. Powder X-ray diffraction seemed to confirm that the single crystal **1a** was representative of the bulk sample,[9] and the polymorphism of aspirin might therefore appear to be clear-cut. However, reconstruction of precession photographs in the a^*c^* planes of our experimental data (Figure 2a) revealed numerous additional reflections lying halfway between those of the principal form II lattice in the odd *l* rows, together with diffuse streaks along a^* between the Bragg reflections. In physical terms, the diffraction pattern demonstrates that aspirin crystals contain layers of O–H···O hydrogen-bonded dimers that are consistent (Figure 1), but that these layers form domains in which they adopt arrangement **A** (form I) and domains in which they adopt arrangement **B** (form II). The existence of the form I and form II domains is shown by the two sets of Bragg reflections, while the streaks indicate some degree of stacking disorder.

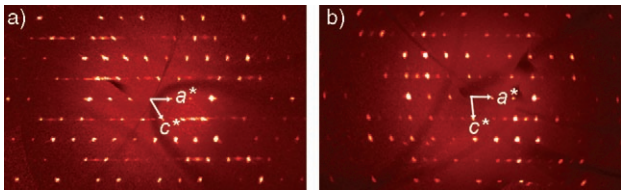

Figure 2. Reconstructed ($h-1\,l$) precession photographs for crystals **1a** and **2**. a) Crystal **1a** exhibits sharp Bragg reflections corresponding to the form II lattice (reciprocal lattice vectors shown), broader maxima halfway between these reflections in the odd *l* rows, and diffuse streaks along a^*. This indicates extended form II domains, smaller domains of form I, and regions in which there is a disordered distribution. b) For crystal **2**, the most intense Bragg reflections correspond to the form I lattice (reciprocal lattice vectors shown), and Bragg reflections of comparable profile exist for the form II lattice. This indicates a relatively more ordered structure than in **1a** (a) with extended form I and form II domains.

From analyses of numerous crystals obtained under various experimental conditions, including crystallization in the presence of acetamide[10] (Table 1), we find that both the relative intensities of the two sets of Bragg reflections and the extent of the streaking are variable. In crystal **2** (Figure 2b), for example, all Bragg reflections are relatively sharp, and there are no obvious streaks, consistent with extended well-ordered domains of form I and form II. In crystals **1a** and **1b**, sharp Bragg reflections for the form II lattice indicate extended form II domains, while the broader Bragg reflections between these lattice points indicate smaller domains of form I. The diffuse streaks also indicate regions with a less ordered pattern of interlayer arrangements **A** and **B**. Thus, both the sizes and distribution of the form I and form II domains are variable.

The interpretation of one-dimensionally diffuse diffraction data has a long history[11] and has been summarized

Table 1: Summary of crystallization conditions and single-crystal refinements.

Crystallization conditions	No.	Conventional refinement of single-crystal data[b]			Single-crystal refinement with batch scaling factors			Refined batch scaling factors[c]
		form	*R*1	*wR*2	form	*R*1	*wR*2	
rapid cooling of solution in hot MeCN	**1a**[a]	I	0.344	0.658	I	0.075	0.202	0.132(1)
		II	0.071	0.197	II	0.054	0.132	0.747(2)
	1b[a]	I	0.544	0.846	I	0.076	0.220	0.038(1)
		II	0.041	0.116	II	0.034	0.080	0.858(2)
rapid cooling of solution in hot MeCN in the presence of 1 equiv acetamide	**2**	I	0.059	0.175	I	0.056	0.140	0.803(3)
		II	0.305	0.631	II	0.076	0.288	0.146(1)
as synthesized (see the Supporting Information)	**3**[d]	I	0.033	0.089	I	0.033	0.089	0.982(4)
		II	unstable		II	0.076	0.141	0.003(1)

[a] Crystals **1a** and **1b** are different single crystals from the same crystallization batch. [b] Based on data sets obtained from two separate standard integrations of the CCD frames, considering only Bragg peaks. Refinements are performed against all F^2 data to $2\theta_{max}=50°$ ($Mo_{K\alpha}$). *R*1 is quoted for data with $I>2\sigma(I)$, *wR*2 is quoted for all data. [c] The high precision refers to that obtained from the least-squares refinement. See the text for discussion of the approximations and limitations of the approach. [d] A pure form I crystal. For form I refinement, the batch scale factor refines to be essentially unity. Conventional form II refinement against all F^2 data is unstable. For batch refinement, the scale factor refines to zero, effectively omitting all odd *l* reflections, thereby emulating a data set that contains only the even *l* reflections. This is exactly the situation that we noted in our previous manuscript.[1]

recently for molecular crystals.[12] The literature includes examples in which layered structures exhibit only one kind of interlayer arrangement, that is, structures for which there are alternative positions of adjacent layers that have exactly equivalent interatomic/intermolecular contacts (as for the close packing of spheres, for example).[13] The aspirin case is apparently the first of its kind in that it exhibits two distinctly different interlayer arrangements (**A** and **B**), both of which are physically and chemically reasonable. The accidental energetic degeneracy of the two possibilities,[5,6] combined with the specific metric relation between the form I and form II lattices, is the reason for the unusual crystallographic observations, since it allows aspirin diffraction patterns to be processed in two different ways to provide two different structures, both of which are physically reasonable. The metric transformation $[1\ 0\ ^1/_2\ 0\ -1\ 0\ 0\ 0\ -1]$ that relates the form I and form II unit cells causes all Bragg reflections *hkl* with even *l* to overlay but places the odd *l* reflections of form II halfway between those of form I.[14] Thus, the Bragg reflections arising from the two types of domain appear to a first approximation as a weighted overlay of the form I and form II diffraction patterns, with the distribution dependent on the relative domain ratio. If such a diffraction pattern is indexed in the usual way to one or other of the form I or form II unit cells, standard integration (that is, considering only Bragg reflections, and discounting any other features),[15] will provide a data set in which the even *l* reflections are of the correct intensity, but the odd *l* reflections are systematically weak. This is the path that was followed by PZ.[7] The extent to which the odd *l* reflections are in error reflects the ratio of the form I and form II domains.

On the basis of our description, a practical procedure to obtain an estimate of the total domain ratio is to introduce a batch scale factor into the crystallographic refinements, applied only to reflections with odd *l*. The refined value of this scale factor gives the relative weights of the form I and form II reciprocal lattices and therefore a direct estimate of the crystal composition. This estimate will be good for crystals that exhibit only sharp Bragg peaks and no diffuse streaks, while it will be more approximate when the streaking is more significant. Thus, the approach would be exact for two perfectly ordered domains with a single domain boundary, but it becomes progressively more approximate for real aspirin crystals as the extent of the domain disorder increases. The procedure gives a total composition estimate but no direct information concerning the sizes of the form I and form II domains or their distribution. For crystal **1a**, such a refinement against the form II data set[16] gives $R1 = 0.054$ and $wR2 = 0.132$, a significant improvement on the standard refinement, and the refined batch scale factor indicates that roughly 75% of the crystal comprises form II domains. The practical effectiveness of the process is illustrated more dramatically by batch refinement of the form I data set obtained from the same crystal. While standard treatment of the form I structure gives $R1 = 0.344$, $wR2 = 0.658$ and does not permit anisotropic refinement, introduction of the batch scale factor allows routine refinement with all non-H atoms anisotropic to give $R1 = 0.075$, $wR2 = 0.202$. In this instance, the refined batch scale factor indicates approximately 15% form I domains. The discrepancy between the two indications of the crystal composition (in other words, that they do not sum to 100%) reflects principally the failure to account for the diffuse features of the diffraction pattern.[17] With this procedure, the refined crystal structure will be either pure form I (100% arrangement **A**) or pure form II (100% arrangement **B**) if the batch scale factor should refine to unity. This is the case for crystal **3** (Table 1), which is pure form I. In all other cases, the intergrowth structure is present, and a more complex analysis of the entire diffraction pattern, including diffuse features, is necessary to extract further information regarding domain size and distribution.[12]

Using our straightforward approach, a general correlation can be derived between approximate domain ratio and the expected crystallographic *R*-values for a conventional treatment of the X-ray data.[18] Figure 3 provides a guide for assessment of the total domain ratio in any aspirin crystal using the *R*-values obtained from F^2 refinement on the basis of either the pure form I or the (hypothetical) pure form II structure if standard data reduction and refinement procedures should be followed. Using the correlation shown in Figure 3, the *R*-factors reported by PZ[7] show that their crystal actually comprised approximately equal proportions of domains with interlayer arrangement **A** and domains with interlayer arrangement **B**.

Chemically speaking, it is reasonable (albeit realized in hindsight) that aspirin crystals should provide intergrowth

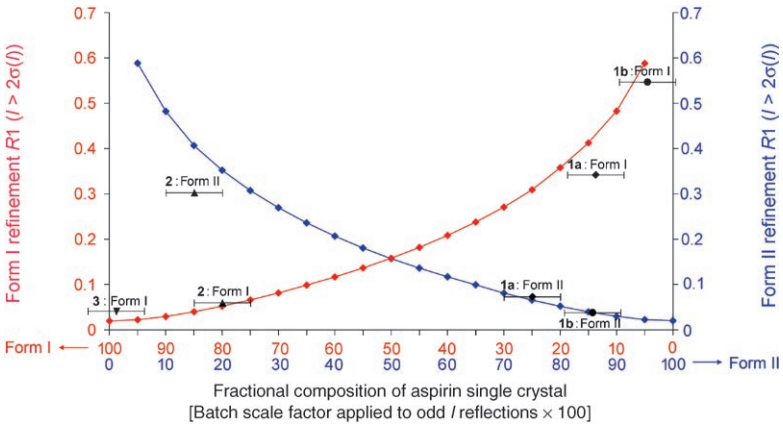

Figure 3. Correlation between total domain ratio and expected crystallographic *R*1 value, obtained for conventional refinement against all F^2 data. The correlation is derived from experimental data for crystal **3** (see the Supporting Information for full details). The red and blue curves refer to standard data reduction and refinement on the basis of the form I and form II structures, respectively, for an aspirin crystal with domain ratio indicated by the horizontal axis. The experimental points correspond to the *R* values obtained for the crystals listed in Table 1. For these, the composition estimate is taken from the batch scale factor refinement, with error bars indicating ±5% composition. For example, conventional refinement of crystal **1a** as form II gives $R1 = 0.071$. The separate batch scale factor refinement indicates 75% form II domains. The same crystal **1a** refined conventionally as form I gives $R1 = 0.344$, with the separate batch scale factor refinement indicating 15% form I domains.

structures in this way. The strongest interactions (O–H···O, herringbone) occur within the layers parallel to the (100) planes, which constitute the persistent building blocks within aspirin crystals. These are presumably the most robust growth units[19] in the system. Shearing of these layers relative to each other along [001], which is in effect the movement that transforms arrangement **A** into arrangement **B**, involves rupture and creation of weak C–H···O interactions. The energy difference between the **A** and **B** arrangements is clearly very small,[5,6] and together with the consistent layer surface at (100), this permits facile turnover between the two possibilities in the composite crystal. If the energy difference were significantly greater, individual crystals of one pure polymorph (either form I or form II) would be accordingly more stable. Ouvrard and Price[5] noted that form II should have "a low shear elastic constant, implying that it is so readily deformed that there may be problems in its growth". In the course of our present study, we have frequently observed crystals of pure form I (at least to the limits of detection possible for single-crystal and powder X-ray diffraction[20]), but the maximum proportion of form II domains that we have observed is approximately 85%. Thus, aspirin form II has not been documented in a pure form so far. Whether this means that arrangement **A** is inherently more stable than arrangement **B**, contrary to the calculations,[5] is a matter that remains to be firmly established. If it were, form II might be a metastable kinetic product[21] which could still potentially be observed, but which might transform to the more stable form I. However, we have not observed any such transformation, at least for single crystals standing in air over a period of two months.[22] It is also possible that arrangement **B** is indeed more stable than arrangement **A**,[5] but that the growth problems associated with arrangement **B** prevent the isolation of a pure aspirin form II. In this case, approximately 85% arrangement **B** may be the most that we can expect. Clearly, much future work remains to clarify completely the thermodynamic and kinetic aspects of crystalline aspirin.

Finally, the case of aspirin raises issues with regard to nomenclature. As for any evolving scientific area, crystal engineering is presently subject to lively and ongoing debate pertaining to the naming of concepts and phenomena. Terms such as "co-crystal" and "pseudopolymorph" have been discussed recently in this context.[23] The term "polymorph" has so far stayed above such controversies and is used to signify a situation where the same substance exhibits different crystal packing arrangements.[24] For crystallographers, this definition might be considered to encompass only crystals for which long-range translational order is dominant; in other words, it is appropriate only at one end of a continuum that ranges from perfect crystals to systems without long-range translational order. To chemists, the accepted distinction is rather more clear. Polymorphism implies that a molecule may adopt one or other type of packing arrangement in the crystalline state, and different polymorphs are distinct entities that display different physical and chemical properties. A single crystal of a given chemical substance is either one polymorph or another. In this context, one might ask how many polymorphs of aspirin actually exist. The domains with interlayer arrangements **A** (form I) and **B** (form II) certainly represent two different crystal structures that serve as reference points. However, considering that aspirin crystals display both arrangements within a single crystal, should aspirin really be described as polymorphic? What is certain is that the PZ description of their crystal as a polymorph distinct from form I is not justifiable. The PZ crystal, like several other aspirin crystals described in this paper, is an intergrowth of two "polymorphic" domains. We emphasize that the intergrowth crystals are exactly that: they are not simply mixtures of form I and form II, and they are not twins. Each aspirin crystal is an integral whole in which the domains are intimately connected with each other, with possibly many turnovers of domain within a single crystal. Further, it seems that the ratio of the domains in aspirin crystals is likely to be constant in any particular batch prepared under the same conditions.

This issue has implications beyond nomenclature. Should individual form I/form II compositions qualify for separate patent protection? Should patents be granted only for ranges of form I and form II domain ratios and not for specific compositions?[25] Is (pure) form II entitled to patent protection considering that it has not been realized as yet? Could this problem be solved by calling these crystals "polytypes", considering the voluminous literature on this topic in inorganic solid-state chemistry?[26] If so, would different polytypes then be entitled to patent protection? These and other issues suggest that one keeps an open mind with regard to definitions in crystal engineering, including that of the term "polymorph".[27] In an evolving subject, no definition should be carved in stone.

The Supporting Information includes details of the synthesis and crystallization procedures, powder X-ray diffraction data, reconstructed precession photographs for single crystals **1a**, **1b**, **2**, and **3**, a description of the geometry and intensities of the Bragg reflections in aspirin diffraction patterns, and details regarding the correlation between *R*-factors and the total domain ratio. The results of all refinements referred to in Table 1 are available in CIF format, with the corresponding *hkl* data available in SHELXL HKLF-4 format. All CCD frames (Bruker APEX2 format) can be obtained from the authors on request.

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[1] A. D. Bond, R. Boese, G. R. Desiraju, *Angew. Chem. Int. Ed.* **2006**, DOI: 10.1002/ange.200602378; *Angew Chem.* **2006**, DOI: 10.1002/anie.200602378.
[2] P. J. Wheatley, *J. Chem. Soc.* **1964**, 6036.
[3] Y. Kim, K. Machida, T. Taga, K. Osaki, *Chem. Pharm. Bull.* **1985**, *33*, 2641.
[4] C. C. Wilson, *New J. Chem.* **2002**, *26*, 1733.
[5] C. Ouvrard, S. L. Price, *Cryst. Growth Des.* **2004**, *4*, 1119.

[6] The minimum-energy structure was just 0.2 kJ mol^{-1} lower in energy than the established crystal structure, and in our opinion this value is so small that the order of energies might just as easily have been reversed.

[7] P. Vishweshwar, J. A. McMahon, M. Oliveira, M. L. Peterson, M. J. Zaworotko, *J. Am. Chem. Soc.* **2005**, *127*, 16802.

[8] The highest form II domain ratio observed from 15 single-crystal data collections is in crystal **1b**. For this crystal, conventional refinement of the form II structure gives: $C_9H_8O_4$, $M_r = 180.15$, monoclinic, space group $P2_1/c$, $a = 12.1515(10)$, $b = 6.5064(5)$, $c = 11.3677(9)$ Å, $\beta = 111.574(3)°$, $V = 835.79(12)$ Å^3, $T = 180(2)$ K, $\mu(Mo_{K\alpha}) = 0.114$ mm^{-1}, $2\theta_{max} = 50°$, 9778 reflections measured, 1474 unique reflections ($R_{int} = 0.029$), 1149 observed reflections, $R1(I > 2\sigma(I)) = 0.041$, $wR2$(all data) $= 0.116$, $S = 1.02$. CCDC-617840 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Compared to the powder X-ray diffraction pattern of pure form I, the principal features that reveal the presence of form II domains are peaks at $2\theta \approx 20.9$ and 26.0° (at 295 K, see the Supporting Information).

[10] With extremely rapid cooling of a hot equimolar solution of aspirin and acetamide in acetonitrile (that is, by plunging the flask directly into liquid N_2 or dry ice/2-propanol), we obtained a 1:1 molecular complex of aspirin and acetamide, which contains the expected acid–amide heterosynthon. This would argue in favor of acetamide acting as a growth inhibitor at the (200) faces of aspirin, leading to platelike crystals that cannot grow easily along [100]. It is likely that levetiracetam would behave in a similar way, and this is the morphology reported by PZ for their aspirin crystal. Crystal data for the aspirin/acetamide (1:1) co-crystal: $(C_9H_8O_4)(C_2H_5NO)$, $M_r = 239.22$, orthorhombic, space group *Pbca*, $a = 9.5268(4)$, $b = 8.7495(3)$, $c = 28.4520(11)$ Å, $V = 2371.61(16)$ Å^3, $T = 203(2)$ K, $\mu(Mo_{K\alpha}) = 0.107$ mm^{-1}, 68487 reflections measured, 3074 unique reflections ($R_{int} = 0.059$), 2586 observed reflections, $R1(I > 2\sigma(I)) = 0.042$, $wR2$(all data) $= 0.119$, $S = 1.04$. CCDC-618012 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) H. Jagodzinski, *Acta Crystallogr.* **1949**, *2*, 201; b) H. Jagodzinski, *Acta Crystallogr.* **1949**, *2*, 208; c) "Disorder Diffuse Scattering of X-rays and Neutrons": H. Jagodzinski, F. Frey in *International Tables for Crystallography*, *Vol. B* (Ed.: U. Shmueli), International Union of Crystallography and Kluwer Academic Publishers, Dordrecht, **2001**.

[12] H.-B. Bürgi, M. Hostettler, H. Birkedal, D. Schwarzenbach, *Z. Kristallogr.* **2005**, *220*, 1066.

[13] a) K. Dornberger-Schiff, H. Grell-Niemann, *Acta Crystallogr.* **1961**, *14*, 167; b) K. Dornberger-Schiff, J. D. Dunitz, *Acta Crystallogr.* **1965**, *19*, 471; c) K. Dornberger-Schiff, *Acta Crystallogr. Sect. A* **1982**, *38*, 483; d) D. Schwarzenbach, K. Kirschbaum, A. A. Pinkerton, *Acta Crystallogr. Sect. B* **2006**, *62*, 944.

[14] In crystallographic parlance, the Bragg reflections with even *l* are referred to as "family reflections" and are common to both the form I and form II structures. The family reflections alone define a "superposition structure", which in the case of aspirin comprises two O–H···O dimers overlaid in a unit cell with *c* dimension half that of the true *c* dimension. The distribution of the intensities along the odd *l* rows contains the information to decompose the superposition structure into chemically reasonable arrangements, that is, the information regarding the particular sequence of the O–H···O layers. See Ref. [12].

[15] Neglecting any diffuse scattering is clearly a simplification. However, the procedures that we describe have the advantage that they are standard (that is, they are based only on procedures used for routine crystallographic analyses), require no specialist knowledge, and can be applied in any crystallographic laboratory.

[16] The term "form II data set" refers to the list of intensities (the *hkl* file) that is obtained when the diffraction data are indexed on the basis of the form II unit cell and integrated using standard procedures. The additional Bragg reflections that could be described on the basis of the form I unit cell and any diffuse features are ignored. The term "form I data set" refers to the opposite situation.

[17] In particular, there may be problems associated with assessment of the background intensity in the presence of diffuse streaks in the vicinity of the Bragg reflections.

[18] The correlation is derived from the experimental form I data set (crystal **3**), with a suitable fractional scale factor applied to the odd *l* reflections (see the Supporting Information for full details). The batch refinement must be based on all F^2 data. The Figure provides an immediate approximate guide, based on standard refinement procedures. Application of the batch refinement procedure will provide an improved estimate.

[19] R. J. Davey, K. Allen, N. Blagden, W. I. Cross, H. F. Lieberman, M. J. Quayle, S. Righini, L. Seton, G. J. T. Tiddy, *CrystEngComm* **2002**, *4*, 257.

[20] Since interlayer arrangements **A** and **B** are structurally and energetically so finely balanced, disorder is thermodynamically inherent in the aspirin system. All aspirin crystals should contain some of arrangements **A** and **B** at real temperatures. They are detectable by X-ray diffraction only when their number becomes significant.

[21] In general, for any system of hydrogen bonds (O–H···O or C–H···O) wherein the dimer and catemer alternatives are well matched, there is a consensus that the catemer is kinetically favored since it is a higher dimensional pattern than the dimer. See: D. Das, G. R. Desiraju, *Chem. Asian J.* **2006**, *1*, 231.

[22] PZ have reported that "form II" transforms into form I at 100 K. Our assessment of the stability of the form II domains is based on re-collection of single-crystal data for **1b** after the crystal had stood in air for two months.

[23] Co-crystal: a) G. R. Desiraju, *CrystEngComm* **2003**, *5*, 466; b) J. D. Dunitz, *CrystEngComm* **2003**, *5*, 468. Pseudopolymorph: c) K. R. Seddon, *Cryst. Growth Des.* **2004**, *4*, 1088; d) G. R. Desiraju, *Cryst. Growth Des.* **2004**, *4*, 1089; e) J. Bernstein, *Cryst. Growth Des.* **2005**, *5*, 1661; f) A. Nangia, *Cryst. Growth Des.* **2006**, *6*, 1.

[24] However, one of us has argued (in Ref. [23d]) that difficulties in the use of the word "pseudopolymorph" might have arisen because the definition of the term "polymorph" is too rigid with respect to identity of chemical composition among substances that are deemed to qualify for the polymorph epithet.

[25] To some extent, this situation parallels that of isomorphous crystalline solvates, for which patents have been granted for ranges of solvent content. However, while variable solvent content is a common occurrence, it is not clear how common the aspirin situation will be.

[26] A. R. Verma, P. Krishna, *Polymorphism and Polytypism in Crystals*, Wiley, New York, **1966**.

[27] G. Coquerel *Chem. Eng. Proc.* **2006**, *45*, 857

