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Why Do Organic Compounds Crystallise Well or Badly or Ever so Slowly? Why Is Crystallisation Nevertheless Such a Good Purification Technique?†

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Abstract:

Observation of the comparative crystallisation behaviour of over 400 related acylanilides has allowed some understanding of the role of conformation and molecular symmetry in determining the time taken by organic compounds to crystallise. This may be related to the number of alternative orientations in which a molecule can attempt to dock at a crystal site. Two- to 3-fold slowing of crystal growth compared with molecules with conformationally symmetric groups would be expected if the process involves simple acceptance of a single molecule at a growth site. The observed reduction in rate is much larger than this. It is suggested that it may be around x^3 where x is the number of alternative orientations. An attempt is made to account for the failure of some compounds to form extended domains of crystal perfection, by considering the fitting of impurity molecules or the misfitting of correct molecules in the lattice. As an explanation of the role of crystallisation in purification, a proposal is made as to why an identical molecule is more likely to fit into an existing crystal lattice than any foreign molecule.

Introduction

It is a matter of common knowledge amongst those involved in the crystallisation of organic compounds, that such compounds show varied crystallisation propensities. They may crystallise well or badly, quickly or slowly. Although purity may play some part in this, it is only part of the story. Some substances crystallise well even from grossly contaminated solutions: for these, purification through crystallisation is exceedingly effective. The process of purification during product development is often accompanied by better crystallisation, but sometimes by a change of polymorphic form.[1] Poor crystallisation covers a multitude of phenomena, including too small, poor size distribution, tendency to agglomerate, extreme morphology of flakes and fine matted needles as well as lack of significant improvement of purity. Despite the enormous expenditure of effort devoted over a century and a half[2−4] to the theoretical understanding of crystal growth, it is probably true to state that it is never possible to understand how to improve a recalcitrant crystallisation from any of this work. In practical situations, one turns to experience, empirical knowledge and trial-and-error. One reason for this state of affairs is that work has been done overwhelmingly by solid-state physicists on the crystallisation of semiconductors, metals and minerals from the melt or from the vapour phase,[4] or by chemical engineers investigating the crystallisation of readily crystallised inorganic salts from aqueous solution.[5] The view, implicit in the texts[3,4,6] and the literature, that the crystallisation of inorganic materials from vapour or melt is the same as that of organic materials from solution is not borne out by experience.[7] Even the transfer of knowledge from inorganic to organic salt crystallisation is limited. Some years ago we attempted to crystallise tartrate salts of simple amines such as methylamine and benzylamine for single crystal studies. Out of 25 bases treated with 0.5 or 1 molar equivalent of enantiomeric or of racemic tartaric acid, amounting to 100 crystallisations in all, only 13 crystallised well. One hundred experiments to produce alkali metal salts of benzene tricarboxylic acids yielded but three useful crystalline salts. No selection of inorganic salts would behave so badly. Another reason for the lack of applicability of current theoretical belief about crystal growth to real experiments is that the models are oversimplistic. The Kossel-Stranski[4,6,8] view of a cube landing on a plane surface may be a possible representation of the mechanism of crystallisation of an element, but it is an unrealistic picture of the growth of a typical organic molecular crystal. This theme will not be developed further here. Rather, we concentrate on the effect on crystallisation of the irregular shape, symmetry and conformational mobility of organic molecules. The attempt to produce more than 400 acylanilides, in the form of good crystals for X-ray diffraction, offered a unique opportunity both to observe comparative crystallisation propensities and to consider the results in relation to contemporary views on crystal growth.

Discussion

Why Do Some Compounds Take Months to Crystallise?

We have been engaged in structural systematics for several years.[9−11] This is primarily a crystallographic exercise of relating

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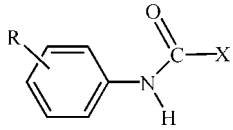

Figure 1. **Acylanilides prepared in this study, in which X = H, CH_3, C_2H_5, C_3H_7, $C(CH_3)_3$, CF_3, OCH_3, $OC_2H_5NH_2$ and Cl; and R = H, CH_3, C_2H_5, $C(CH_3)_3$, OCH_3, OC_2H_5, OCF_3, F, Cl, Br, I, CF_3, OH, NH_2, COOH, etc.**

molecular structure to crystal structure by the comparison of polymorphs, hydrates, cocrystals or sets of closely related molecules. Our latest set is the acylanilides, Figure 1. We have made over 400 of these and have so far solved over 200 crystal structures, plus the crystal structures of 50 related salts and ureas formed as byproduct. Up to 10 acylamino groups are associated with each substituted phenyl ring. In addition, a few heterocyclic analogues have been made. In all, there are around 60 × 10 possibilities, but not all combinations have been tried. The compounds made, crystallised and characterised structurally are set out in Table 1. Nearly all the structures so far determined are based on one of three amide hydrogen-bonded chains[12] with translational, glide or two-fold screw symmetry, respectively. The preference for the different chain types appeared to be determined by steric requirements both of the phenyl ring substituents and of the acyl group. The synthesis of these compounds is detailed later.

No attempt was made to prepare acylanilides disubstituted on the phenyl ring, because the main objective of the exercise was to establish how the size and position of the substituent might influence the crystal packing options, how the electronic effects might determine hydrogen bond strengths[13] and therefore crystal preferences, and how hydrogen bond acceptor or donor substituents on the phenyl ring might disrupt common bonding patterns. Di- or trisubstitution would make it more difficult to disentangle a situation already complex enough.

An unintended bonus was the opportunity to compare the crystallisation of these compounds. Since there were at least 25−30 sets or partial sets of substituted anilides for each X group, the crystallisation behaviour could be observed as an overview unhampered by individual peculiarities. The order of ease of crystallisation was generally acetanilides, trimethylacetanilides, trifluoroacetanilides > ureas > propionanilides, butyranilides, methylurethanes > ethylurethanes≫formanilides. Too few of the carbonyl chlorides were made for meaningful comparison; furthermore, the preparation of the ureas and isolation of the carbonyl chlorides differed from those of the other compounds. From Table 1 a further overall indication of the comparative rapidity of crystallisation and quality of the ensuing crystals can be inferred. Note that the ethylurethanes, carbonyl chlorides and *o-tert*-butylanilides were the last sets to be prepared. Account needs to be taken of this when judging the overall rates of crystallisation. Para compounds crystallised more easily than ortho, and ortho more easily than meta. Hydrogen bond acceptors or particularly hydrogen bond donors

Table 1. **Summary of the acylanilides prepared and crystallised[a]**

X/R	H	CH_3	C_2H_5	C_3H_7	$C(Me)_3$	CF_3	OMe	OEt	NH_2	Cl
p-CF3O	○	∗	∗	○	∗	∗	+	+	∗	
p-EtO	+	∗	+	∗	∗	∗	∗	○	∗	
p-MeO	∗	∗	○	∗	∗	∗	∗	∗	∗	
p-Et	○	∗	∗	○	∗	●	+		+	
p-iPr	○	∗	○		∗	+	∗		+	
p-tBut	○	∗	∗	○	∗	∗	+		○	
p-CH3	∗	∗	∗	+	∗	∗	∗	●	∗	
H	+	∗	∗	∗	∗	+	+	+	∗	
p-F	+	∗	∗	∗	∗	∗	∗	+	∗	+
p-Cl	+	∗	∗	∗	∗	∗	∗	+	∗	○
p-Br	∗	∗	∗	∗	∗	∗	∗	+	∗	+
p-I	∗	∗	∗	∗	∗	+	∗	∗	●	
p-CF3	∗	∗	∗	∗	∗	∗	∗	+	∗	○
p-CN	+	∗	∗	∗	∗	∗	∗	○	+	
p-NO2	+	∗	∗	∗	∗	∗	+	○	+	
p-OH	○	∗	○		○					
p-COOH		∗	∗		○	∗	○			
p-COOMe		∗			∗	∗	+			
p-COOEt	○	∗			●	∗	○			
p-COMe	+	∗			+	○	○			
p-NH2		∗								
p-NHCOMe	○	∗			+	+	○			
p-OCOMe		∗								
p-SO2OMe		●								
p-SO2OEt		∗								
p-SO2NH2		∗								
m-MeO	∗	○	○	○	∗	○	○	○	∗	
m-Et	○	○	○	○	∗	○	○	○	∗	
m-CH3	○	∗	+	+	∗	●	+	●	∗	
m-F	+	∗	∗	∗	∗	∗	+	○	∗	+
m-Cl	∗	∗	∗	∗	∗	○	+	+	∗	○
m-Br	∗	∗	∗	●	∗	+	●	+	∗	+
m-I	∗	∗	∗	○	∗	∗	●	○	∗	
m-CF3	+	∗	+	○	∗	∗	+	+	∗	+
m-CN	+	∗	∗	○	+	∗	+	+	○	
m-NO2	+	∗	○	○	∗	∗	∗	+	∗	
m-OH	○	∗	∗		∗	○	○			
m-COOH		+	○		○					
m-COOEt	+	∗	∗	○	+	∗	∗		○	
m-COMe	+	∗	+	○	○	∗	○		∗	
m-NH2		∗			○					
m-NHCOMe		∗	○		+					
m-OCOMe		∗	+							
	H	CH_3	C_2H_5	C_3H_7	$C(Me)_3$	CF_3	OMe	OEt	NH_2	Cl
o-CH3	+	∗	∗	∗	∗	∗	●	+	+	
o-F	+	∗	○	∗	∗	∗	○	○	∗	+
o-Cl	●	∗	∗	∗	∗	+	●	+	∗	+
o-Br	∗	∗	+	∗	∗	∗	●	○	∗	+
o-I	∗	∗	○	○	∗	+	∗	○	∗	
o-CF3	∗	∗	∗	∗	∗	∗	∗	+	∗	○
o-CN	●	∗	●	●	∗	○	+	∗	○	
o-NO2	+	∗	○	+	∗	∗	+	○	○	
o-tBu	○	+	+		+	∗	+	○	○	
2-pyridyl	∗	●			+	+	+		○	
3-pyridyl	∗	●			+	●	+		+	
4-pyridyl	+	∗	+		+	+	+		+	
2-pyrimidyl	+	∗			+		+		+	

[a] ∗ = crystal structure obtained, + = crystallised and awaiting crystal structure determination, ○ = synthesised, but not yet crystallised, ● = wrong crystal structure obtained. In most cases this was the amine salt, the diacylanilide, or the substituted diphenylurea by further reaction.

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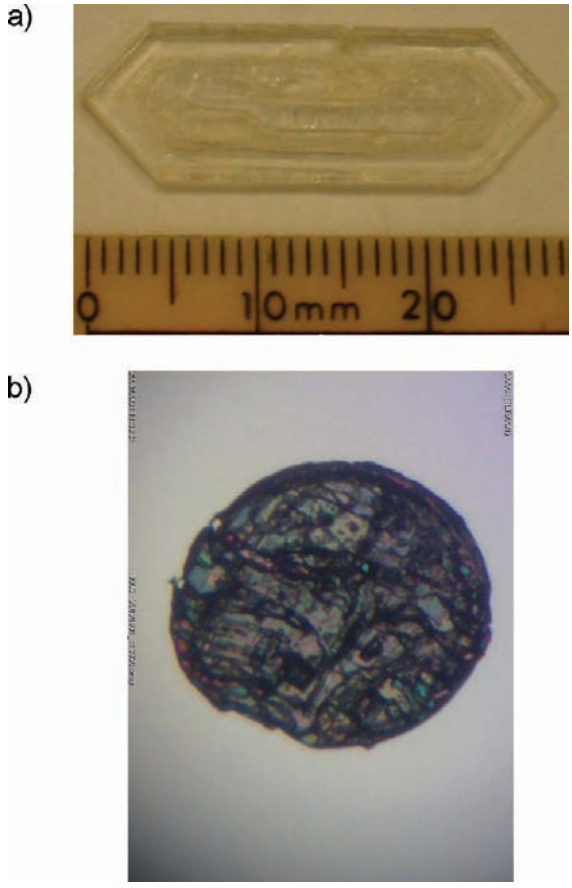

Figure 2. **(a) Photograph × 2 of a crystal of 2-chloroacetanilide from ethanol. (b) Photomicrograph × 40 of round crystals of 2-chloroacetanilide.**

on the phenyl ring generally caused the crystallisation to be worse, unless the hydrogen bond complemented rather than competed with the amide-bonding chains as in the case of para-acetamidobenzoic acid. The time taken to crystallise overall varied from minutes to months. Some of the earliest samples made (June 2008) are still crystallising/are gums/are microcrystalline or amorphous powders. Although generally the case, difficulty of nucleation does not necessarily equate with poor crystallinity: the *o*-chloroacetanilide crystal shown in Figure 2a appeared only after two months storage. Nor is a long time to the first appearance of crystals always related to slow crystal growth or bad quality. Several solutions quiescent for months suddenly began to crystallise and did so totally within a few minutes, often giving acceptable single crystals.

Nucleation. The word 'nucleation' is much misused in the literature. None of the usual methods that claim to detect nucleation actually do so.[14] What is measured is the point at which crystals have grown sufficiently in size to be detectable instrumentally, for example by light scattering, or have become visible to the eye. Such sizes are many orders of magnitude greater than the probable size of a nucleus. Probably the only method which has detected the true point of nucleation is the emission of luminescent pulses, first described by Garten and Head[15] in 1963. That work, which reported the luminescence of crystallising solutions of impure sodium chloride, has been largely ignored. Apart from some subsequent work by those authors,[16] no attempt has been made to establish how widely applicable it might be. The implication of those observations is that nucleation involves a sudden ordering phenomenon, rather than the usually presented picture of gradual accretion. Occasional suggestions have been made that nucleation involves such a mechanism,[17] either from amorphous or from quasi-crystal precursors[18] and it has been given the name of 'two-stage mechanism'[19−22] but it is still the 'one-stage' process which is generally discussed, presented and accepted. It is difficult to understand how nucleation is to be distinguished mechanistically from crystal growth if it involves no differentiating characteristic beyond the attainment of stability. The word crystallisation will generally be used here, but it will be understood that this covers both the induction period[23] and crystal growth process, even though different mechanisms and different considerations are involved in the two-stage process. 'Ease of crystallisation' as used here, is the time taken to form crystals suitable for structural determination by X-ray diffraction. In general, ease of crystallisation and quality of crystals were related: acetanilides, trimethylacetanilides, trifluoroacetanilides and ureas, especially of para-substituted anilines without hydrogen bonding substituents, gave better crystals than others listed in Table 1. What is reported is not a quantitative study. It was not until long into the project that crystallisation patterns were noticed. Even then the main thrust of the project was to produce suitable crystals, not to record accurately their time of appearance.

Conformational Effects. The rapidity of nucleation/crystallisation indicated earlier is most clearly related to conformation and mobility. This has been long known, for example, for sugars, but we believe that it has been the first time that any comparative overview has been possible. Acetanilides, trimethylacetanilides and trifluoroacetanilides have three equivalent rotational conformations as opposed to propionanilides, butyranilides, methyl and ethyl urethanes, for which only one out of three of the rotamers will fit into a potential lattice. In the case of ethylurethanes and butyranilides the further flexibility can result in multiple-chain conformations as shown by *p*-methylbutyranilide,[24] Figure 3. The rotamers are shown in Figures 4 and 5. Statistically, if a molecule arrives at a growth site on a crystal in the correct orientation on only one-third of

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(23) Söhnel, O.; Mullin, J. W. *J. Colloid Interface Sci.* **1988**, *123*, 42–50.
(24) $C_{11}H_{15}NO$, MW = 177.24, Monoclinic setting, space group *C*2/*c*, *Z* = 16, *a* = 42.887(5) Å, *b* = 5.1367(5) Å, *c* = 19.263(3) Å, β = 108.372(5)°, *V* = 4027.2(8) Å^3, *T* = 120(2) K, μ = 0.075 mm^{-1}, Mo Kα (λ = 0.71073), 20139 reflections collected of which 4537 are unique (R_{int} = 0.1253) and 2276 with $I > 2\sigma(I)$, R1 = 0.1191/0.2225 and wR2 = 0.2299/0.2771 for $I > 2\sigma(I)$/all data, GOF = 1.045.

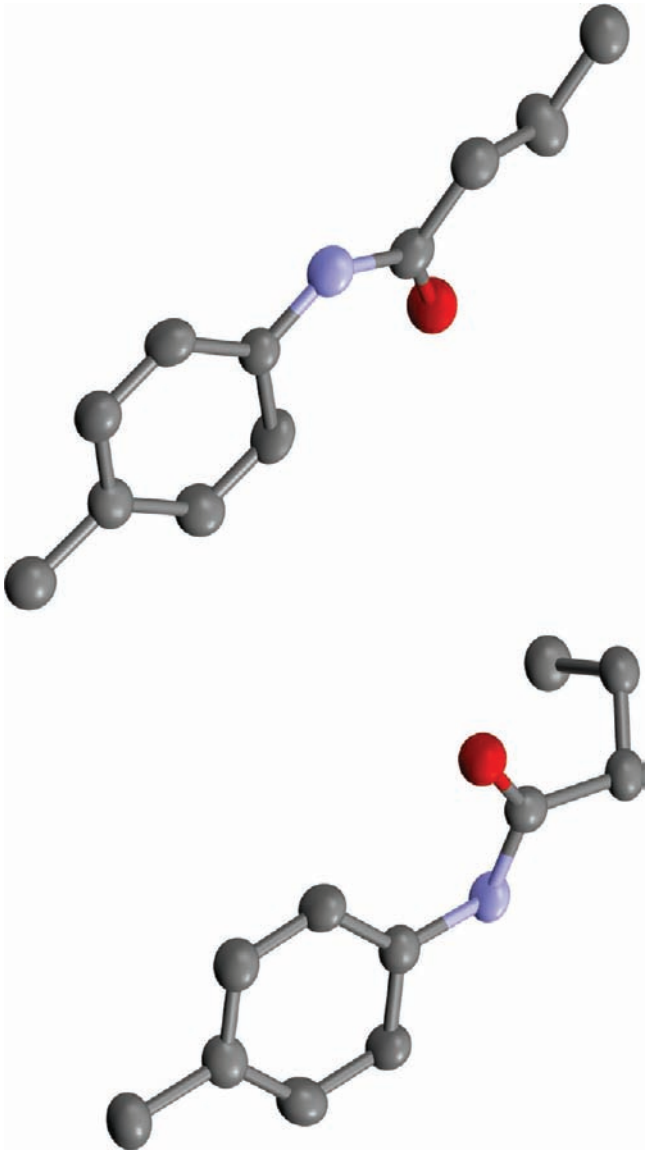

Figure 3. **Asymmetric unit of the crystal structure of 4-methylbutyranilide contains two crystallographically independent molecules. The different conformations of the propyl chain are clearly visible. Hydrogen atoms are omitted for clarity, and thermal ellipsoids are drawn at the 50% probability level.**

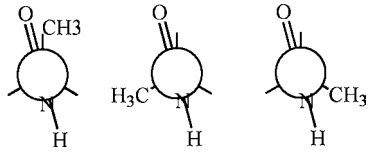

Figure 4. **Conformations of propionanilides. In the molecule, two of the rotamers are equivalent, but there is a difference in the crystal.**

the occasions, then the retardation of growth would be expected to be 3-fold. If the molecules could dock and rotate simultaneously, it might be less. Experimentally, the differences in crystallisation time between acetanilides and propionanilides, for example, were much longer than this. Typically, if a substituted acetanilide took an hour to crystallise, then the analogous propionanilide would take a day: if the acetanilide took a day, the propionanilide took a month. The slowing thus seemed generally to be around 3^3. A similar power of three

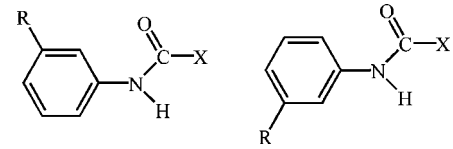

Figure 5. **Alternative conformations of meta-substituted acylanilides. The rotation is about the aromatic carbon to nitrogen bond.**

seemed also to apply to the phenyl ring variations, as discussed below. For a valid analysis of relative growth rates, like should be compared with like. This is generally the case here. For example, the structures of 4-chloroacetanilide,[25] 4-chloropropionanilide[26] and 4-chlorotrimethylacetanilide[27] are all based on the same hydrogen-bonded amide chain with glide symmetry. All were made by substantially the same procedure and crystallised from ethanol by slow cooling. Two possible implications for this 'factor of 3' spring to mind, although there is no means of distinguishing the alternatives from this study. Indeed, given the conflicting views of the mechanism of nucleation, it would be difficult to devise an experiment to decide. Either in the nucleation process at least 3 molecules need to coalesce in order to form a nucleus, or during growth molecules attach and leave the crystal surface three times on average. Kashchiev and van Rosmalien[28] have suggested that for calcium carbonate as few as three ion pairs may be needed to form a nucleus. In the growth model proposed by Perlstein,[29] a chain of three molecules in a given dimension suffices to determine the subsequent growth and packing and therefore the polymorphic form. The rate of crystal formation will thus be reduced by a factor of 3^3 if this is the rate-determining step, i.e. hours to days, or days to months. As already stated, this is the sort of difference observed. Nuclear size is dependent on both substance and supersaturation;[28] much larger nuclei, perhaps up to thousands of molecules have been suggested. One does not know, however, what numbers might be involved in subsets of these large nuclei. A further unresolved problem is that compounds crystallise tardily on first synthesis, almost as though they need to learn how to crystallise. A famous example is xylitol, which took over 50 years to crystallise, but is now normally obtained in crystalline form.[30] The usual explanation is seeding, but since such crystallisation can occur inside sealed vessels, it is not a complete explanation. Many of the compounds made here may be considered to be crystallising for the first time in these laboratories, so it is possible that subsequent crystallisation patterns may not be exactly the same as those reported here.

(25) Gowda, B. T.; Foro, S.; Fuess, H. *Acta Crystallogr.* **2007i**, *E63*, o3392.

(26) $C_9H_{10}ClNO$, MW = 183.63, Orthorhombic setting, space group *Pbca*, $Z = 8$, $a = 9.4251(2)$ Å, $b = 9.2575(2)$ Å, $c = 20.1686(5)$ Å, $V = 1759.77(7)$ Å^3, $T = 120(2)$ K, $\mu = 0.382$ mm^{-1}, Mo Kα ($\lambda = 0.71073$), 10886 reflections collected of which 1990 are unique ($R_{int} = 0.0294$) and 1778 with $I > 2\sigma(I)$, R1 = 0.0372/0.0428 and wR2 = 0.0863/0.0905 for $I > 2\sigma(I)$/all data, GOF = 1.054.

(27) $C_{11}H_{14}ClNO$, MW = 211.68, Orthorhombic setting, space group *Pbca*, $Z = 8$, $a = 9.7381(2)$ Å, $b = 10.01510(10)$ Å, $c = 22.9501(4)$ Å, $V = 2238.28(6)$ Å^3, $T = 120(2)$ K, $\mu = 0.309$ mm^{-1}, Mo Kα ($\lambda = 0.71073$), 17044 reflections collected of which 2562 are unique ($R_{int} = 0.0381$) and 2215 with $I > 2\sigma(I)$, R1 = 0.0331/0.0401 and wR2 = 0.0812/0.0859 for $I > 2\sigma(I)$/all data, GOF = 1.023.

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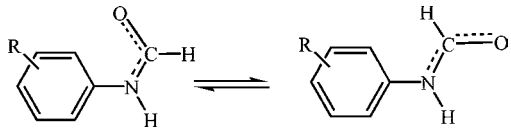

Figure 6. **Rotation of the amide bond in formanilides. Because of the partial double-bond character of the carbonyl carbon to nitrogen bond, rotation is slow.**

There are two rotational possibilities for meta as opposed to para shown in Figure 4. Therefore, the expected growth rates are in the ratio 2^3, that is, 1 to 8. Again the experimental observations would be broadly in agreement with this. Ortho was observed to lie between meta and para. The reason for this is that steric effects will tend to favor the same conformation in both the solution and in the crystal. We have carried out calculations of gas-phase conformational preferences and compared these with crystal conformations to support this claim.[12]

Formanilides. Most amides adopt the *trans* configuration, but formamides crystallise as *cis*, e.g. *m*-bromoformanilide,[31] or *trans*, e.g. *p*-bromoformanilide,[32] sometimes as *cis* in one polymorph and *trans* in the other, e.g. *o*-methylformanilide,[33] or even as a 1:1 mixture of *cis* and *trans* in the crystal structure ($Z' = 2$), e.g. formanilide,[34] *p*-trifluoromethylformanilide.[35] All these conformers are shown in the Supporting Information. The rotation of the amide bond is much slower than that of a C−C bond, due to its partial double bond character, Figure 6. The magnitude of the barrier to rotation can be determined from variable temperature NMR measurements.[36] Values of a fraction of a second for the rotation e.g. 0.3 s at room temperature can be calculated from the rotational barrier. As a consequence, although there are only two possible conformations, the retardation of crystal growth is much more dramatic. This can be up to 100-fold slower than for the acetanilides. Making reasonable assumptions about the rate of arrival of molecules at a growing crystal surface from a 10% solution, and layer-by-layer growth, such a reduction in crystallisation rate can be understood.

Most of the phenyl ring substituent groups chosen originally were cylindrically symmetrical or pseudosymmetrical (e.g., methyl), but groups of lower symmetry were included later. There is a tendency of the symmetrical groups to crystallise better than nonsymmetrical ones. It is uncertain whether this difference is due to symmetry alone; many of the unsymmetrical groups contain hydrogen bond donor or acceptor sites or possess greater complexity or polarity. Finally, heteroaromatic compounds crystallised more poorly than aromatic compounds, which we have noted repeatedly in our other structural systematics studies. The crystallisations were slower and produced less satisfactory crystals and often gave hydrates and solvates. In the context of protein crystallisation, it must be stated that few of the amide bonds therein, those related to function, are conformationally mobile. The steric requirements of attached groups force preferred dihedral angles. Nevertheless, most protein crystals grow more slowly and with greater difficulty than those encountered here.

In order to put the above rough observation of crystal growth rates on a sounder footing, we intend to undertake some quantitative measurements including metastable zone width determinations.

Why Do Molecules Crystallise Badly? *Natural Size of a Crystal.* Although most of the acylanilides crystallised easily, around 20% of those compounds synthesised crystallised badly, or not at all, see Table 1. The received wisdom for producing better/larger crystals for single crystal crystallography is to use another solvent. In our experience this is often ineffective, unless the problem is one of too much solubility leading to increased viscosity and ultimately gums, or of inadequate solubility—saturated but extremely dilute solutions of poorly soluble substances rarely give large crystals. Even then, crystallisation is frequently unsatisfactory for any compound that has proved troublesome in another solvent. Slower cooling or slow evaporation is usually a better option, but sometimes neither slow cooling nor temperature cycling alters the crystal size, nor does vapour replacement crystallisation. Crystals tend to a 'natural size', a concept that seems not to have been noted in the literature. Sometimes purification can be effective, suggesting that it is the incorporation of impurities or the accumulation of impurities at the surface which inhibits growth. This also suggests that the propagation of defects may render the surface inert. Our attempts to determine structures by X-ray crystallography from minute crystals supports this—very small crystals (10 μm) of a substance which easily gives 1 mm crystals will solve, but often will not, when 10 μm is the maximum size ever seen. This implies that it is the defective structure of the crystal which has limited the growth. Although such small crystals are possible for single crystal diffraction work with sensitive modern laboratory instrumentation or with synchrotron radiation, the typical comfortable size of a crystal for single crystal diffraction work on a traditional diffractometer is about 0.3 mm in the longest axis.

Impurities. Such a crystal weighs over 1 μg and so contains at least 10^{16} molecules of an organic compound of molecular mass around 500 Daltons. The purest organic materials commonly have a purity of around 99.9%. Thus, there are around 10^{12} impurity molecules in such a crystal, any one of which could produce a defect or growth anomaly. Alternatively, the impurity could crystallise as a separate crystal or in a solvent inclusion. The surprising fact is not that solutions sometimes crystallise erratically or unsatisfactorily, but that they ever

(31) C_7H_6BrNO, MW = 200.04, Monoclinic setting, space group $P2_1/c$, Z = 4, a = 9.1595(8) Å, b = 11.8459(10) Å, c = 6.6063(5) Å, β = 93.952(6)°, V = 715.10(10) Å^3, T = 120(2) K, μ = 5.67 mm^{-1}, Mo Kα (λ = 0.71073), 9195 reflections collected of which 1632 are unique (R_{int} = 0.059) and 1418 with $I > 2\sigma(I)$, R1 = 0.0401/0.0476 and wR2 = 0.0982/0.1023 for $I > 2\sigma(I)$/all data, GOF = 1.066.

(32) C_7H_6BrNO, MW = 200.04, Orthorhombic setting, space group *Pbca*, Z = 8, a = 10.8480(4) Å, b = 9.8017(3) Å, c = 13.5375(4) Å, V = 1439.43(8) Å^3, T = 120(2) K, μ = 5.634 mm^{-1}, Mo Kα (λ = 0.71073), 9312 reflections collected of which 1628 are unique (R_{int} = 0.0347) and 1411 with $I > 2\sigma(I)$, R1 = 0.0255/0.0326 and wR2 = 0.0614/0.0668 for $I > 2\sigma(I)$/all data, GOF = 0.987.

(33) Boeyens, J. C. A.; Denner, L.; Evans, D. G. *J. Crystallogr. Spectrosc. Res.* **1988**, *18*, 175.

(34) Omondi, B.; Fernandes, M. A.; Layh, M.; Levendis, D. C. *Acta Crystallogr.* **2008**, *C64*, o137.

(35) $C_8H_6F_3NO$, MW = 189.14, Triclinic setting, space group $P\bar{1}$, Z = 4, a = 7.1142(3) Å, b = 10.3129(6) Å, c = 12.2349(8) Å, α = 77.686(3)°, β = 79.631(4)°, γ = 70.525(4)°, V = 821.03(8) Å^3, T = 120(2) K, μ = 0.147 mm^{-1}, Mo Kα (λ = 0.71073), 19318 reflections collected of which 3762 are unique (R_{int} = 0.062) and 2449 with $I > 2\sigma(I)$, R1 = 0.0577/0.1004 and wR2 = 0.1384/0.1617 for $I > 2\sigma(I)$/all data, GOF = 1.119.

(36) Stewart, W. E.; Siddall, T. H. *Chem. Revs.* **1970**, *70*, 517–551.

crystallise reproducibly. The role of impurities is mentioned in the theoretical literature as a source of dislocations and therefore of the promotion of crystal growth, which is rarely the case for organic materials, but not in connection with the inhibition of growth, which is what impurities often do.[3] Only those research groups interested primarily in the experimental crystallisation of organic materials have observed the predominantly inhibiting role of impurities.[37,38]

When one of the authors was in industry, a patent dispute arose over a manufacturing route. A GC−MS method was used to identify the impurity fingerprints of products made by the patented route at different sites. Over several orders of magnitude, for every 10-fold increase in sensitivity, the number of impurity peaks detected increased 3- to 5-fold. If this picture were to continue to the limit of one-molecule detection, it would imply that a single crystal of 1 μg might contain molecules of more substances than are presently known to chemical science. Around 25 of these substances were identified with considerable certainty by GC−MS and GC−MS−MS, but the origin of many remained obscure. Some of the most eminent organic chemists of the time were unable to propose realistic chemical routes. The conclusion was drawn that our knowledge of chemical synthesis is limited to the production of major components and that the formation of these trace impurities involved as-yet unrecognised chemical reactions. The message of the above digression is that the purest crystals available contain unimaginably vast numbers of molecules belonging to enormous numbers of compounds, largely of unpredictable structure. Obviously, no detailed explanation of their role in crystal growth is possible, but their existence and potential for involvement in the crystal growth process needs to be acknowledged and more widely appreciated.

Blagden, Davey, Roberts and Rowe[39] have shown that small concentrations of acetylsulfathiazole will prevent sulfathiazole Polymorph I transforming to sulphathiazole IV (of pharmaceutical nomenclature, equivalent to Polymorph II of the CSD). The mechanism of inhibition would appear to involve the docking of the acetylsulfathiazole molecule, followed by its failure to build hydrogen bonds essential for subsequent crystal growth. Gong et al.[40] have recently observed the inhibition of sulfamethoxazole transformation due to the presence of acetylsulfamethoxazole. Similarly, the presence of pregnenolone[41] inhibits the formation of progesterone Polymorph I. In each case the inhibited polymorph is the thermodynamically stable form. Borchardt[42] showed in a detailed study that the polymorphic preference of an aldosterone compound under development was related to conformation. The formation of the unwanted polymorph was steered by two epoxide impurities of fixed conformation. Scott and Black have examined the effect of biuret on urea crystallisation and of an ester on carboxylic acid crystallisation.[43] For numerous other examples in the literature, the detailed mechanism of inhibition or promotion of a particular form or even the key impurity is unknown. Because crystal growth is essentially zero-dimensional (addition at a site), a small concentration of impurity can have a disproportionate inhibitory effect. This has been much studied experimentally for inorganic salts in the older literature[3] and is recognised also in industrial practice. There are several ways in which impurities can inhibit growth. A particular impurity at relatively high concentration (0.1−0.5% seems typical of the examples) blocks sites, thereby interfering with further growth. Or the defect may propagate layer by layer throughout the crystal. Or molecules may become absorbed at the surface, thereby cocooning the crystal against further addition of molecules. Reverting to the 99.9% pure sample introduced earlier, if all the impurity molecules accumulated at the surface, no crystal could grow to a size greater than about 3 μm. This result follows from consideration of the surface growing as the square of the diameter, but the number of molecules contained as the cube of the diameter.

The problem is not restricted to impurities. A molecule of the proper structure might dock in an unacceptable orientation and so act as an inhibitor to growth.[44] This might be the case for unsymmetrical *p*-diacylanilides, which were observed in this study to crystallise particularly badly. If the substituents are sufficiently alike, a good but disordered structure might form, in which the two orientations are randomly distributed. If the groups are sufficiently different, for example in size, misfitting is less likely. In an intermediate region problems may occur, in which molecules enter the lattice, but in the wrong orientation, and then disrupt it, as discussed below.

Mosaicity. So far this discussion has focussed on the inability of isolated crystals to attain a useful size for single crystal structure determination.

The other major problem is that the crystal itself may not be single or the growth may be spherulitic, perhaps as twisted fibres. Such growth is strongly one-dimensional in terms of the individual crystal and may give rise to friable powders with poor filtration characteristics. The concept of mosaicity is known to all crystallographers but does not appear to have been discussed[45] in the literature for 50 years, except as a surrogate term describing the diffraction quality of protein crystals. We here revert to earlier concepts of polycrystallinity as mosaic structure in which the domains are set at much greater angles than are encountered in 'good' crystals. In a good crystal the minute offsetting impairs neither optical nor experimentally attainable crystallographic perfection. Indeed, but for this mosaic structure, single crystal diffraction would be extremely difficult because of multiple interference effects.[46] Although infrequently measured today, typical mosaic spread values of 0.3−0.5° are commonly encountered for well-diffracting crystals. The spread of the diffracted beam may include crystal bending effects in

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(38) Black, S. N.; Davey, R. J.; Halcrow, M. *J. Cryst. Growth* **1986**, *79*, 765–774.
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(44) Heijna, M. C. R.; van Enckevort, W. J. P.; Vleig, E. *Cryst. Growth Des.* **2008**, *8*, 270–274.
(45) For an exception, see: Harding, M. M.; Rule, R. J.; Oldman, R. J.; Davey, R. J. *J. Cryst. Growth* **1992**, *123*, 373–384.

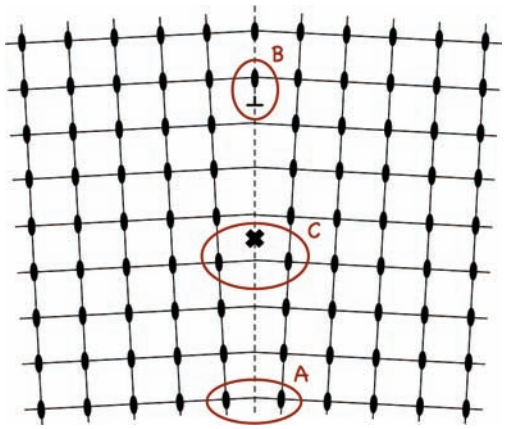

Figure 7. **Schematic section through a mosaic block structure of a crystal. In conventional dislocation theory, based on atomic structures, the dislocation begins at the circled point B where a new line of atoms begins. This is represented by the usual symbol ⊥. As suggested in Figure 8a, the problem actually begins at A in organic structures. Circled areas B or C (compare Figure 8b or c) are merely consequences of the need to try to close-pack the growing divide between the blocks. Filled vertical oval = aligned molecules, x = misaligned molecules. In Figures 7 and 8b and c, x conveniently represents molecules with their long axes pointing out of the plane of the paper, but of course in reality this could be in any 'wrong' direction.**

the case of soft organic crystals, but for the sake of simplicity and to have some concrete values to work with, it will be assumed here that all the spread is due to mosaicity. In the crystal growth literature, it was realised that Frank networks of dislocations[47] could probably be equated with mosaic block structure. In the limit of few dislocations (10^6 per cm^2) randomly spread, the 'blocks' are erratic in shape and size, even unidentifiable. Solid-state physicists were interested in highly perfect materials with low dislocation densities, and hence, dislocations were a better descriptor. In the present context the mosaic block description has some advantages. Typical mosaic blocks will be considered to be domains of perfect packing up to about 1000 Å in extent. Two such blocks shown schematically in Figure 7 are supposedly tilted by one or two degrees but are exaggerated in the figure for visibility. The source of the misalignment of the block (dislocation source) could be an impurity molecule or a misoriented molecule of the major component of the crystal, for example, as in Figure 8. The shape shown is an idealised picture of a real molecule, but more realistic than the spheres or cubes usually drafted for the task, as comparison with Figure 9 shows. Unintended surfaces of two adjacent molecules AA in Figure 8 are in juxtaposition, causing misalignment of the molecules on either side. Each generates a separate crystal block. Such misalignment could also arise from small changes of conformation. These crystal blocks fit each other where they touch by chance, rather than in any crystallographically meaningful way. Further molecules may then fit elsewhere in a nonperiodic way, as shown in Figures 7 and 8. The irregular shape of organic molecules encourages myriad possibilities of orientation, thus allowing almost any defective point in the crystal to be used as a source of defective growth. The local structure so produced may fit

(46) James, R. W. *The Optical Principles of the Diffraction of X-Rays*; Bell: London, 1962.

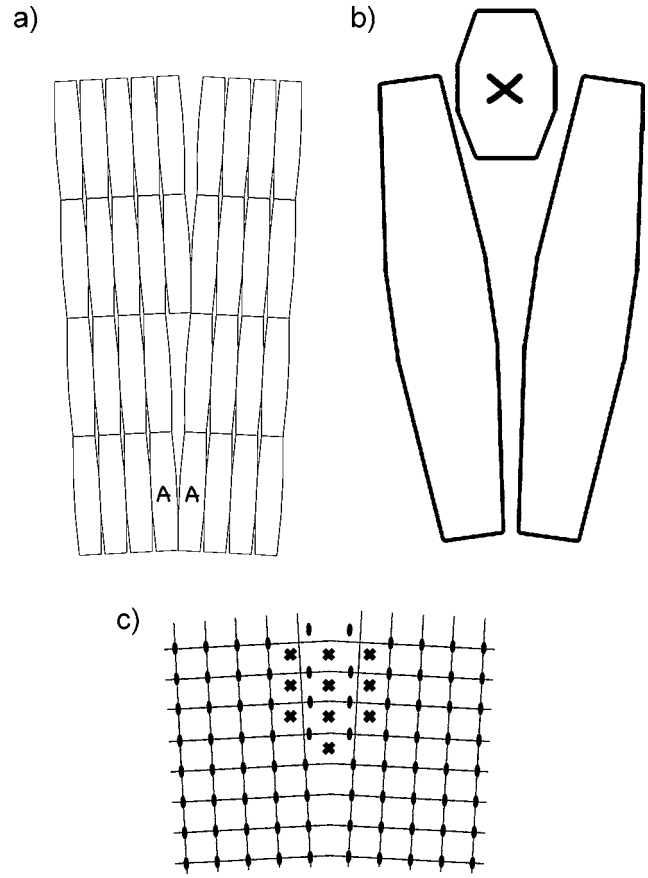

Figure 8. **(a) One of many ways in which organic molecules could misalign, thereby generating defects and dislocations that lead to mosaicity or polycrystallinity. (b) Further molecular addition with misalignment. In this case, the long axis of the molecule is pointing out of the plane of the paper and what is shown is a supposed cross-section of the molecule, see Figure 9b. (c) One possible consequence of the insertion of a misoriented molecule x is the growth of a new mosaic block, possibly of a new phase, or possibly an amorphous region.**

no known structural packing and so either stops growth, encourages further amorphous accumulation, or generates further properly or improperly aligned blocks. In principle almost any site can be fitted by some impurity molecule. Presumably, only the vast concentration difference between a particular impurity and the main component prevents every organic crystal becoming a jumble. Both the size of the block and the angle of misalignment determine the optical and X-ray diffraction characteristics, but in different ways because of the different wavelengths involved. Sometimes crystals of excellent optical transparency are found which fail to diffract well. One possible cause might be related to multiple twinning. The crystal of Figure 2a illustrates another problem. It distorted during cutting for diffractometry due to its softness. By contrast, the round crystal of Figure 2b containing no apparent plane faces and generally of hopeless appearance, yielded a good diffraction pattern and derived structure.

Referring back to Figure 8a, the gap between the blocks reaches 6 Å in a 1000 Å block at a 0.3° misalignment angle. It will therefore accommodate such a misoriented molecule as suggested. By contrast, the misalignment of planes in the *y* direction reaches only 0.02 Å over the length of a mosaic block, insufficient to produce a growth point. Blocks can also misalign

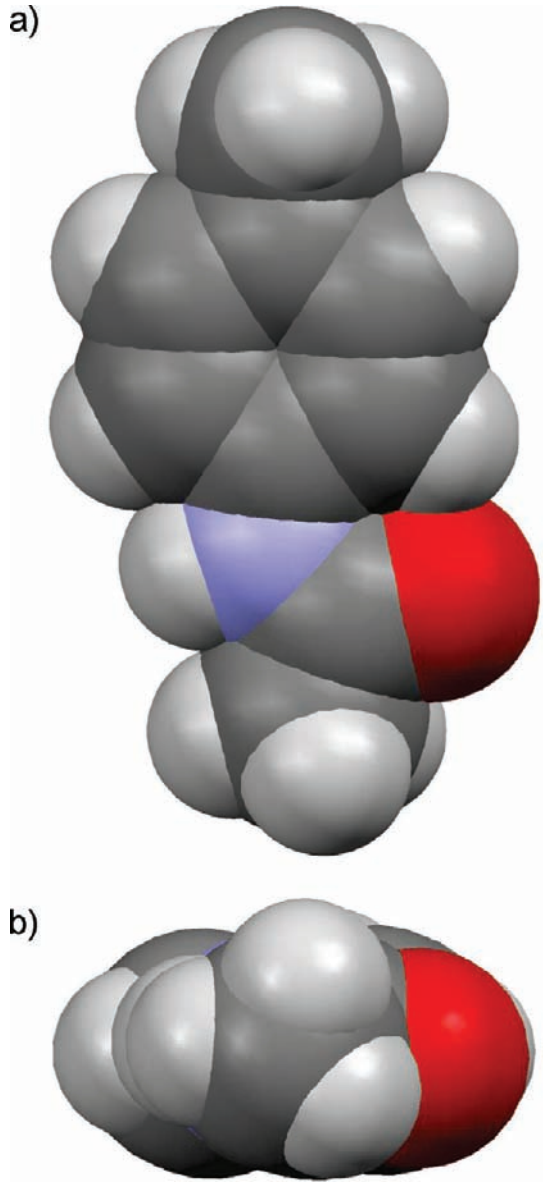

Figure 9. **Picture of 4-methylacetanilide computed using conventional van der Waal's radii. (a) Viewed so as to show the maximum area section; (b) viewed so as to show the minimum area section. Compare these pictures with those of Figures 8a and b.**

by twisting relative to each other. This gives rise to the screw dislocations much discussed in the literature[4] in relation to spiral growth, so this aspect will not be considered further here. However, the twisted threads ('gedrillte Faderne' of the older literature in German, where many of the examples are to be found[48]) must be related to such dislocations. Presumably this occurs at the faces of mosaic blocks, because otherwise the pitch of the extinction pattern is minute, or the individual twist between molecules would be meaninglessly small, around 10^{-4} of a degree. Many of the photomicrographs in Bernauer's book[48] show a close resemblance to the poorly crystalline samples encountered in this study.

Why Is Crystallisation Such a Good Purification Process? The immediate answer to this has been given by several authors, that molecules prefer their own company in the crystal environment, but this begs the essential question of why molecules prefer their own company. Most models of crystal growth concentrate on the attachment of one molecule to the growing crystal, as a key element of crystal growth.[49]

However, there is no requirement or reason that one face of a molecule should be a better template for the opposite face than for any surface of any other molecule in the universe. We think that this approach to the question of purification is misleading, and that the more useful view is that **only** the **molecule of the same material approaching a crystallising surface out of all the other molecules from all possible substances in the universe will have identically the same height, width, length, breadth**—indeed exactly the same dimensions in every direction. Therefore, it is the only molecule that will maintain every plane in the crystal, and so progress the growth of the crystal. It is very easy to deceive oneself from a diagram in two dimensions that another molecule will fit as well. For example, in Figure 10a, rows A and B are incommensurate, so that this is a poor lattice. This is true also in a local way in Figure 10b. Even if there is commensurality in the view shown, there might be a problem in the third dimension. In Figure 10c, which looks like a better fit, the same good pattern needs to be repeated in the third dimension. Then the fit of A to B on each of two faces in the three orthogonal directions needs to be better overall than any arrangement of A alone.

This is sometimes the case, for example, in cocrystal formation or where two different conformations of A interlock as in crystallographic $Z' = 2$ (or higher) structures. The belief from crystal engineering experiments is that only 1 compound in 100 chosen at random will form a cocrystal. The evidence from crystallography[50] is that 11% of structures have Z' greater than 1. Since the molecules adopt different conformations in only 10% of multiple Z′ structures,[51] the proportion of all structures with nonidentical molecules is again only 1%. Only chiral molecules do not follow this pattern. The expectation from the above proposal would be for equiprobability for racemate mixtures and compounds. Jacques, Collet and Wilen[52] have discussed reasons for the preference of racemic compounds over racemic mixtures, but their statistical basis has been criticised.[53]

A high rate of rejection of impurity molecules is expected both on grounds of fitting into the lattice and of solubility. Since the impurity molecules are of low concentration, the surprise is perhaps that crystallisation, wonderful though it is, is not easily capable of producing better than 99.9% pure organic compounds. For a crystal surface to sense whether a given molecule is maintaining the progress of that growth rather than interfering with it implies a mechanism of ascertaining the progress of that growth for at least a few further molecules. This in turn implies a favorable equilibrium and therefore the need for equilibrium to be established by acceptance, deposition and redissolution of molecules. In this context the suggestion from the acylanilide crystallisation experiments that growth may involve acceptance and rejection of molecules before final incorporation an average of 3 times may be of significance. To revert to the question posed in the title, of the role of

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(48) Bernauer, F. *Gedrillte Kristalle*; Borntraeger: Berlin, 1929.
(49) Hartman, P. *J. Cryst. Growth* **1963**, *49*, 145–156.
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(51) Zorkii, P. M. *J. Mol. Struct.* **1996**, *374*, 9–28.

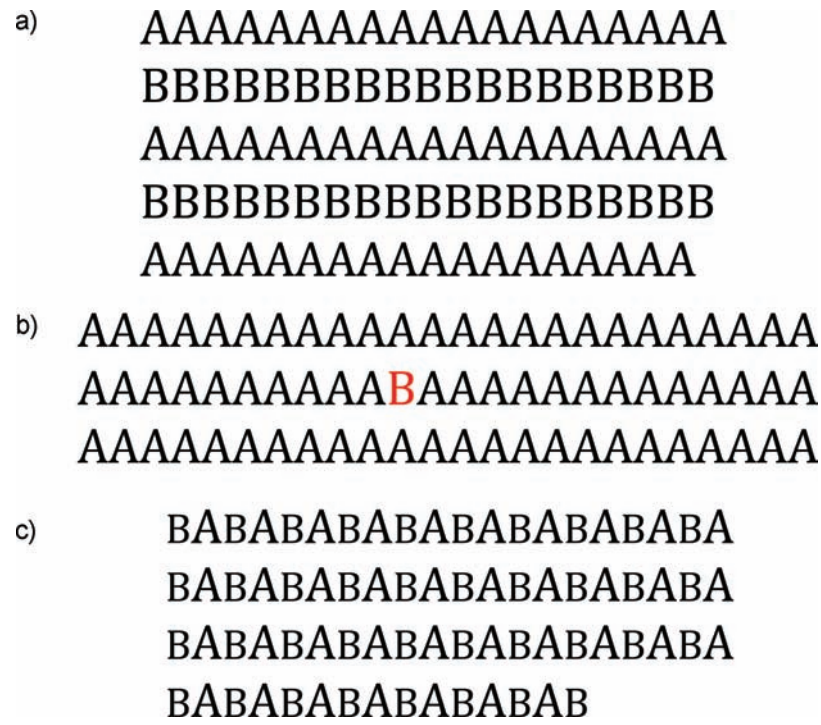

Figure 10. **(a) Attempted formation of a cocrystal in which the incommensurality of A and B leads to poor fitting. (b) Insertion of a single impurity molecule of similar size would also lead to incommensurate structures if the size difference were not eliminated in the crystal by local distortion. (c) Alternative packing in which close-packing in the plane of the paper probably leads to a better structure, but still disguises possible packing problems in the third dimension (see text).**

crystallisation in purification, any crystallisation is likely to involve some rejection of impurity molecules. A poor crystallisation from the point of view of crystal perfection is likely to be less successful at purification, because the incorporation of impurities into the lattice may be the reason for the poor crystallisation. There is only one piece of practical advice, which originates in the GC−MS investigation discussed earlier: many of the identified trace impurities in the final product derived, surprisingly, from reaction with impurities in the solvent in excess used in the first stage of the process. Therefore, the solution to crystallisation problems may lie further back in the synthesis than might be thought likely.

Experimental Section

Synthesis. Acetyl chloride, propionyl chloride, butyryl chloride, pivaloyl chloride (trimethylacetyl chloride), trifluoroacetyl chloride, methyl chloroformate and ethyl chloroformate are readily available. For these the following procedure for the preparation of the acylanilides was adopted:

The substituted aniline, generally 1/100th mol, but less in the case of expensive anilines, was dissolved in pyridine (2 mL or more if required). The acylating agent (1.1 mol) was added carefully, and after the vigorous reaction had subsided, the solution was boiled and then evaporated under nitrogen. When copious fumes of pyridine hydrochloride began to appear, the residue was cooled and water added. When the initial oil had solidified, the water was pipetted or filtered off. Crystallisation of the solid was attempted from ethanol in the first instance. For very soluble compounds, water, aqueous ethanol, toluene, benzene or cyclohexane−benzene mixtures were often more appropriate. For less soluble compounds dimethyl formamide, dimethyl sulfoxide, pyridine or butyrolactone were sometimes successful. Other solvents included acetonitrile and acetone. The addition of a second molecule of the substituted aniline to ethyl chloroformate or methyl chloroformate often gave the diphenyl urea. Reverse addition was better: the substituted aniline in pyridine was added slowly to the chloroformate ester in acetonitrile solution.

For anilines with electron-donating groups, acetic anhydride was added to the aniline dissolved in glacial acetic acid. An analogous procedure was used for some of the trifluoroacetanilides. Neither the acid chloride nor the anhydride of formic acid exists as a usable reagent. For the formanilides, the substituted aniline was dissolved in formic acid, and a formylating mixture of 1 mol of acetic anhydride mixed with 2 mols of formic acid was used.[54] It is known that this acts exclusively as a formylating reagent. For anilines with strongly electron-withdrawing substituents, a 1:2 mixture of acetyl chloride with formic acid proved superior.

Carbonyl chlorides were prepared by reverse addition of phosgene in toluene. The purification step involved an extraction of the target product with ether to remove the amine hydrochloride and the diphenyl urea that were inevitably produced as substantial products during the reaction.

Monosubstituted ureas are most conveniently made using sodium cyanate.[55] The substituted aniline (0.01 mol) dissolved

(52) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Wiley-Interscience: New York, 1981.
(53) Brock, C. P.; Schweitzer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811–9820.
(54) Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081–1118.
(55) Vishnyakova, T. P.; Golubeva, I. A.; Glebova, E. V. *Russ. Chem. Rev.* **1985**, *3*, 249–261.

or in some cases suspended in aqueous 4 M HCl (4 mL) was cooled to 0−10 °C, and portions of XS sodium cyanate (3 × 1 g) were added whilst agitating. After standing overnight, the resulting solid was filtered off and crystallised.

Crystal Structure Determination. X-ray diffraction data were collected by means of combined ϕ and ω scans on a Bruker-Nonius KappaCCD area detector situated at the window of a rotating anode (Mo Kα radiation, $\lambda = 0.71073$ Å; graphite monochromated radiation or 10 cm confocal mirrors radiation). The structures were solved by direct methods with SHELXS-97[56] and refined on F^2 using SHELXL-97[56] as implemented in the WinGX[57] suite of programs. Anisotropic displacement parameters were assigned to all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were positioned geometrically, and thermal parameters were constrained to ride on the atom to which they are bonded. Any other hydrogen atoms (mostly amide hydrogens) were located on the difference map, and the bond distances were restrained to idealised values. Thermal parameters for those hydrogen atoms were refined isotropically in the majority of structures, or if badly behaved were refined as riding on the atom to which they are bonded. The data were corrected for crystal anomalies and absorption effects using SADABS V2.10.[58]

(56) Sheldrick, G. M. *SHELX* , Suite of programs for crystal structure solution and refinement; University of Göttingen: Göttingen, Germany, 1997.

(57) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

(58) Sheldrick, G. M. *SADABS*, Siemens Area Detector ABSsorption correction program, V2.10; Bruker AXS GMBH: Karlsruhe, Germany, 2003.

Conclusions

The conformational mobility of an organic material can and, in the case of acylanilides, does have a significant effect on the rate of crystallisation because of the need to dock as the appropriate rotamer. It can also have a significant effect on the quality of the crystal, because of the possibility of the 'wrong' conformer becoming incorporated as a defect in the crystal. In even the purest samples of organic compounds the concentration and nature of impurities can play an important role in the ease of crystallisation and perfection of the product. The concepts of crystal growth need to be revisited to take account not only of conformation and impurities but also of many other observations made during the past 80 years or more, which have been largely overlooked.

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Supporting Information Available

This material is available free of charge via the Internet at http://pubs.acs.org.

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