

Solvent Binding to Benzamide Crystals: Morphology, Induced Twinning and Direct Observation by Surface X-ray Diffraction

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Abstract: Single crystals of benzamide which form hydrogen-bonded (001) bilayers are obtained from ethanol or 1-propanol solutions. The added presence of amide cosolvent such as X-CONH₂, X = CH₃ or CF₃, yields very thin (001) plates which are twinned. Grazing incidence X-ray diffraction (GIXD) measurements from the (001) surface of pure benzamide indicates that the surface almost exclusively exposes the phenyl substituents. The observed GIXD data from the (001) surface of the affected crystals revealed lamellar twinning. Structural modeling of the data showed that the top surface layer contains about 15% adsorbed amide cosolvent, all oriented with their -X moieties exposed to air. A simple structural model has been invoked to account for the solvent-induced twinning.

Introduction

The morphology of a crystal is determined by the relative growth rates of its various faces, the general rule being that faces which grow the slowest are expressed in the crystal habit. Minor amounts of a tailor-made additive, which structurally mimics the host molecule present in the solution, has been found to induce dramatic changes in the nucleation properties, growth rate, and morphology of the crystal.¹ This effect occurs via selective adsorption of the additive molecule on those surface sites where the modified moiety emerges from the crystal surface, followed by inhibition, via steric repulsion, of the regular deposition of oncoming crystal layers. Recently² it proved possible, with the use of grazing incidence X-ray diffraction (GIXD) to observe an ordered layer of (*S*)-methionine additive adsorbed on a growing face of α -glycine. Although the additive concentration in solution was 8%, the additive occupancy found on the crystal face was as high as 80%.

Solvent has a strong influence on the habit of crystalline materials.^{3–10} The interactions between solvent and crystal

surfaces are generally less specific, weaker, and thus, less predictable than those between tailor-made additives and specific faces. Nevertheless, solvent tailored to bind specifically to a particular face by replacing host molecules thereon can retard growth of the face since the solvent has to be stripped from the face before the oncoming host layer can be fully deposited.^{8,9}

Here we show that strong selective binding of a tailored solvent to a specific face of a growing crystal can induce solvent-induced twinning at the affected face. Furthermore, we were able, by GIXD using synchrotron radiation, to make a direct observation of the surface-bound solvent which replaces only a crystallographic subset of the surface sites. Benzamide (C₆H₆-CONH₂) was chosen for this study, in view of its bilayered crystal structure in which the molecules are interlinked by hydrogen bonds, yielding large and high quality crystals. Suitable tailor-made solvents would naturally be formamide, acetamide and their derivatives. Ethanol, or 1-propanol, was used as a principal solvent, with addition of the cosolvent in a desirable molar concentration.

Effect of Solvent on the Morphology of Benzamide.

Benzamide crystallizes from alcoholic solutions in space group *P*₂₁/*c* with *a* = 5.6 Å, *b* = 5.0 Å, *c* = 22.1 Å, β = 90.7° as rectangular (001) plates extended in the *b* direction. The crystal structure of benzamide¹¹ (Figure 1) contains hydrogen-bonded cyclic dimers interlinked by N-H...O bonds along the *b* axis forming ribbons, which are stacked along the *a* axis generating (001) layers.

Pure benzamide crystals were prepared by either seeding a supersaturated benzamide alcoholic solution (ethanol or 1-propanol) followed by slow cooling with a temperature control apparatus or by slow evaporation without seeding, yielding thick (001) plates (Figure 1). With the amide cosolvents, formamide, acetamide, trifluoroacetamide, and 2-chloroacetamide (X-CONH₂, X = H, CH₃, CF₃, ClCH₂, respectively) the benzamide

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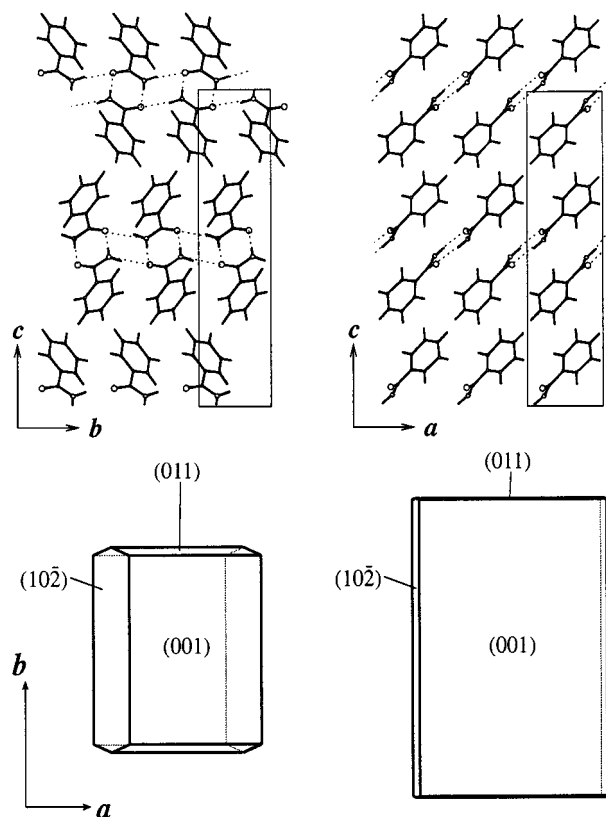


Figure 1. Top: packing arrangement of benzamide ($\text{NH}\cdots\text{O}$ hydrogen bonds denoted by dashed lines). Left: view along the a axis, right: along b . Bottom: benzamide morphology. Left: pure form, right: grown from an equimolar benzamide–amide cosolvent solution (acetamide, trifluoroacetamide, or chloroacetamide).

solution was supersaturated with respect to benzamide, while containing a desired amount of one of the above cosolvents. When grown in the presence of the cosolvents, extremely thin (001) plates were obtained.¹² For a 1 cm^2 area of the (001) face, the pure crystal was typically a few millimeters thick, whereas the affected crystal, with an amide cosolvent ($\text{X} = \text{CH}_3, \text{CF}_3, \text{ClCH}_2$)–benzamide molar ratio of 1:1, was only 60–100 microns thick. The analogous acid cosolvents, such as acetic acid, did not display any distinctive effect on crystal morphology.

The inhibition of growth along the c direction may be explained as resulting from heterocyclic dimers, composed of amide cosolvent X-CONH_2 , hydrogen-bonded to benzamide, stereospecifically adsorbed onto the (010) face, with the group $-\text{X}$ emerging from the face. This molecular orientation shall be experimentally proven by GIXD. The formation of such defect sites during crystal growth would retard the regular deposition of oncoming benzamide layers since the bound cosolvent must be stripped from the surface for regular growth of the pure material to proceed. This proposed model suggests the existence of benzamide–cosolvent dimers in solution, which is supported by mass spectra, when mixed dimers have been observed when sublimed from mixed solution of the two amides.¹³

Solvent-Induced Twinning. Thin benzamide crystals, grown by slow evaporation from an equimolar concentration of the amide cosolvents XCONH_2 , $\text{X} = \text{CH}_3, \text{CF}_3, \text{ClCH}_2$, were always

(12) With formamide the effect is far weaker, and a high concentration of formamide (ca. 5:1) is needed for obtaining an observable effect.

(13) Molecular peaks of the mixed benzamide–acetamide were observed by direct chemical ionization (DI-CI) on a Finnigan quadrupole detector.

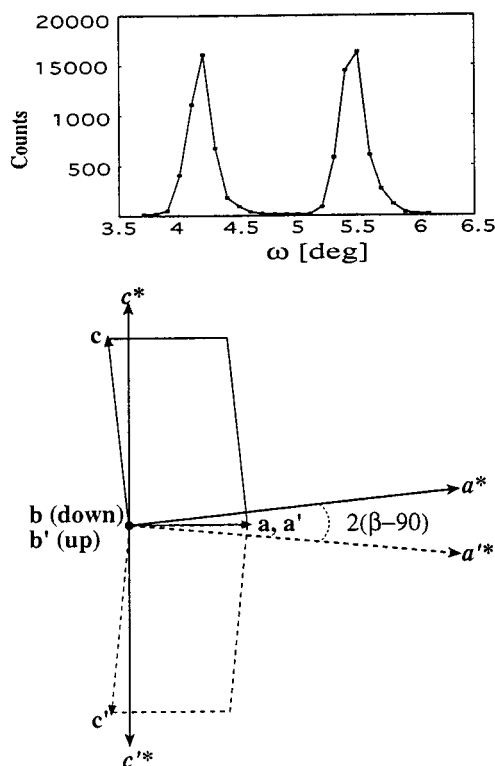


Figure 2. Top: four-circle diffractometer ω -scan of the (100) reflections from a twinned crystal grown in a solution of 1:1 benzamide–acetamide. Bottom: relative orientation of the real and reciprocal lattice vectors of the twinned benzamide crystal. For clarity, the β angle was increased from the actual value of 90.7° .

found to be twinned.¹⁴ Twinning occurs about the ab plane; the twinned ($h00$) reflections are clearly separated on ω scans measured on a conventional four-circle diffractometer, as shown in Figure 2 for the (100) reflections. The angular difference of 1.3° along ω between the twinned peaks agrees with the expected value of $2(\beta - 90)^\circ$.

The minimal molar concentrations of acetamide as cosolvent which induced crystal twinning of benzamide was approximately 10%. With formamide as cosolvent, twinning was found only at higher concentrations (5:1) of formamide in the mother solution. We also checked whether the crystal growth rate is an important factor in the twinning process. Crystals of benzamide grown with acetamide at 5°C by slow evaporation were found to be twinned just the same as crystals grown by evaporation at room temperature ($\sim 23^\circ\text{C}$).

The extent of amide cosolvent occluded within the twinned crystals was examined using crystals of benzamide grown from a mother solution containing acetamide as cosolvent in an equimolar concentration. Proton NMR experiments revealed the presence of only 1% occluded acetamide.¹⁵

Neighboring hydrogen-bonded bilayers make intermolecular van der Waals contact via the two-fold screw symmetry element, parallel to the b axis. The most probable symmetry alternative, which would lead to the observed twinning about the ab plane

(14) Zero-level ($h0l$) Weissenberg camera diffraction photographs were taken of numerous crystals of benzamide, grown from all of the cosolvents mentioned above. Twinning was observed in all cases by virtue of doubled diffraction spots for reflections containing a nonzero h Miller index.

(15) The crystals of benzamide were thoroughly washed with chloroform (in which acetamide is highly soluble and benzamide only sparingly so) to remove any acetamide nonspecifically bound to the outer surface of the crystal. Proton NMR measurements of the benzamide crystals dissolved in CD_3OD revealed the presence of about 1% acetamide. Progressively rewashed portions of the affected crystals gave similar results.

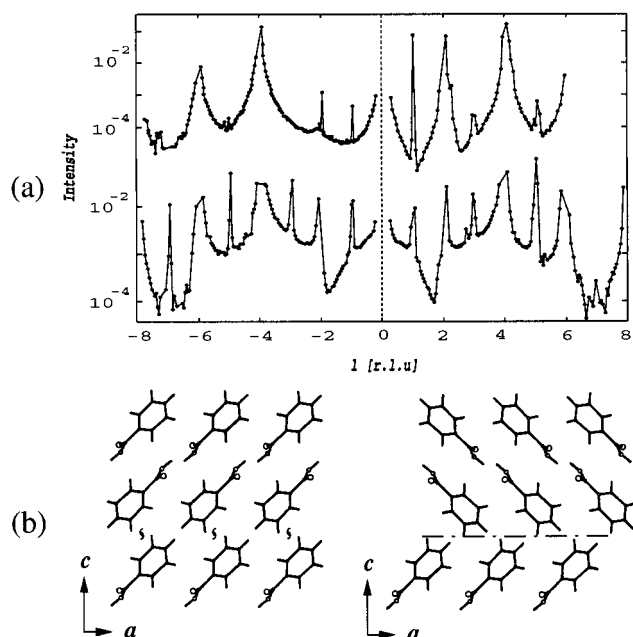


Figure 3. (a) $(10l)$ crystal truncation rods (CTRs) measured from the (001) face of: (top) pure benzamide, and (bottom) grown in 1:1 benzamide–trifluoroacetamide solution. (r.l.u. = reciprocal lattice units). (b) Interlayer arrangement of benzamide viewed along the b axis. Left: untwinned structure in which the layers are related by 2_1 symmetry (denoted by symbol). Right: layers are related by the proposed n -glide (dash–dot line) yielding twinned structure.

and to nearest-neighbor interlayer contacts akin to that induced by the two-fold screw symmetry, is an n glide whose plane is parallel to the axial ab system (Figure 3b). The twinning may, *a priori*, occur only once at the nucleation phase¹⁶ or during growth which could result in lamellar twinning. The following experiments demonstrate the latter process to take place.

Crystals of benzamide were grown by immersing seeds of pure benzamide (001) plates, about 25 mm^2 in area and 2 mm thick, into a solution supersaturated in benzamide and containing either acetamide or trifluoroacetamide in an equimolar concentration. On slow cooling the crystals reached an (001) surface area of about 100 mm^2 and increased in thickness by only about 0.1 mm. By applying the method of GIXD using synchrotron radiation (described in detail in the next section on surface structure), we measured the X-ray intensities of the $(10l)$ Bragg peaks whose contribution came from the top newly grown (001) -layers of the crystal.

The incident angle of 0.5° of the X-ray beam to the (001) surface resulted in X-ray penetration depths¹⁸ of 10 and 30 microns in different measuring sessions. Figure 3a shows the $(10l)$ Bragg rods for the pure form and a crystal grown with trifluoroacetamide. The $(10l)$ and $(10-l)$ rods from the (001) surface of pure benzamide crystal, where the reciprocal lattice unit l ranges from 1 to 8, are not equal in intensity, in keeping with the space group symmetry. On the other hand, the crystal grown with trifluoroacetamide exhibits approximately equal

(16) Twinning at the nucleation phase has been proposed for the formation of the twinned crystals of α -glycine when grown in the presence of (*S*)-leucine.¹⁷ The proposed structure involves the formation of a pair of hetero-bilayers of glycine and leucine.

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(18) The depth of penetration Λ of the X-ray beam into the crystal is $\alpha\mu^{-1}$ where α (in radians) is the incident glancing angle and μ is the linear absorption coefficient of the X-rays in the crystal.¹⁹ For wavelengths $\lambda = 1.53, 1.13 \text{ \AA}$; $\mu(\text{benzamide}) = 7.4 \text{ cm}^{-1}$ and 3.2 cm^{-1} , respectively, yielding the calculated penetration depth.

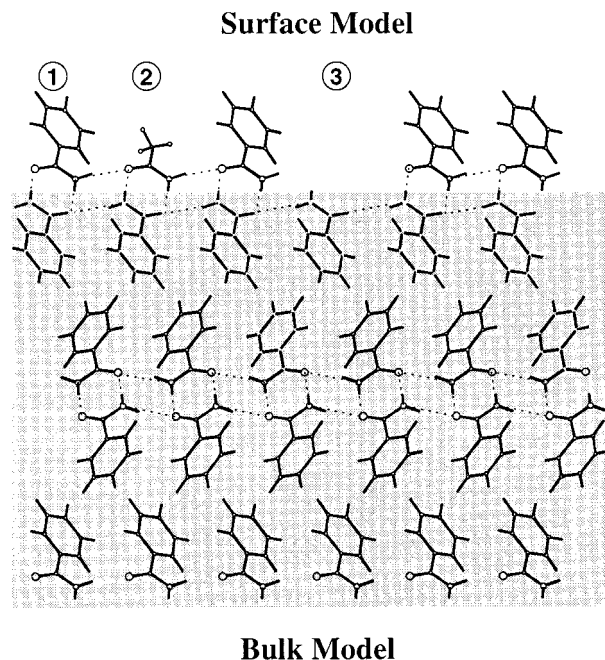


Figure 4. Bulk and surface models used for CTR calculations of the pure and affected benzamide crystals. The top surface layer is occupied by: (1) benzamide molecule, (2) amide cosolvent, or (3) a vacancy.

$(10l)$ and $(10-l)$ intensities, consistent with the presence of lamellar twinned crystallites. We have also measured an affected benzamide crystal grown from a thicker seed plate, this time with acetamide as cosolvent; once again, the $(10l)$ and $(10-l)$ intensities were equal. Upon cleaving this crystal parallel to the (001) plane, GIXD measurements made from the cleaved surface showed unequal $(10l)$ and $(10-l)$ intensities, in agreement with the space group symmetry of the pure form.²⁰

Direct Observation of Surface-Bound Solvent. The (001) face of benzamide crystals grown under different conditions, was characterized by GIXD, making use of the six-circle surface X-ray diffractometer²¹ on the Wiggler BW2 beamline at the Hamburg Synchrotron Radiation Laboratory (HASYLAB), DESY, Germany.

The sharp termination of a crystal at its surface gives rise to rods of diffuse scattering in addition to the Bragg peaks,²² in the direction of the surface normal and passing through the bulk Bragg reflection. The shape of these rods between the Bragg points, called *crystal truncation rods* (CTR),²³ contains information about the molecular structure at the interface, such as changes in interlayer distances, atomic rearrangements, and

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(20) In such affected crystals, therefore, only the thin crystal layer that had been further grown along the c direction from a pure seed, is twinned.

(21) For nonspecular CTR measurements the surface was vertical and aligned with a laser such that the surface normal was parallel with the ω axis of the diffractometer, which ensures a constant angle of incidence throughout the measurements. The angle of incidence was set at 0.5° . The CTR scans were measured by a rocking scan around the surface normal at each momentum transfer in the direction perpendicular to the surface in order to measure the integrated intensity. For the specular reflections $(00l)$ the sample was remounted with the surface nearly horizontal to keep a vertical scattering plane. The scan along the specular rod was performed along the ridge of scattering. The background was measured along a slightly off-specular direction by off-setting the ω angle to lower the radiation damage. The intensities were corrected for Lorentzian and polarization factors and variations in active area in order to achieve a structure factor intensity for both specular and nonspecular CTRs.

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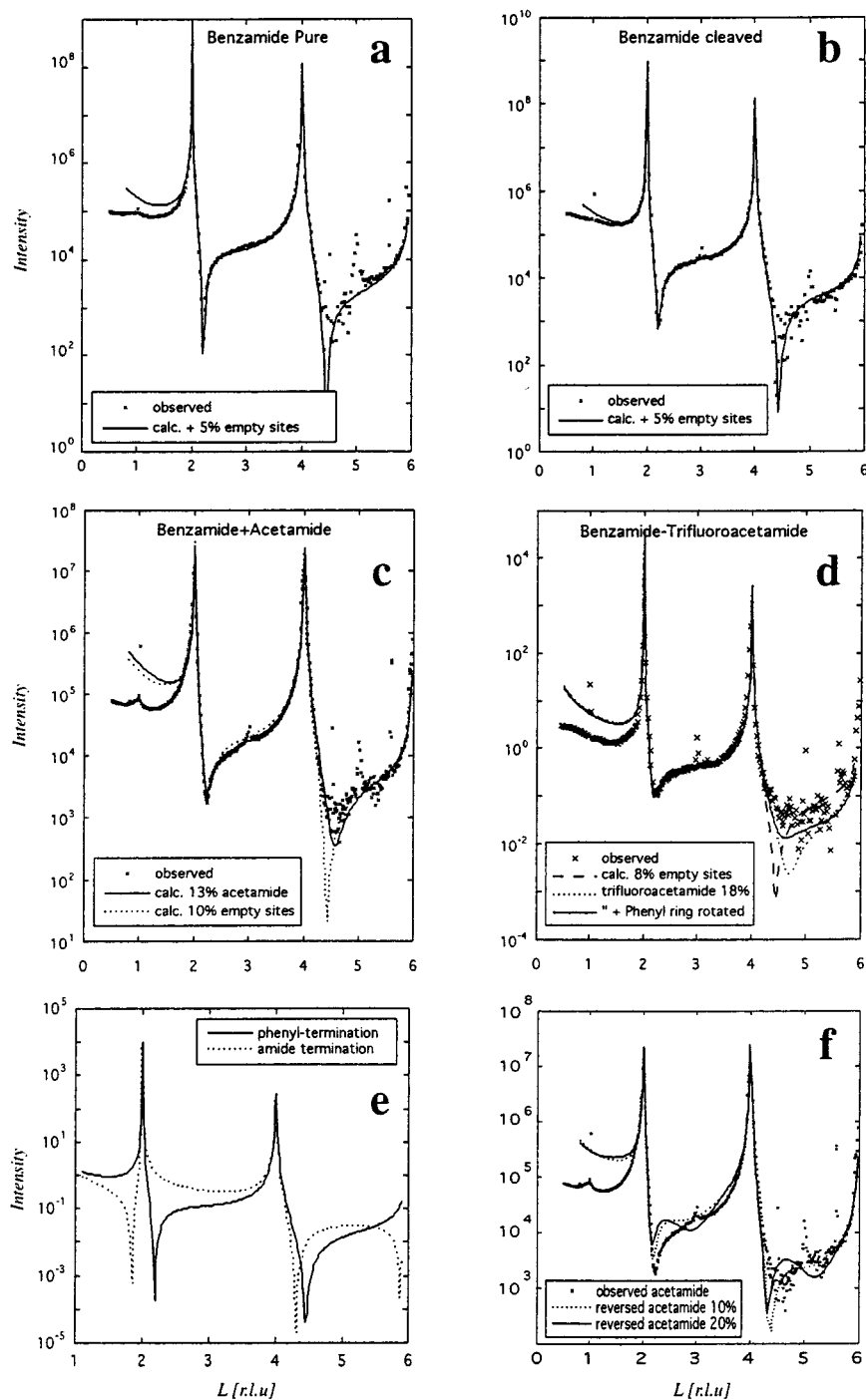


Figure 5. Observed (x) and calculated (lines) (00*l*) crystal truncation rods for pure and affected benzamide crystals. (a) Pure crystal, surface modeled by layer containing 5% empty sites. (b) Cleaved surface of pure crystal. (c) Grown with (1:1) benzamide–acetamide mixture. The model surface layer contains either 13% acetamide or 10% empty sites. (d) Grown with (1:1) benzamide–trifluoroacetamide. The model surface layer contains either 8% empty sites (---), or 18% trifluoroacetamide (···). Improvement to the calculated model is achieved with rotation of the phenyl rings (—). (e) Calculated intensity profile for a model terminated by amide groups or phenyl groups. (f) Calculated intensity profiles for a structure in which the acetamide moiety (CH_3) is incorporated into the second layer with the $-\text{CH}_3$ group pointing toward the bulk.

surface roughness.^{24,25} The observed CTR data, may be fitted via molecular model X-ray structure factor calculations.

All of the GIXD measurements were carried out with fresh crystals exposed to air and at room temperature. The crystal truncation rods were measured from the solution-exposed (001) face of a series of benzamide crystal plates. These include the pure form grown from 1-propanol and crystals grown with an equimolar concentration of cosolvent, either acetamide or

trifluoroacetamide, and the principal solvent 1-propanol. The intensity variation of the (10*l*) rods helped to demonstrate the presence of lamellar twinning as discussed previously. For surface structure elucidation we focused on the specular (00*l*) CTRs which are very sensitive to the surface layer, being dependent only on the atomic *z*-coordinates. The measured CTR data were fitted by calculating the scaled intensity from a model structure (Figure 4), which consists of the underlying bulk molecular arrangement, taken from the published crystal structure of benzamide; and a surface model which accounts

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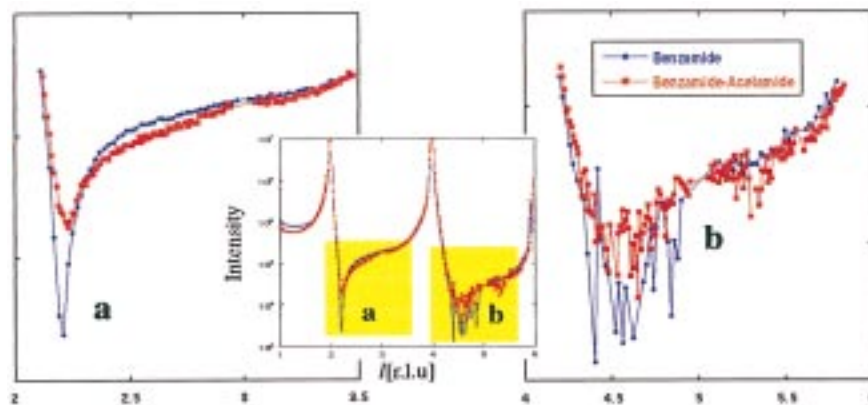


Figure 6. Superposition of the observed (00*l*) CTRs of pure benzamide (Figure 5a, in blue), and of benzamide grown in the presence of acetamide (Figure 5c, in red). The forbidden reflections were removed for clarity.

for structural variations. The bulk model terminates with an *ab* layer of benzamide exposing amide groups; the surface model consists of a layer of either pure benzamide, or benzamide plus the amide cosolvent, whose residue groups, $-\text{C}_6\text{H}_5$, $-\text{CH}_3$, $-\text{CF}_3$, are exposed to air.

The observed and model-fitted intensity profiles of the (00*l*) truncation rods are shown in Figure 5. The observed dip in intensity of the (00*l*) rod from the pure benzamide crystal (e.g., Figure 5a) at $l \approx 2.2$ is fingerprint evidence that the surface layer is terminated essentially by phenyl rings.²⁶ This conclusion is evident from Figure 5e which shows the calculated intensity profiles for the (001) face exposing a complete layer of phenyl rings (solid line) or amide groups (dotted line). The data were best-fitted with a model in which the surface layer of benzamide has an occupancy of 95% and the remaining 5% of the (001) face terminated with exposed amide groups from the layer below. This result is in agreement with a model in which the crystal growth unit is composed of the cyclic hydrogen-bonded dimer.²⁷ The (00*l*) truncation rods, measured from a freshly cleaved (001) surface of the same specimen benzamide crystal in Figure 5b, is almost the same as in Figure 5a, indicating that the two crystal surfaces are essentially similar. The sharp Bragg peaks at $l = \text{odd}$ seen in Figure 5, are glide-symmetry forbidden. It is unlikely that these reflections arise from multiple diffraction. A continuous reduction in layer occupancy upon reaching the top surface and thus destroying the glide symmetry is one possible cause of the effect.

The (00*l*) CTRs from a crystal of benzamide grown from an acetamide–alcohol solvent mixture (Figure 5c) and from the alcohol solvent (Figure 5a) are distinctly different in the regions $l \approx 2.2$ and 4.5 (see Figure 6), pointing to a systematic difference in the surface structure. The intensity profile in Figure 5c was fitted by two possible surface layer models, with or without acetamide molecules. The first model was composed of benzamide sites and empty sites in a 90:10 occupancy ratio (dashed line profile in Figure 5c); the second model was composed of benzamide and acetamide sites in a 87:13 occupancy ratio (solid line profile). The latter model clearly fits the measured CTR data better.

The (00*l*) intensity profile of a benzamide crystal grown from a trifluoroacetamide–alcohol solvent mixture (Figure 5d) is

(26) The parameter which determines the shape of the profile in the region $l \approx 2.2$ is the molecular occupancy given to the surface layer.

(27) We may deduce that the benzamide molecules dock on the growing (001) face as hydrogen-bonded cyclic dimers. An analogous conclusion on surface docking of hydrogen-bonded dimers was deduced from a surface diffraction study of α -glycine and β -alanine,²⁸ as well as from a theoretical analysis of crystal growth of α -glycine²⁹ and of benzoic acid,³¹ and an experimental study of glycine in aqueous solution.³⁰

decidedly different from that of pure benzamide (Figure 5a) in the region $l = 4-6$. Once again we assumed two different surface models: a pure benzamide–empty site surface layer and a mixed benzamide–trifluoroacetamide surface layer with an 82:18 occupancy ratio.³² The latter model fits the measured data better, despite the low signal-to-noise ratio in the $l = 4-6$ region.

The calculated intensity profile is extremely sensitive to variations in the surface model. We have tested models in which the CH_3 and CF_3 moieties of the amide cosolvent are incorporated into the second layer facing into the bulk, which yields a poor fit to the data (Figure 5f). Thus the amide cosolvent is not incorporated with its CF_3 or CH_3 moiety in contact with the underlying layer of the bulk.

Discussion

Characterization of the (001) plate face of benzamide grown from alcohol solution by surface X-ray diffraction is consistent with the cyclic hydrogen-bonded dimer of benzamide as the crystal growth unit, in keeping with the presence in solution of cyclic hydrogen-bonded dimers. The amide cosolvents, which inhibit growth of benzamide by stereospecific adsorption onto the (001) face, induce lamellar twinning of the (001) plates. The absence of an effect on the crystal growth properties of benzamide when using acetic acid as cosolvent may be explained in terms of a lack of binding of the acid to the (001) face.³⁴ Surface X-ray diffraction studies of benzamide grown in the presence of cosolvents X-CONH₂, X = CH₃, CF₃, have yielded concentrations of amide cosolvents stereospecifically adsorbed

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(32) To best fit the observed data, the benzamide phenyl ring of the exposed surface layer was twisted about the exocyclic $\text{C}_6\text{H}_5-\text{CONH}_2$ bond, reducing the dihedral angle between the planes of CONH₂ and C_6H_5 from 28 to 18°. The requirement for a torsion angle of 28° has been ascribed to reduce intermolecular repulsion between the phenyl rings along the 5 Å hydrogen-bonding axis and intramolecular H(ortho)⋯H(N) repulsion. Relief of the latter requires a twist of about 15° according to the crystal structure of *N*-methylbenzamide.³³ We therefore rationalize that the presence of trifluoroacetamide in the surface layer induces reduction of the torsion angle.

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(34) We may rationalize the absence of adsorbed acetic acid onto the (001) face by replacing surface-bound acetamide in Figure 4 by acetic acid. The (acetamide)N–H⋯O(amide) hydrogen bond would be replaced by an O(hydroxyl)⋯O(amide) electron lone-pair repulsion. Indeed, such a type of repulsion has been invoked to account for the inhibition of crystal growth of primary amides in the presence of the corresponding carboxylic acids.^{35,36}

on the top exposed layer of the (001) face, in concentrations of about 15%. The cosolvent occupies only those surface sites whose $-X$ moieties emerge from the crystal, and not the centrosymmetrically related counterpart, resulting in a reduction in crystal symmetry of the top (001) molecular bilayer. Thus, the affected (001) surface may be regarded as composed of phenyl rings and random sites occupied by the amide cosolvent exposing cavities. We propose that the lamellar twinning is induced by a concentration of amide cosolvent onto the (001) face sufficiently large to lower the interlayer specificity, so that the oncoming benzamide layer docks into position via the proposed n glide rather than the regular two-fold screw symmetry. It is noteworthy that the growth of the (001) faces of benzamide can be strongly inhibited with the presence of

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p-substituted benzamide additives in the solution^{35,36} although induced twinning was not reported.³⁷

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(37) We repeated such a type of growth experiments of benzamide in the presence of 10% *p*-chlorobenzamide; the resulting crystals were thin (001) plates, as expected, but twinning was not observed.