

Solution Chemistry and Twinning in Saccharin Crystals: A Combined Probe for the Structure and Functionality of the Crystal–Fluid Interface

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Abstract: The frequency of twin occurrence in saccharin crystals grown from ethanol and acetone has been quantified and the solubility of saccharin in these solvents measured. Structural and thermodynamic interpretation of the data are consistent with a solvent dependence of both the molecular structure of the (10 $\bar{2}$) surface (the twin plane) and the identity of the growth synthon. In acetone solutions this surface is terminated by the polar functional groups of saccharin and the crystal grows from a solution rich in monomer species, while in ethanolic solutions it is terminated by aromatic hydrogens and the growth solution is rich in dimeric species. This is the first time that such a combined study of solution and solid-state chemistry has led to a clear indication of how surface structures may change with solvent.

Introduction

The nature of the crystal–liquid interface is of enormous importance and underlies much current technology by which active ingredients are isolated and converted to stable products in the pharmaceutical, agrochemical, food, and specialty chemicals businesses.¹ Much of our understanding and manipulative ability in this area derives from advances in colloid science and its considerable success in defining conditions for stability in emulsion and dispersion systems. Overall, this progress has been achieved through a consideration of the global characteristics of interfaces defined in terms of their electrostatic and interfacial thermodynamic properties.² From the developing arena of materials chemistry in which crystal engineering occupies a central position, a different perspective on the nature of the crystal–liquid interface has developed. Here, initially by extrapolation from crystal structure data,³ but more recently using state of the art scanning probe and glancing incidence X-ray diffraction (GID) techniques,^{4,5} the interface is viewed as having periodicity, functionality, and stereochemistry determined by a combination of the terminated crystal structure and its interaction with the adjoining fluid phase. This level of structural understanding has made it possible to use specifically tailored additive molecules to control both the morphology^{6,7}

and polymorphic form^{8,9} of molecular crystals, factors which are of considerable practical importance. In this context, too, it has been appreciated for many years that the choice of solvent in crystallization processes can have a significant influence on the nucleation, growth, and morphology of molecular crystals¹⁰ either as a result of specific recognition processes between solvent molecules and subsets of surface sites or because of global adsorption of solvent and the stabilization of surface structures whose interfacial tensions are solvent dependent (surface roughening). Until now all attempts to define the nature of the crystal–solution interface and its solvent dependency have been based on data derived from the solid side of the interface. Thus, for example, crystal morphology,¹¹ polymorphic form,¹² contact angle measurement,¹³ and most recently GID^{4,5} have all been used to infer not only details of the molecularity of the crystal surface but in some cases⁵ to suggest the nature of the growth synthon. The work reported here continues our previously reported¹⁴ study of twinning in saccharin crystals and shows how a combination of solid state (the occurrence of twinning) and solution chemistry (solubility and thermal data) probes can be used to determine the solvent dependence of both the growth synthon and the functionality of the crystal surface.

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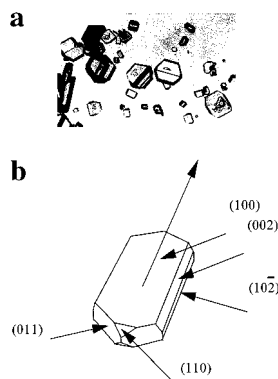


Figure 1. The morphology of single and twinned saccharin crystals: (a) optical micrograph, (b) schematic indexed morphology of single crystal.

Program Objective and Strategy

The objective of this work was to extend our previous experimental and modeling studies¹⁴ in which we concluded that the nucleation of a twinned saccharin crystal was driven by the formation of a three-centered hydrogen bond across the $(10\bar{2})$ twin plane. Of specific interest to us was the possibility that this twinning process might be solvent dependent. Strategically three avenues were explored. First, a solvent was sought in which twinning was less common than in the original growth solvent, acetone. Second, the relationship between the frequency of twinning and supersaturation was measured in each solvent in order to separate solution chemistry and kinetic effects. Third, the solution chemistry of saccharin in ethanol and acetone was quantified through solubility measurements, to define the likely nature of the growth synthon in each case. Molecular modeling and visualization have been used throughout to aid interpretation and support the experimental findings.

Experimental Section

Crystallization Procedure. Crystallization assays were carried out at 40 °C by a simple batch cooling procedure in both stirred and unstirred experiments. The former employed a 20 mL thermostated glass vessel and a magnetic stirrer, while unstirred experiments were performed in a 100 mL conical flask held in a water bath. Initially, a selection of solvents was scanned in unstirred experiments in order to identify two solvents, one in which twinning occurred and one in which it was rare. Saccharin was found to be insoluble in toluene, cyclohexane, and acetonitrile; it grew as single and twinned crystals from THF and acetone and grew mainly as single crystals from ethanol and *n*-propanol. On the basis of these data, acetone and ethanol were chosen as representative solvents for subsequent experiments. To explore and compare the conditions over which twinning took place, crystallization was carried out from each solvent at supersaturations of 0.1, 0.2, 0.3, 0.4. These were calculated from the measured solubility data using the relationship:

$$\sigma = \ln(x/x_s) \quad (1)$$

in which x is the starting mole fraction, before the onset of crystallization, and x_s is the saturation mole fraction at 40 °C.

Identification of Twinned Crystals. Figure 1 shows an optical micrograph of single and twinned crystals together with the indexed morphology of a single crystal. Twinned crystals are easily identified by the presence of a central line separating the two halves. To quantify differences between solvents, the crystals obtained from 100 mL of solution (typically about 40 in each experiment) were examined individually and the number of twinned crystals counted. Counting was performed manually and the twin plane checked in selected samples using single-crystal Weissenberg X-ray diffraction as discussed previ-

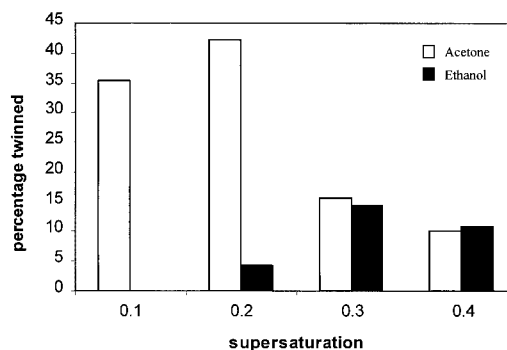


Figure 2. The frequency of twinning in acetone and ethanol over a range of supersaturations.

ously.¹⁴ Intergrown crystals and those deformed by growing in contact with the vessel walls were not included.

Solubility Determination. In the absence of literature data, the solubility of saccharin in acetone and in ethanol was determined experimentally. The method described by Mullin¹⁵ was used with a sample volume of approximately 100 mL and a 60 W lamp as a heating source. Each data point was repeated twice, and the mean values are reported. For a given composition the saturation temperature was measured with a reproducibility of ± 0.1 °C.

The measurements of melting point and heat of melting were performed on a Mettler TA 4000 DSC.

Modeling. The lattice energy of saccharin was calculated using CERIU¹⁶ together with the Dreiding 2.21 force field. Charges were generated using the AM1 method within MOPAC.¹⁷ Solvation calculations were carried out using the commercial program GRID,^{18,19} which calculates the interaction potential (the sum of Lennard-Jones, hydrogen bonding, and electrostatic potentials) between a chemical probe group and a target molecule. Both a saccharin monomer and dimer (extracted from the crystal structure) were chosen as target molecules and scanned for possible hydrogen bond interactions using probes corresponding to an aliphatic hydroxy group (to simulate ethanol) and a carbonyl oxygen (to simulate acetone). Using Iris Explorer²⁰ isosurfaces were drawn around the saccharin molecules at a level of -4 kcal mol⁻¹ (typical of a hydrogen-bonded interaction²¹) in order to visualize the likely extent of solvation in both solvents.

Results and Discussion

Crystallization Experiments: The Solvent Dependence of Twinning. For both solvents, when the solutions were stirred, the crystals produced were very small (30 μ m) and adhered to the side of the crystallizing vessel, making collection and observation difficult. Most of the crystals grew as singlets, and the occurrence of twinning was infrequent regardless of solvent or supersaturation, presumably due to the mechanical action of the agitator. Crystals grown in unstirred solutions, however, showed significant differences in twinning as a function of supersaturation and growth solvent as shown in the histogram of Figure 2. Weissenberg X-ray data confirmed that in all cases, independent of solvent, the twin plane was $(10\bar{2})$. The importance of these data is that they make it possible to deconvolute the effects of kinetics and solvent-solute interactions. A priori,

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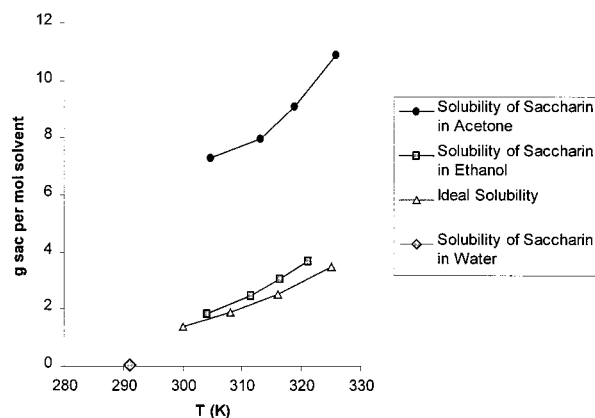


Figure 3. The solubility of saccharin in acetone and ethanol compared to ideal solubility.

if the process of twinning was determined by the probability of errors occurring during crystal growth, it might be anticipated that the proportion of twins would increase with growth rate, i.e., with increasing supersaturation.²² Clearly, while this is the case in ethanol it is not so in acetone where the greatest proportion of twinned crystals were in fact grown at low supersaturations of 0.1 and 0.2. At these values almost no twins were observed in ethanol, while at higher supersaturation both solvents produced similar proportions of twins. This provides clear evidence that the solvent plays a specific role in the formation of twins, with acetone in particular able to override the expected effect of kinetics.

Probing Solute–Solvent Interactions: Solubility Data. The measured solubility data are shown in Figure 3, and it is immediately clear that saccharin is significantly more soluble in acetone than in ethanol.

By comparing these measured data with the calculated ideal solubility, the relative importance of solvent–solute interactions in the two solvents can be inferred. The ideal solubility has been calculated using the standard relationship²³

$$\ln x_{\text{ideal}} = \frac{\Delta H_m}{R} \left(\frac{1}{T_m} - \frac{1}{T} \right) \quad (2)$$

(x is the solubility in mole fraction, ΔH_m is the heat of melting, and T_m is the melting temperature, measured as $7.23 \text{ kcal mol}^{-1}$ and 501 K , respectively). It is clear from Figure 3 that, independent of temperature, at saturation

$$x_{\text{ac}} \gg x_{\text{eth}} \approx x_{\text{ideal}}$$

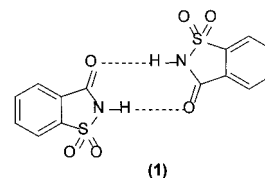
Since all the solutions are saturated, it follows that the activity coefficients ($\gamma_{\text{sac(eth)}}$, $\gamma_{\text{sac(ac)}}$, relative to pure liquid saccharin) and the saturation mole fractions of saccharin in ideal, ethanolic and acetone solutions (x_{ideal} , x_{eth} , x_{ac} , respectively) are related by

$$\gamma_{\text{sac(eth)}} x_{\text{eth}} = \gamma_{\text{sac(ac)}} x_{\text{ac}} = x_{\text{ideal}}$$

Therefore, at saturation at 304.8 K , for example, $\gamma_{\text{sac(eth)}} = 0.91$ and $\gamma_{\text{sac(ac)}} = 0.24$.

This result shows quantitatively the extent of the negative deviation of acetone solutions and the relative ideality of saccharin in ethanol. It implies the solvation of saccharin in acetone solutions with molecules more likely to exist as monomers than

as self-associated aggregates. Conversely, in ethanol, the solution being close to ideal exhibits a balance of solute–solvent interactions leading to significantly more self-association than in acetone. Given the known crystal structure of saccharin,²⁴ the most likely form of self-aggregation would be the formation of intermolecular dimers utilizing the amide hydrogen bond (1).



To probe the thermochemistry of these interactions, the measured solubility data were plotted in the form of eq 2 and from the gradients of these lines the enthalpies of solution at saturation, ΔH_s , for acetone and ethanol were estimated to be 3.5 and $7.7 \text{ kcal mol}^{-1}$, respectively. Comparison with the measured heat of melting ($7.23 \text{ kcal mol}^{-1}$) again reflects the ideality of ethanolic solutions. For each solvent

$$\Delta H_{\text{solv}} = \Delta H_s - \Delta H_{\text{sub}}$$

in which ΔH_s is the heat of solution, ΔH_{solv} is the heat of solvation, and ΔH_{sub} is the enthalpy of sublimation. ΔH_{sub} can be estimated from the calculated lattice energy²⁵ E_{latt} since

$$E_{\text{latt}} = \Delta H_{\text{sub}} - 2RT$$

Using the lattice energy calculated here of $-19.13 \text{ kcal mol}^{-1}$, it has then been possible to evaluate the solvation enthalpies of saccharin in the two solvents as $\Delta H_{\text{solv}}^{\text{ac}} = -16.5 \text{ kcal mol}^{-1}$ and $\Delta H_{\text{solv}}^{\text{eth}} = -12.3 \text{ kcal mol}^{-1}$ in acetone and ethanol, respectively. From these estimates it is again clear that in acetone the solvation process is more favorable than in ethanol as expected from the activity coefficients. The assignment of this enthalpy difference to specific interactions is difficult, but taking the enthalpy of a hydrogen bond to be $\approx 4 \text{ kcal mol}^{-1}$ ²¹ suggests that in acetone the solvation process is associated with an overall net gain of one more hydrogen-bonding interaction than in ethanol.

Probing Solute–Solvent Interactions: Molecular Modeling. The results of molecular modeling throw further light on this issue. For simplicity, only the monomer and dimer states of saccharin have been considered. Being both a hydrogen bond acceptor and donor, ethanol can form several interactions with both species; while in acetone, which has no donor hydrogens, the monomer can form only one hydrogen bond and the dimer can form no formal hydrogen bonds. The results of the GRID calculations are shown in Figure 4 as isosurfaces for both monomer and dimer with acetone and ethanol probes. From this approach, it can be seen that in ethanol both the monomer and the dimer are strongly stabilized by hydrogen-bonding interactions, whereas only the monomer can form a hydrogen bond with acetone. Since these calculations only explore the solvent–solvent interactions, they cannot be compared directly with the solubility data which reflect the balance between solvent–solute, solute–solute, and solvent–solute interactions. Nevertheless, they do support the conclusion that while in ethanol saccharin may be solubilized as either monomer or dimer, in acetone only the monomer can form a significant solvent–solute interaction.

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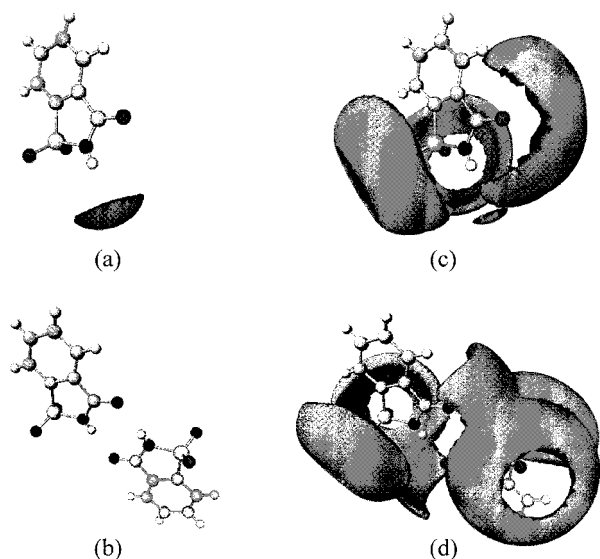


Figure 4. Isosurfaces drawn at -4 kcal mol^{-1} for the interaction of acetone with monomer and dimer species (a and b) and ethanol with monomer and dimer species (c and d).

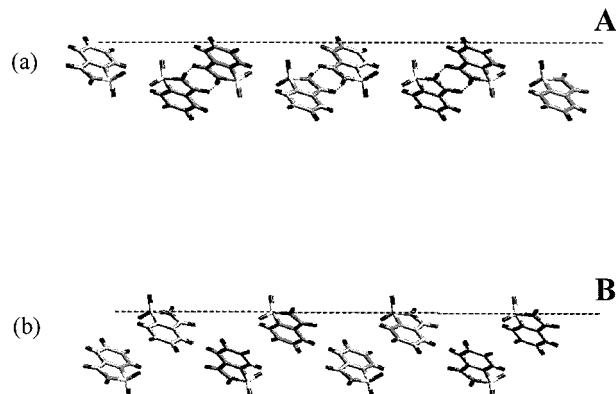


Figure 5. The surface structures of the $\{10\bar{2}\}$ faces: (a) cut A exposing phenyl hydrogens, (b) cut B exposing sulfoxide and amide functionality.

Taken together, the combination of solubility measurements and modeling demonstrate a clear difference in the solution chemistry of saccharin in a solvent that favors twinning compared with one that does not. The solvent, acetone, which favors solvation and a high concentration of monomeric saccharin also promotes twin formation. Twinning is not favored in ethanol which stabilizes molecular dimers.

Conclusions: Combining Solution Chemistry and Structural Processes

In this section, with the aid of molecular graphics and the known crystal chemistry of saccharin, the data is interpreted in its entirety.

Given that the $(10\bar{2})$ surface is the twin plane¹⁴ and a relatively fast growing facet in solution-grown crystals (Figure 1), we have focused our structural interpretation of the data on this surface. Examination of the crystal structure²⁴ shows that there are two possible $(10\bar{2})$ surfaces depending on how the facet is cleaved. Cleaving between dimers gives the surface **A** as displayed in Figure 5a and exposes the phenyl hydrogens to the growth environment. Breaking the hydrogen bonds joining the dimers exposes the functional groups of saccharin, shown in Figure 5b as surface **B**. The surface structure corresponding to **A** can only be conserved if growth occurs by the addition of dimer pairs to the surface. Surface **B**, on the other hand, can only be

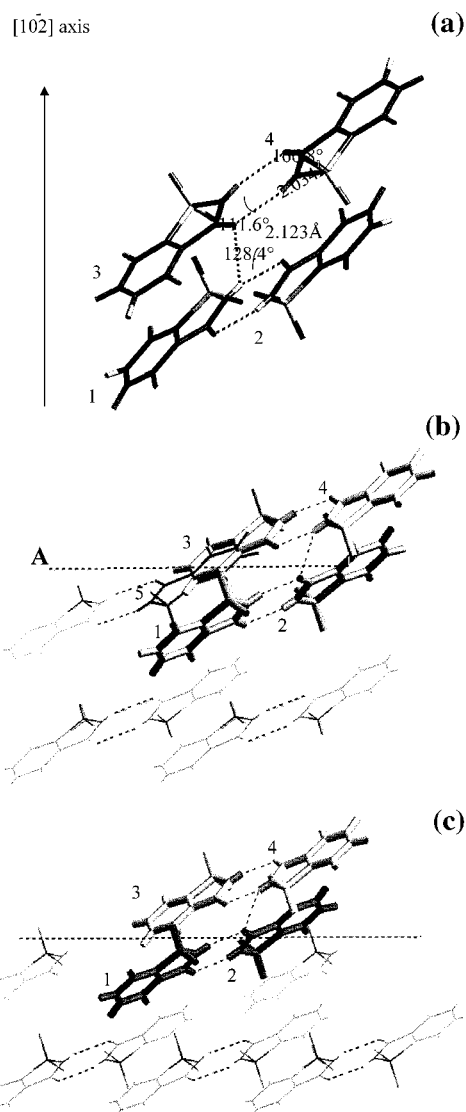


Figure 6. The development of a twinned interface: (a) the hydrogen-bonded dimer pair taken from the proposed twin interface (14), (b) docking a dimer onto surface A, (c) docking a dimer onto surface B.

maintained by addition of single molecules to the surface and differs from **A** in that the exposed surface amide and carboxyl groups would be able to form hydrogen bond contacts with solvent molecules.

Given the solution chemistry of saccharin in ethanol and acetone, as analyzed above, it may be proposed that only in growth from acetone where the synthon is expected to be monomeric can the surface be maintained with structure **B** and only in ethanol where the synthon is dimeric can **A** be stabilized. This suggests a solvent dependency of the surface structure. As a test of the above assignment of the solvent dependent surface structure of the $(10\bar{2})$ face, we now discuss the observed solvent dependency of twinning. In twinned crystals of saccharin we have previously shown that dimers are juxtaposed about $(10\bar{2})$ such that a new three-center hydrogen bond across the twin plane gives additional stability to the crystal. Molecules linked by this bond are related by the necessary mirror symmetry, and Figure 6a shows two such dimers with molecules labeled 1, 2, 3, and 4. To examine how the different surface structures might impact upon the twinning process, a pair of such dimers have been docked with surfaces **A** and **B** in turn so as to mimic the structural change needed for twinning to occur. This is shown in Figures 6b and 6c. Molecules 1 and 2

adopt $(10\bar{2})$ surface sites in each case with molecules 3 and 4 taking the positions required to form the new twinned crystal.

In doing this it is clearly apparent that in docking onto surface **A** (Figure 6b) molecule 3 would have to occupy a site already occupied by the neighboring molecule, 5, which forms part of the existing $(10\bar{2})$ surface. On the other hand, docking into structure **B** allows the dimer pair, molecules 3 and 4, to adopt the “twinned” position without any significant steric clashes. This structural interpretation can only be reconciled with the enhanced propensity to twin in acetone if the surface has the structure **B** in acetone and **A** in ethanol. In addition, it is entirely consistent with the analysis of the solution chemistry given above and the previously proposed model of the twin interface.¹⁴ Thus from both structural and thermodynamic standpoints the

same picture emerges: the surface structure of $(10\bar{2})$ and the growth synthon for saccharin crystallization are solvent dependent. This leads to solvent dependency in the propensity of saccharin crystals to twin. Overall we believe that this central issue of crystal engineering has never been addressed by this combined approach before and that this is the first time that such a clear change in surface structure and growth synthon with solvent have been demonstrated.

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