Crystal Growth

Solvent Effect on Crystal Polymorphism: Why Addition of Methanol or Ethanol to Aqueous Solutions Induces the Precipitation of the Least Stable β Form of Glycine

Isabelle Weissbuch, Vladimir Yu. Torbeev, Leslie Leiserowitz,* and Meir Lahav**

Dedicated to Professor J. Michael McBride on the occasion of his 65th birthday

Crystal polymorphism, which embodies the ability of molecules to form diverse packing arrangements displaying different physical and chemical characteristics, is of paramount importance in fields such as pharmacology, solid-state chemistry, and material science.[1] However, the conditions to induce the precipitation of various (metastable) polymorphs is invariably achieved by "mix and try" methods, which are kinetically driven. Various factors should be considered in trying to understand these complex processes, for example, the formation of structured clusters in solution prior to crystallization, the structure of growing surfaces that delineate emerging nuclei, the interaction between these surfaces and the solvent, as well as solvent–solute and solute–solute interactions. Herein, we attempt to unravel some of these factors to rationalize the preferred crystallization of the β form of glycine (gly) in water–alcohol solutions as opposed to the more stable α or γ polymorphs.

The thermodynamic stability of the three polymorphs of glycine at room temperature is in the order $\gamma > \alpha > \beta$.[2–5] The α form[6] (space group $P2_1/n$), grown from supersaturated aqueous solutions (33.3 g/100 mL water) at 25 °C, has a bipyramidal habit and is composed of centrosymmetric bilayers formed by strong NH···O hydrogen-bonding interactions between cyclic hydrogen-bonded zwitterionic molecular pairs. These bilayers are related along the *b* axis by glide symmetry through weak CH···O interactions (Figure 1 a). Previous studies indicated that α-gly crystallizes primarily in aqueous solutions through hydrogen-bonded cyclic dimer growth units: Diffusion-coefficient[7] measurements of supersaturated aqueous solutions of glycine point to the formation of clusters with an average of 1.8 molecular growth units. Furthermore, atomic force microscopy (AFM) and phase interferometry microscopy measurements established that steps approximately 1 nm in size were formed, which correspond to the thickness of a glycine bilayer.[8,9] Grazing-incidence X-ray diffraction studies on growing α-gly {010}

[*] Dr. I. Weissbuch, V. Yu. Torbeev, Prof. Dr. L. Leiserowitz, Prof. Dr. M. Lahav
Department of Materials and Interfaces
The Weizmann Institute of Science
76100-Rehovot (Israel)
Fax: (+972) 8-934-4138
E-mail: isabelle.weissbuch@weizmann.ac.il
leslie.leiserowitz@weizmann.ac.il
meir.lahav@weizmann.ac.il

  DOI: 10.1002/ange.200500164

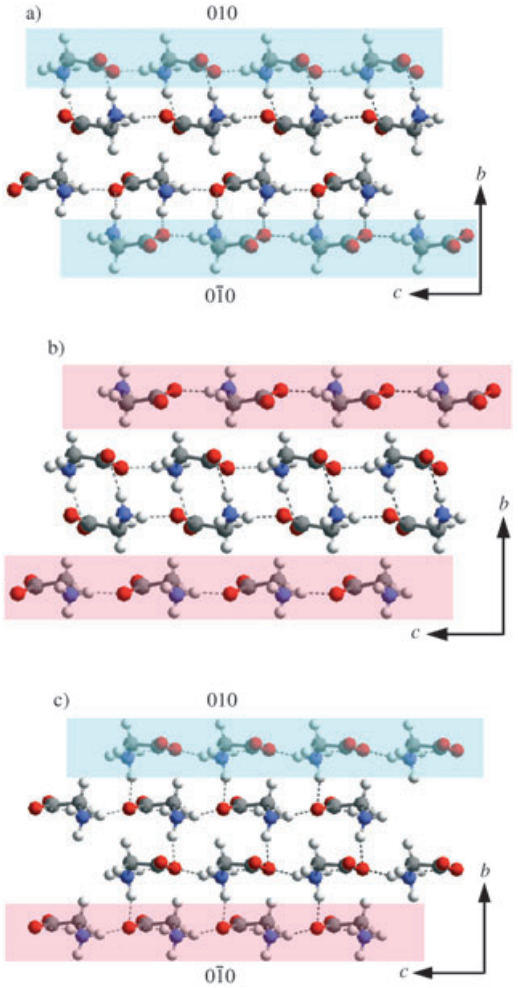

Figure 1. Packing arrangements of the a), b) α and c) β polymorphs of glycine. a), b) α-Gly exposing either weak solvent-binding C–H bonds to the solution at the (010) surface (azure) or strong solvent-binding N–H bonds to the solution at the (010) surface (pink). c) β-Gly exposing (010) "azure" and (0–10) "pink" surfaces, similar to that in α-gly, but at the two opposite poles of the crystal.

crystal faces[10] showed that the crystals primarily had exposed C–H bonds, thus indicating that glycine cyclic dimers are the growth units for α-gly formation.[9]

The first crystallization of β-gly from water–alcohol solutions was reported by Fischer.[11] The crystal structure[12,13] is polar (space group $P2_1$) and comprises hydrogen-bonded layers, which are akin to those observed in the α form, but which are interlinked by NH···O and CH···O interactions through a twofold screw-symmetry axis perpendicular to the layer plane (Figure 1c). The addition of alcohol reduces the solubility of glycine from 25.0 g/100 mL water (25 °C) to 2.65 g/100 mL solvent in 50.1 % (v/v) ethanol–water mixtures. This reduced solubility should result in an increased concentration of solvated glycine monomers relative to that of hydrogen-bonded cyclic dimers. Such behavior is apparently consistent with the preferred precipitation of β-gly from alcohol–water solutions because the crystal structure consists of hydrogen-bonded monomer units, as opposed to α-gly which comprises cyclic hydrogen-bonded pairs.

Long needles of β-gly were grown in water–ethanol mixtures containing 50, 26.1, and 10 % (v/v) ethanol and also from 1:1 water–methanol mixtures containing 4.0, 19.0, 35.9, and 5.0 g gly/100 mL solvent, respectively (Figure 2a).

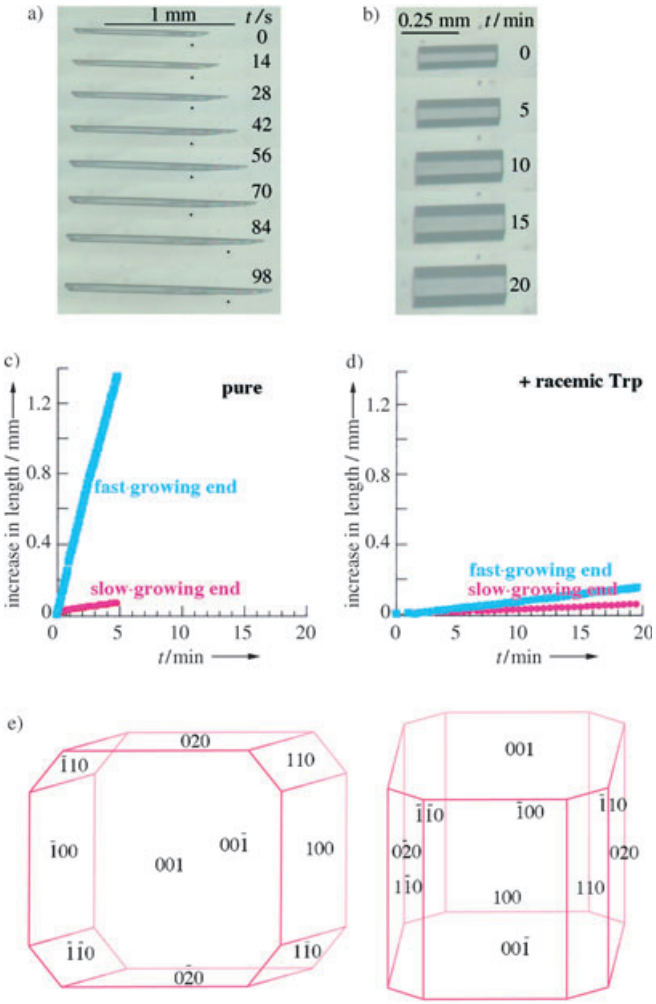

Figure 2. Photographs showing the growth of β-gly crystals in a 1:1 water–ethanol solution in a) the absence and b) the presence of 5 % (w/w) racemic Trp. c, d) Corresponding increase in length at opposite ends of the β-gly crystals. e) The theoretical growth form of β-gly viewed along the *c* and *a* axes.

Therefore, we were faced with the conundrum that the more thermodynamically stable α- and γ-gly polymorphs do not generally precipitate in aqueous solutions containing methanol or ethanol under the specified experimental conditions. We thought that an answer to this problem might be gleaned from the growth kinetics of the three polymorphs of glycine coupled with an analysis of the action of the solvent at the various crystal faces.

Growth kinetic measurements of single β-gly crystals in 1:1 water–ethanol solutions at 25 °C reveal a fast growth at one pole of the needle and a very slow growth at the opposite end (Figure 2a, c). We determined the absolute polarity[14] of

β-gly by employing "tailor-made" additives, in this case racemic tryptophane (Trp). The packing arrangement of β-gly (Figure 1c) dictates that an (*R*)-tryptophane additive may occupy the site of a glycine molecule at the end of the (010) crystal with exposed C–H bonds and subsequently retard its growth. If this end is the faster growing of the two crystal poles, tryptophane would induce the formation of short prismatic crystals, as observed experimentally (Figure 2b, d). Therefore, we conclude that β-gly grows faster at the side with exposed C–H bonds (colored azure) than at the opposite side with exposed N–H bonds (colored pink; Figure 1c). Previous studies have shown that the relative rates of growth at the opposite ends of polar crystals in polar solvents can be correlated directly with the relative rates by which solvent molecules are stripped from the opposite ends.[15–18] The faster growth rate at the β-gly pole with exposed C–H bonds is in agreement with this model; the water or alcohol solvent molecules can be attached more effectively to the slow-growing glycine surface with exposed N–H bonds through strong $OH_{sol}\cdots O_{gly}^-$ and $NH_{gly}\cdots O_{sol}$ interactions than to the fast-growing β-gly pole with exposed C–H bonds with strong $OH_{sol}\cdots O_{gly}^-$ interactions but only weak $CH_{gly}\cdots O_{sol}$ interactions. The surface of the fast- and slow-growing ends of β-gly (Figure 1c) are very similar in structure to the {010} surfaces of α-gly with either exposed C–H or N–H bonds, as shown in Figure 1a, b, respectively.[19] On the basis of the realistic assumption, which is supported by experimental evidence,[8,9] that glycine molecules in aqueous solution dock onto the crystal surface primarily as hydrogen-bonded cyclic glycine pairs, it is thought that an {010} face will expose the faster-growing surface with exposed C–H bonds to a much larger extent than the slower-growing surface with exposed N–H bonds. We anticipated that the reduced solubility of glycine in solution caused by the presence of ethanol would lead to a higher proportion of solvated glycine monomer units docking onto the α-gly {010}-surface sites with exposed N–H bonds. Thus, the time required to strip the overlying solvent molecules, prior to formation of the glycine cyclic dimer growth units and propagation of the glycine bilayer with exposed C–H bonds on its {010} surface, would lead to an overall reduction in growth rate along the $\pm b$ directions of the α-gly crystal. Indeed, the α-gly crystals obtained from a 9:1 water–ethanol solution tended to display more well developed {010} faces (Figure 3a) than crystals obtained from purely aqueous solutions. Therefore, embryonic α-crystallites would expose slow-growing {010} surfaces at higher concentrations of the alcohol in contrast to β nuclei, which has only one slow-growing polar end and so results in a preferred kinetic precipitation of the latter.

A further consequence of the pronounced effect of solvent on the crystal morphology of β-gly can be observed by comparing its needlelike habit (Figure 2a) with the regular shape resulting from the theoretical growth form (Figure 2e), which was computed by using Cerius[2] according to the attachment energy hypothesis by Hartman and Perdock.[20,21] Thus, water or alcohol as solvent impedes growth normal on the {*h*0*l*} faces of the needle crystals as a result of strong solvent attachment to these faces through $OH_{sol}\cdots O_{gly}$ and $NH_{gly}\cdots O_{sol}$ hydrogen-bonding interactions.

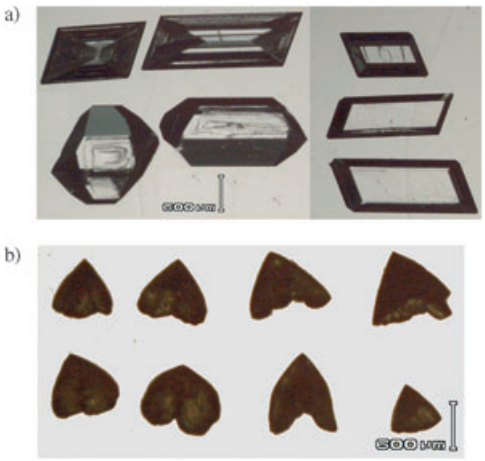

Figure 3. a) α-Gly crystals grown from 9:1 water–ethanol. b) γ-Gly crystals observed in several crystallizations from a 1:1 water–ethanol solution.

The absence of the stable γ-gly form[22] in crystals formed in alcohol–water solutions may be explained by examination of its growth properties. The polar crystal structure of γ-gly (space group $P3_1$; Figure 4), which is not composed of cyclic glycine pairs, is delineated by a (00–1) face at which CO_2^- groups emerge and capped crystal faces at the opposite end that expose NH_3^+ groups. Previous studies[23] have shown

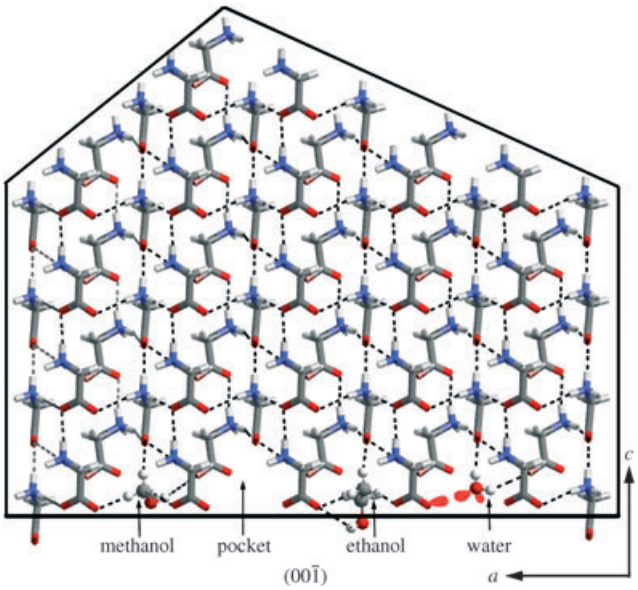

Figure 4. Packing arrangement of γ-gly showing the pockets on the fast-growing (00–1) face that are poisoned by the adsorption of ethanol and methanol molecules (shown as "balls and sticks"). In addition to the $OH_{sol}\cdots O_{gly}^-$ interaction, three $CH_{sol}\cdots O_{gly}^-$ interactions are formed that are similar in geometry to, but weaker than, the three $N{-}H_{gly}\cdots O_{gly}^-$ interactions that glycine would make. Note that a water molecule within the pocket is only weakly bound as the two possible $OH_{sol}\cdots O_{gly}^-$ hydrogen-bonding interactions would be counterbalanced by a lone-pair $O_{sol}\cdots O_{gly}^-$ repulsion (shown in red); therefore, the pocket is relatively accessible to approaching glycine molecules.

that γ-gly, grown in aqueous solutions and in the presence of auxiliaries that inhibit the crystallization of α-gly, appear as [001] needles that grow along the polar *c* axis much faster at the end of the crystal with the CO_2^- groups than at the opposite capped end. This unidirectional growth was interpreted in terms of a "relay" mechanism, according to which the corrugated face at the CO_2^- end will have ridges covered by bound water and pockets that are weakly hydrated, if at all. These pockets are then amenable to being quickly filled with NH_3^+ groups from glycine molecules that, in turn, will induce stripping of the water molecules from the ridged surfaces.[16] However, ethanol and methanol solvent molecules can reside within the pockets through $OH_{sol}\cdots O_{gly}^-$ and $CH\cdots O_{gly}^-$ hydrogen-bonding interactions, thus inhibiting growth at the CO_2^- end of the crystal (Figure 4). In several of the crystallization experiments carried out in water–ethanol mixtures, the few γ-gly crystals that were observed exhibited a morphology in keeping with the proposed inhibition by ethanol or methanol of growth along the otherwise fast-growing CO_2^- end of the crystal (Figure 2b).

In conclusion, the analysis of the growth kinetics of different polymorphs in terms of their crystal structures and solvent–surface, solute–solvent, and solute–solute interactions allows a rationale to be proposed for understanding the crystallization of kinetically controlled polymorphs.[24] Herein, focus was placed on the interplay between the various solute species[25] and solvent–surface interactions to account for the polymorph precipitated. These results also support the established model that removal of the solvent molecules is an important rate-determining step in the growth of a given face. The ideas presented herein should be relevant for understanding and controlling crystal morphology and the polymorphism of systems that form hydrogen-bonding patterns, such as amino acids, carboxylic acids, and primary and secondary amides.

Experimental Section

Crystallization experiments were performed in covered crystallizing dishes at room temperature without stirring. α-Gly crystals were grown from aqueous solutions containing 33.3 g gly/100 mL water. β-Gly crystals were grown from ethanol/water solutions (50, 26.1, and 10% ethanol (v/v)) and 50% (v/v) methanol/water solutions containing 4.0, 19.04, 35.9, and 5.0 g gly/100 mL solvent, respectively. X-ray single-crystal and powder-diffraction measurements were used to characterize the crystals. Crystals of β-gly were also grown in the absence and in the presence of racemic tryptophane in crystallizing dishes on the stage of an optical microscope with an attached digital video camera. Snapshots taken every 7 s were used to determine the growth of β-gly at both ends of the needlelike crystals by measuring on each image the increase in length at each end of the specimen crystals relative to a reference point.

Received: January 16, 2005
Published online: April 21, 2005

Keywords: crystal growth · glycine · polymorphism · solvent effects

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