Tailor-Made? and charge-transfer auxiliaries for the control of the crystal polymorphism of glycine

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calcd. for $C_{40}H_{35}MoPS_{10}$ (Found): C, 49.88 (50.20); H, 3.66 (3.71); S, 33.28 (32.01); P, 3.22 (3.01).

$Cp^*Mo(dmit)_2^{\ominus}$. Electrocrystallization of $Cp^*Mo(dmit)_2^{\ominus}PPh_4^{\oplus}$ (30 mg) dissolved in Cl_2CHCH_2Cl (30 mL) was conducted in a two-compartment cell, with Pt electrodes ($\varnothing = 1$ mm, $L = 2$ cm) at a constant current of 2 μA at 20 ± 1 °C. Black platelets were harvested on the anode after one week and washed with a little Cl_2CHCH_2Cl.

X-ray data for $[Cp^*Mo(dmit)_2^{\ominus}][Ph_4P^{\oplus}]$: $C_{40}H_{35}MoPS_{10}$, $M = 953.15$, tetragonal, $P\text{-}42_1m$ (no. 113); $a = b = 17.221(2)$, $c = 6.976(2)$ Å; $V = 2068.8(7)$ Å^3, $Z = 2$, $d_{calc} = 1.546$ g cm^{-3}, $\mu = 12.5$ cm^{-1}; Enraf-Nonius diffractometer with Mo-Kα radiation, $\lambda = 0.71073$ Å. The structure was solved by direct methods and successive Fourier difference synthesis. The Cp* ring was disordered on two major positions related by one of the mirror planes. Refinement of 122 variables with anisotropic thermal parameters (except for the Cp* carbon atoms refined isotropically) gave $R = 0.076$, $R_w = 0.088$ by using 1193 absorption corrected (ψ-scan) reflections with $I \geq 3\sigma(I)$.

X-ray data for $Cp^*Mo(dmit)_2^{\ominus}$: $C_{16}H_{15}MoS_{10}$, $M = 623.83$, monoclinic, $P2_1/n$; $a = 8.534(2)$, $b = 22.238(3)$, $c = 11.651(2)$ Å, $\beta = 90.66(1)°$; $V = 2210.9(7)$ Å^3, $Z = 4$, $d_{calc} = 1.874$ g cm^{-3}, $\mu = 15.4$ cm^{-1}. Enraf-Nonius diffractometer with Mo-Kα radiation, $\lambda = 0.71073$ Å. The structure was solved by direct methods and successive Fourier difference synthesis. Refinement of 244 variables with anisotropic thermal parameters gave $R = 0.034$, $R_w = 0.056$ by using 3467 reflections with $I \geq 3\sigma(I)$.

Further details of the crystal structure determinations may be obtained from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK, on quoting the names of the authors, and the journal citation.

Magnetic studies: ESR and AFMR experiments were conducted on a Varian X-band spectrometer (9.3 GHz) equipped with an Oxford ESR 900 helium cryostat.

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[17] In the (X, Y, Z) frame, where X and Y are obtained from *a* and *c* after a rotation of 30° around *b*, and where Z = *b*, the transformation from the molecular frame in which the *g* tensor is diagonal with eigenvalues of g_u, g_v, g_w to the new frame (X, Y, Z) requires a rotation of an angle φ around u followed by a rotation of $-\theta$ around Y. A straightforward calculation from structural data gives $\theta = 14°$ and $\varphi = 20°$. The second molecular orientation corresponds to rotations with $-\varphi$ and $+\theta$. The resulting *g* tensor is the average between the tensors obtained with each transformation and reads:

$$g_X = g_u \cos^2\theta + \sin^2\theta\,[g_v \sin^2\varphi + g_w \cos^2\varphi]$$

$$g_Y = g_v \cos^2\varphi + g_w \sin^2\varphi$$

$$g_Z = g_u \sin^2\theta + \cos^2\theta\,[g_v \sin^2\varphi + g_w \cos^2\varphi]$$

For similar determinations of a *g*-tensor eigenvalues and axes, see for example: A. Guirauden, I. Johannsen, P. Batail, C. Coulon, *Inorg. Chem.* **1993**, *32*, 2446.

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"Tailor-Made" and Charge-Transfer Auxiliaries for the Control of the Crystal Polymorphism of Glycine

By *Isabelle Weissbuch,* Leslie Leisorowitz,** and *Meir Lahav**

Crystal polymorphism is a widespread phenomenon which takes place when the same molecule packs in the solid phase in different arrangements. Owing to their different physical and mechanical properties, polymorphs play an important role in a large variety of fields, ranging from bioavailability of solid drugs in pharmacology to the preparation of functional materials. However, the discovery of new polymorphs requires effort or in McCrone's words "the number of forms known for a given compound is proportional to the time and money spent in research on that compound".[1] Recently, we proposed a stereochemical approach for the control of crystal polymorphism with the assistance of stereospecific nucleation inhibitors.[2, 3] The method follows a working hypothesis that in supersaturated solutions molecules assemble to form coexisting clusters of structures resembling the crystals into which they eventually develop. Consequently, on the basis of the structural information from the corresponding crystalline forms, it became possible to design nucleation inhibitors (Scheme 1) which can be stereospecifically recognized and bound at the surfaces of clusters of the stable polymorph, thus preventing their growth and possibly causing their disintegration. Unaffected clusters of structures akin to those of the metastable polymorph will transform into crystals by a kinetic controlled process.

This empirical working hypothesis has been successfully applied for the design of polymeric auxiliary reagents to

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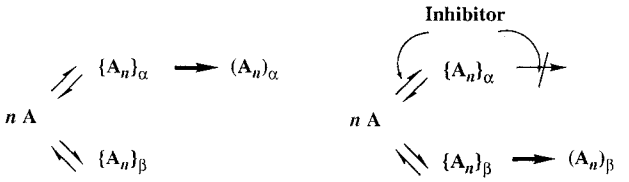

where:
A - molecules
{ }- nuclei
( ) - crystals

Scheme 1.

induce spontaneous resolution by crystallization[4] and to explain the induced twinning of racemic alanine grown in the presence of other resolved α-amino acids.[5]

Here, we demonstrate that in the design of the auxiliary molecules one should consider not only the overall packing arrangement of various polymorphs but also their crystal morphologies, as well the kinetics of growth normal to the developed crystal faces. Furthermore, inhibitors which form charge-transfer complexes with the substrate can also be used. On the basis of these approaches, we report the design of auxiliaries for the precipitation from aqueous solutions of the γ-form of glycine.

Three polymorphic forms of glycine, $^{\oplus}H_3N-CH_2CO_2^{\ominus}$, have been reported: a stable centrosymmetric α-form,[6] an unstable β-form[7,8] and a polar γ-form[9] which transforms slowly into the α-form upon heating above 165 °C.[9] From aqueous solutions glycine crystallizes as bipyramids (Fig. 2a) in the centrosymmetric α-form,[10] of space group $P2_1/n$ with cell dimensions $a = 5.10$ Å, $b = 11.97$ Å, $c = 5.46$ Å and $\beta = 111.8°$. The crystal is composed of centrosymmetric hydrogen-bonded bilayers related by twofold screw symmetry along the unique b-axis (Fig. 1a).

The γ-polymorph of glycine has been grown from aqueous solutions in the presence of sulfuric acid, acetic acid or ammonia. Thus we shall not only probe the new auxiliaries for crystallization of γ-glycine, but, as a result of the same approach, explain the role of induced crystallization by acid and base additives. The crystal of γ-glycine assumes the polar space group $P3_1$ or $P3_2$, with cell dimensions $a = 7.037$ Å, $c = 5.483$ Å, and contains hydrogen-bonded chains along the polar c-axis such that the crystal exposes $CO_2^{\ominus}$ groups at the one end of the trigonal axis and $NH_3^{\oplus}$ groups at the opposite end (Fig. 1b).[11]

The crystals grown in the presence of acetic acid (4% by volume) either appear as short trigonal prisms with a set of smooth faces at one end of the trigonal axis, six side faces and a poorly defined $(00\bar{1})$ face at the opposite end of the polar axis, as shown in Figure 2c, or display only the pyramidal part, as shown in Figure 2b. The absolute arrangement of the molecules vis-à-vis the polar morphology has been determined by several methods,[12] whereby the $NH_3^{\oplus}$ groups emerge at the capped end of the polar axis and $CO_2^{\ominus}$ groups at the opposite end, as shown in Figure 1b. The crystals dissolve in water almost unidirectionally along the polar axis at the $(00\bar{1})$ face which exposes $CO_2^{\ominus}$ groups, a fact which has been explained in terms of a relay mechanism discussed elsewhere.[13]

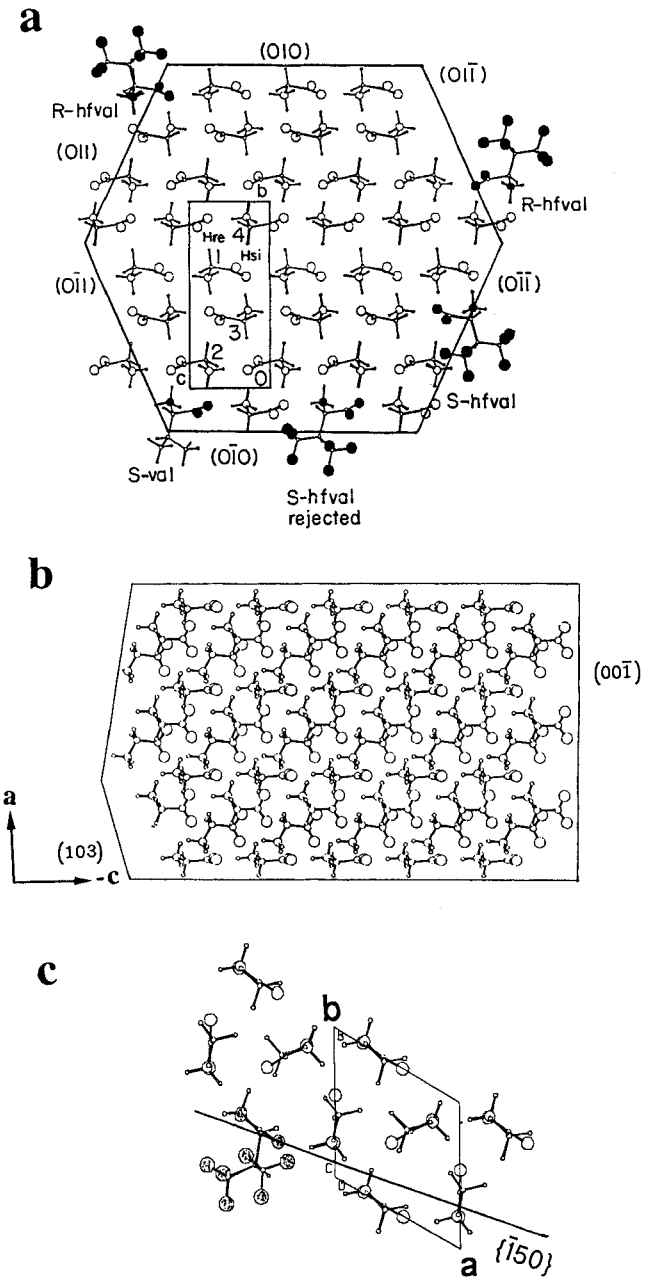

Fig. 1 a) Packing arrangement of the α-form of glycine viewed along the a axis as delineated by the crystal faces and showing the effect of the following auxiliaries: an (*S*)-valine [val] molecule adsorbed at the $[0\bar{1}0]$ face, two (*R*)-hexafluorovaline [hfval] molecules adsorbed at the [011] and $[01\bar{1}]$ faces and an (*S*)-hfval molecule adsorbed at the $[0\bar{1}\bar{1}]$ face. Note that the (*S*)-hfval molecule cannot be adsorbed at the [010] face due to steric and electronic repulsion. b) Packing arrangement of the γ-form of glycine viewed along the b axis. c) Packing arrangement of the γ-form of glycine viewed along the c axis showing a hexafluorovaline molecule adsorbed at the $\{\bar{1}51\}$ faces. Note that the $[\bar{1}51]$ plane is not seen in this figure, but rather $[\bar{1}50]$.

A primary difference between the packing arrangements of the α- and γ-polymorphs is that in the centrosymmetric

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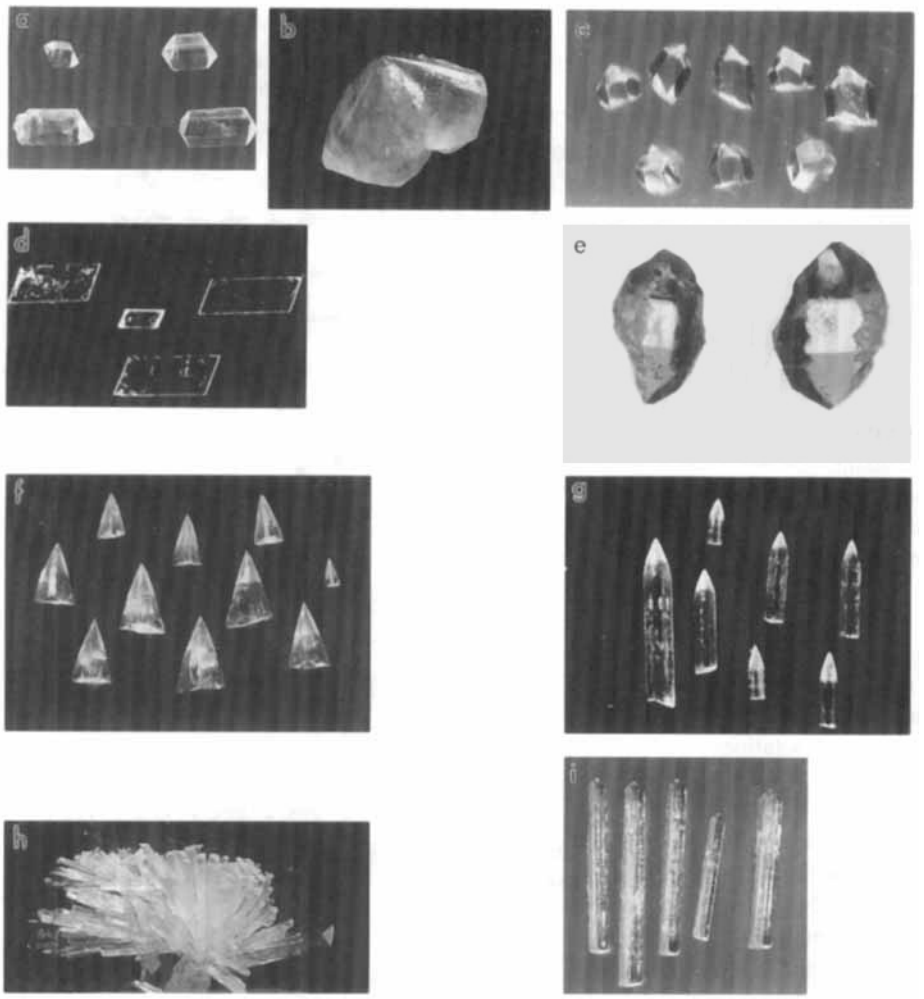

Fig. 2 a) α-Glycine bipyramids grown from pure aqueous solutions. b,c) γ-Glycine crystals grown from 4% (by volume) acetic acid aqueous solutions. Note that twinned pyramidal crystals as in (b) were often formed. d) α-Glycine plate-like crystals grown from aqueous solutions in the presence of racemic naturally occurring α-amino acids. e) Affected α-glycine crystals grown from aqueous solutions in the presence of 1–2% [w/w of glycine] racemic hexafluorovaline. f) γ-Glycine pyramidal crystals grown from aqueous solutions in the presence of 3% [w/w of glycine] racemic hexafluorovaline. g) γ-Glycine crystals grown from aqueous solutions containing traces of chloranil. h) Bunch of elongated γ-glycine crystals all growing at the flat end of the polar *c* axis which exposes the $CO_2^{\ominus}$ groups. i) γ-Glycine crystals grown from 4% [by volume] acetic acid aqueous solutions in the presence of naturally occurring α-amino acids.

α-form the hydrogen-bonded chains are arranged antiparallel whereas in the polar γ-form all the chains are aligned parallel. Such a characteristic has been taken advantage of for the induced exclusive precipitation of the metastable polar form of *N*-(2-acetamido-4-nitrophenyl)pyrrolidine (PAN), by making use of an additive which was adsorbed onto, and so inhibited the growth of the opposite faces of the centrosymmetric form, but affected only one end of the polar axis of the metastable form, so leaving its overall growth relatively unhindered.[14] Previous attempts at applying this simple principle for the induced precipitation of the γ-polymorph of glycine, at the expense of the centrosymmetric α-form, by using racemic mixtures of naturally occurring α-amino acids, were not successful.

The packing arrangement of the α-form contains four symmetry-related molecules (1,2,3,4 Fig. 1a). Molecules 1 and 2, of the same handedness, have their $C-H_{re}$ bonds emerging from the (010) face and, by inversion symmetry, molecules 3 and 4, which are enantiomeric, have their $C-H_{si}$ bonds emerging from the $(0\bar{1}0)$ face. The (*R*)-α-amino acid additives, $X\text{-}CH(NH_3^{\oplus})CO_2^{\ominus}$, can be adsorbed at the (010) face and inhibit the growth through the steric effect of the side chain X. By symmetry, the (*S*)-α-amino acid additives inhibit growth of the $(0\bar{1}0)$ face. Racemic mixtures of the naturally occurring α-amino acid additive should inhibit crystal growth at both + b and − b sides of the crystal. Indeed, a very strong effect has been observed when growing glycine in the presence of these α-amino acid additives, since they induce a habit modification of the bipyramids into plate-like crystals (Fig. 2d).[15] The presence of increased concentrations of the racemic additives produce thinner and thinner plates and eventually a crystalline powder but always of only the α-form. No inhibition of formation of the α-form was observed, presumably, because the α-amino acid additives inhibit the stacking of the hydrogen-bonded *ac* bilayers but do not disturb the fast growth within such bilayers. We anticipated that in order to inhibit nucleation of the α-polymorph it is imperative to design additives that will stop the growth within the hydrogen-bonded bilayers.[16] Such an effect may be achieved by an additive designed to be strongly adsorbed at the four {011} crystal faces of the α-form. Concomitantly the additive must be designed such that it will bind at only one pole of the polar crystal, thus leaving the crystal free to grow at the opposite pole.

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Racemic hexafluorovaline, $(CF_3)_2-CH-CH(NH_3)CO_2^{\ominus}$, was found to satisfy the above requirements. The addition of 1–2% (w/w of glycine) of hexafluorovaline to the supersaturated solution of glycine yielded crystals of unusual morphology, i.e. not plate-like, but rather bipyramidal with affected, step-like {011} side faces (Fig. 2e). For comparison, the regular α-amino acid additives do not affect the morphology of the {011} side faces of α-glycine.

The different behavior of racemic hexafluorovaline can be understood in terms of its molecular structure and conformation as found in its crystal structure.[17] This additive molecule cannot substitute a glycine molecule within the stable hydrogen-bonded *ac* layer because of steric and electronic repulsion imposed by the hexafluoroisopropyl moiety which prevents adsorption on the two {010} faces, as shown in Figure 1a. But the hexafluorovaline molecule can be very effectively adsorbed on the four {011} side faces. (*R*)-Hexafluorovaline (hfval) can be adsorbed only at the (011) and $(01\bar{1})$ faces and on only those surface sites 1 and 2 respectively which expose $NH_3^{\oplus}$ groups. By symmetry, the *S* additive can be adsorbed at the $(0\bar{1}1)$ and $(0\bar{1}\bar{1})$ faces at the corresponding 4 and 3 surface sites (Fig. 1a). In this way the additive blocks growth not only along the fast growing *c* direction, but also in the *b* direction.

Addition of 3% w/w racemic hexafluorovaline led to the precipitation of the γ-polymorph of glycine as trigonal pyramids (Fig. 2f). Hexafluorovaline does not inhibit formation of γ-glycine since it is bound at the slow growing $NH_3^{\oplus}$ end of the polar axis and so does not interfere with the fast growing $CO_2^{\ominus}$ end. Hexafluorovaline can also be adsorbed on the newly developed $\{\bar{1}51\}$ side faces of the trigonal pyramidal crystals, as shown in Fig. 1c.

The very efficient inhibition of the α-form by hexafluorovaline can be also explained not only in terms of the stereospecific binding to {011} faces, but also by invoking charge-transfer interactions at these faces, evidence for which we now provide. When racemic hexafluorovaline is added (1–3% w/w of glycine) to the supersaturated solution of glycine, a pink color develops with an absorption band at $\lambda = 494$ nm, where neither glycine nor hexafluorovaline absorb. The time required for appearance of the color is temperature dependent and, at ~80 °C, takes about 5–10 minutes. This absorption band suggests the formation of a charge-transfer (CT) complex between glycine and hexafluorovaline.

The color of the solution becomes weaker with time, but persists even when the colorless crystals develop. The interaction occurs presumably via the acidic carboxylate group of hexafluorovaline ($pK_2 = 1.21$) and the amino group of glycine. The stoichiometry of the CT complex could be estimated by optical density measurements as a function of concentration of either glycine of hexafluorovaline and the ratio glycine/hexafluorovaline was found to be 2:1.

It has been already reported that the electron acceptor chloranil (tetrachlorobenzoquinone) forms a charge-transfer complex with glycine as an electron donor.[18] The formation of the complex is associated with the appearance of a new absorption band at $\lambda = 370$ nm and the decrease of the chloranil band at $\lambda = 295$ nm.[19] It has been proposed that the charge-transfer is between the amino group of glycine and the carbonyl group of chloranil $O(C_6Cl_4)O\cdots H_2NCH_2COO^{\odot}$.

One may anticipate that a CT complex of this structure can bind at the various faces of α-glycine clusters which expose $NH_3^{\oplus}$ groups such as {011}, {110} and {010}, and so inhibit the nucleation of this crystalline phase. This CT complex can also bind at the slow growing capped end of γ-glycine but not at its fast growing $(00\bar{1})$ face. On these grounds, it was expected that chloranil will induce precipitation of the γ-form. Indeed, less than 0.1% (w/w glycine) chloranil (as ethanol solution) added to the supersaturated solution of glycine led to the precipitation of only the γ-polymorph. The crystals are elongated trigonal prisms with a very sharp capped end as shown in Figure 2g. The crystals grow along the polar axis at the flat end since, when bunches were formed, the crystals grew from a common point, all exposing their flat ends (Fig. 2h). This result is in keeping with the unidirectional growth of γ-glycine at the $(00\bar{1})$ flat face that exposes carboxylate groups. The morphology of the γ-glycine crystals obtained in the presence of chloranil is also consistent with the interaction between the additive and the $NH_3^{\oplus}$ groups exposed at the capped ends of the crystals.

The present mechanism may also explain the role played by acetic acid and ammonia in inducing the precipitation of the γ-form of glycine. Following the above stereochemical analysis, we propose that acetic acid and ammonia can interact with the amino or carboxylate groups at the side {011} faces of the α-glycine and inhibit their growth. Regarding the precipitation of the γ-form, acetic acid may bind to the slow growing amino end of the crystal by strong electrostatic interactions. To account for the crystal stubbiness, we deduce that acetic acid also binds, but less strongly, to the carboxylate end by (acetic acid)C–H···O(glycine) and (acetic acid)O–H···O(glycine) hydrogen bonds. Ammonia on the other hand affects essentially the $(00\bar{1})$ face of γ-glycine. Therefore the crystals grow through the slow growing faces at the + *c* side of the crystal.

The overall effect of the controlled crystallization of the γ-polymorph of glycine can be understood in terms of inhibition of the {010} layer formation in the α-form by stereospecific and charge-transfer interactions, without interfering with the normal growth of the γ-form. The naturally occurring α-amino acids do not prevent precipitation of the α-form presumably because they are strongly bound only at the {010} faces. Neither do they inhibit formation of the γ-form because crystallization of glycine from 4% (by volume) acetic acid aqueous solution in the added presence of increasing amounts (1–10% w/w of glycine) of valine, leucine, phenylalanine, alanine, serine, threonine yielded γ-glycine crystals as very elongated trigonal prisms (Fig. 2i). The appearance of crystals exhibiting well-developed {*hk*0} side faces is consistent with the adsorption of the α-amino

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acid additives on these faces. It is noteworthy that hydrophobic α-amino acids induce the nucleation of α-glycine by virtue of their self-aggregation at the solution surface,[20] despite the competitive effect of acetic acid.

The ability to control the polymorphic behavior of glycine confirms once again the working hypothesis that the supersaturated solutions contain coexisting ordered nuclei with structures which resemble those of the mature crystal phases. In order to prevent growth of particular crystal nuclei, additives should be designed by taking into consideration the structure, morphology and kinetics of growth of the corresponding polymorph to inhibit as many different surfaces as possible preferably of a fast growing nature. Recently, applying a variety of surface-sensitive techniques on crystalline self-assemblies of normal hydrocarbons, α-ω aliphatic diols, and diacids on water and mica surfaces demonstrated formation of crystallites two to several layers thick. These crystallites are very similar in structure to that of the mature crystal forms and respond to tailor-made auxiliaries yielding monolayers or bilayers, in a manner akin to the inhibiting effect on three-dimensional crystals. One such example is presented in the following communication.[21]

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Inhibition of Self-Aggregation of α,ω-Docosanediol into 3D Crystallites by "Tailor-Made" Amphiphilic Auxiliaries**

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In the first stages of the process of crystallization, molecules assemble into structured aggregates or nuclei, driven by intermolecular interactions. Such aggregates are destabilized by the interface created with the environment and thus are metastable or nucleation transients en route to crystal formation. Only nuclei which exceed the critical size develop into mature crystals.[1, 2] The assumption that each such crystal originates from a nucleus compatible with its structure was previously used to design auxiliary molecules that can recognize and interact selectively with nuclei or small crystallites of certain phases and inhibit their growth into mature crystals.[3–5] Such specific interactions of the additives with structured aggregates could be inferred from morphological changes in the mature crystals or from the appearance of metastable polymorphs, but could not be observed directly at very early stages of crystallization.

Recently, we reported the spontaneous self-aggregation of the bolaamphiphile α,ω-docosanediol $HO-(CH_2)_{22}-OH$ into embryonic three-dimensional (3D) crystallites when spread at the air–water interface.[6] This self-aggregation is probably driven by the relatively high surface energy created by the two-dimensional (2D) Langmuir layer of vertically aligned α,ω-alkane-diols, which exposes one of the hydroxyl groups to the air.[7, 8] Such instability may be overcome by forming 3D multilayers, which stabilize the system through interlayer hydrogen bonds. The 3D multilayer crystallites obtained were 3–5 layers thick, indicating early stages of crystal formation. We employed here a technique involving molecular recognition by "tailor-made" additives[9–11] that were inserted in the system in order to study their effect on these embryonic crystallites using analytical tools that can directly sense structural changes at the nanometer level. The idea was to use amphiphilic additive molecules that are of a similar chemical nature to the bolaamphiphile and which may randomly mix within the host matrix owing to favorable lateral interactions, but hinder the interlayer interactions and thereby inhibit the formation of multilayers.[12] As additives we have used miscible aliphatic alcohols or acids having hydrocarbon chains equal to or longer than that of the host α,ω-docosanediol. Molecular recognition in these mixtures occurs through the lateral hydrophobic methylene–methylene

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