CrystEngComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/crystengcomm

Salt-Dependent Growth Kinetics in Glycine Polymorphic Crystallization

Guangjun Han[a,*], Pui Shan Chow[a] and Reginald B. H. Tan[a,b,*]

Received (in XXX, XXX) Xth XXXXXXXXX 201X, Accepted Xth XXXXXXXXX 201X
First published on the web Xth XXXXXXXXX 201X
DOI: 10.1039/b000000x

Mechanistic exploration of salt-dependent polymorphic outcome of solution crystallization of an important classical model compound, glycine, was carried out by measurements of growth rates of α-glycine and γ-glycine single seed crystals in the presence of typical inorganic salts. The most surprising finding was that all the three divalent cation salts examined here inhibit the growth of γ-glycine far more severely than that of α-glycine, thereby tending to reinforce the preferential formation of α-glycine. This strongly indicates that crystal (nucleus) growth kinetics plays an important role in determining the outcome of glycine polymorphic crystallization in the presence of these associated divalent cation salts. On the other hand, monovalent cation salts of different cations (Na^+, K^+ and NH_4^+), in general, do not significantly change the relative growth competitiveness of α-glycine and γ-glycine but they readily alter the polymorphic selectivity from α-glycine to γ-glycine. It is therefore inferred that nucleation phenomena (e.g., clustering and ordering of solute molecules in solution) also make a great contribution to directing the path of glycine polymorphic crystallization. As such, the observations from this study provide new insights into the additive-directed glycine polymorphic crystallization.

Introduction

It is of practical importance to control the polymorph[1-4] (i.e., crystalline structure) of crystals produced from solution crystallization which is a key technique for separation and purification in many industries, since the polymorph determines the physical and chemical properties of the crystal products. However, it has been a challenging task to achieve a robust polymorph control. The major challenge arises from the poor fundamental understanding[2] of solution crystallization, as it was typically demonstrated by the widely studied polymorphic crystallization[1-27] of a classical model compound[3], glycine. Mechanistic exploration of glycine polymorphic crystallization[1-4,15] has been a hot research topic for decades. One of the major intentions behind such an intensive exploration of glycine polymorphic crystallization is to establish a relationship[1,2] between polymorphic selectivity and species self-association in solution, which may provide fundamental insights into general polymorphic crystallization.

Glycine is the simplest amino acid. Glycine molecules (neutral form H_2NCH_2COOH) exist as zwitterions ($^+H_3NCH_2COO^-$)[1] in aqueous solution due to intra-molecular proton transfer. Through solution crystallization, three (α, β and γ) common polymorphs[1,2] of glycine crystals can be produced. Under ambient conditions, α-glycine (space group $P2_1/n$) is metastable, β-glycine (space group $P2_1$) least stable and γ-glycine (space group $P3_1$) most stable. The β-glycine, highly unstable and transforming to α-glycine nearly instantaneously[5] in aqueous solution, may be formed by addition of anti-solvents (hence generation of a substantially high supersaturation)[1,3] or under other specific conditions.[6] Remarkably, previous studies[1-2] have revealed that, in pure aqueous glycine solutions under usual conditions, the metastable centrosymmetric dimer-based α-glycine[7,8] (Fig 1a) is formed preferentially over the noncentrosymmetric monomer-based polar γ-glycine[1,2,4] (Fig 1b) despite the stability of γ-glycine. Nevertheless, γ-glycine may be obtained from solutions in the presence of additives[1] especially the typical inorganic acids, bases and salts which are readily available.

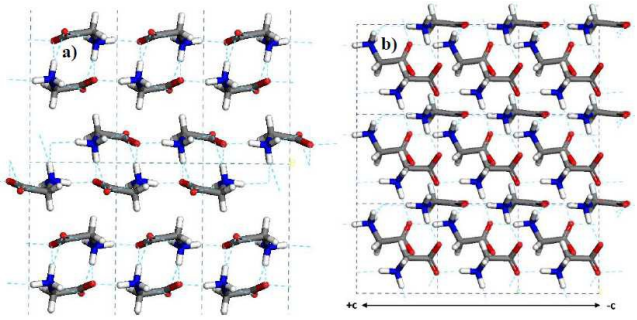


Figure 1. Crystalline structures of a) α-glycine and b) γ-glycine, illustrating centrosymmetric cyclic dimer-based α-glycine and head-to-tail monomer-based polar γ-glycine. Colour scale of atoms in packing: C (dark gray), N (blue), O (red) and H (white)

It is well-known that strong acids and bases readily change the polymorphic selectivity[1,2,4] from the metastable α-glycine to the stable γ-glycine, showing a very interesting pH-associated phenomenon. However, it was a longstanding riddle[1,2,4] how solution pH alters the polymorphic outcome of glycine nucleation, though it is well understood that a shift in solution pH can profoundly convert glycine species[1] from dimers to ionic monomers (glycine ions). This riddle was not resolved until recently.[4,9] It was discovered[9] that the relative growth rates of α-glycine and γ-glycine are altered by an acid or a base but the altered growth rates are not the major factor for the preferential formation of γ-glycine at a low or a high solution pH. Furthermore, a study[4] using *in situ* Raman spectroscopy with dynamic principal component analysis (PCA) showed that typical inorganic acids and bases accelerate the nucleation of γ-glycine far more than that of α-glycine, thereby favouring γ-glycine. It was hypothesized that glycine ions, readily formed in an acidic or basic

environment, induce head-to-tail molecular ordering which structurally matches γ-glycine packing and primarily directs nucleation path from α-glycine to γ-glycine.

Inorganic salts are another category of additives which were also used to produce γ-glycine. As pointed out,[1] this salt-aided formation of γ-glycine should not be attributed to the shift of solution pH, as inorganic salts (e.g., NaCl and Na_2SO_4) generally do not cause the pH of a glycine solution to shift significantly. A study by Davey and coworkers[1] presented an interesting observation that, among the six salts they examined, all the three sodium salts (NaCl, Na_2CO_3, Na_2SO_4) effectively induce γ-glycine while all the three non-sodium salts ($MgSO_4$, $Ca(NO_3)_2$ and $Mg(NO_3)_2$) hardly showed any effect. Based on this observation, it was postulated that a specific Na^+–α-glycine interaction inhibits α-glycine so as to permit γ-glycine to appear. Such a postulation has yet to be supported by other experiments. This is because the same observation may also suggest that the valences of the salt cations play a primary role, perhaps implying that divalent cation salts are far less effective in inducing γ-glycine than monovalent cation salts.

In order to shed some light on the salt-aided formation of γ-glycine, solution-mediated glycine polymorphic transformation[10] from pure α-glycine to γ-glycine was performed in the absence and in the presence of an additive, NaCl, showing that NaCl promotes the nucleation of γ-glycine. It was proposed[10] that Na^+ cations and Cl^- anions disturb the cyclic glycine dimers, weakening the nucleation of the dimer-based α-glycine and hence relatively favouring nucleation of the monomer-based γ-glycine. In addition, it was also postulated[10] that, in solution, the COO^- group of a glycine zwitterion ($^+H_3NCH_2COO^-$) is closely surrounded by a few Na^+ cations while its NH_3^+ group is closely surrounded by a few Cl^- anions. This suggested ion-glycine interaction pattern was believed to facilitate the alignment of glycine zwitterions to head-to-tail orientation, thereby favouring the formation of head-to-tail packed γ-glycine. Such a proposed mechanism is doubtful because studies had shown that glycine cyclic dimers are neither the dominant species[2] in solution nor the major favourable building blocks[9] of α-glycine. Furthermore, it failed to explain how the ion-surrounded glycine zwitterions enhance their head-to-tail alignment in solution. Perhaps, the weakest part of this suggested mechanism is that it does not rationalize the observation[1] that divalent cation salts (e.g., $MgSO_4$, $Ca(NO_3)_2$ and $Mg(NO_3)_2$) hardly induce γ-glycine nucleation.

A recent computational study[11] investigated the impacts of NaCl (1.37M) on development and stabilization of unstable glycine polymorphic nuclei. Interestingly, it was revealed that a significant double layer of the Na^+ and Cl^- ions is particularly formed around the polar NH_3^+-rich (001) and COO^--rich (00-1) faces at γ-glycine nucleus c-axis. In comparison, a relatively insignificant double layer of the Na^+ and Cl^- ions is formed around the less polar faces of α-glycine. Due to the appreciable difference in double layers, the effective interfacial free energy of the α-glycine nucleus is increased by 3.1 mJ/m^2 while that of the γ-glycine nucleus is decreased by 7.7 mJ/m^2. By doing so, the nucleation barrier for α-glycine nucleation is increased while the barrier for γ-glycine nucleation is reduced, thereby retarding α-glycine nucleation and meanwhile enhancing γ-glycine nucleation. However, a previous analysis on double layers[1] indicated that the interfacial energy reduction might not be a governing factor. As rationalized, at the same ionic strength at which various salts are supposed to decrease the interfacial energy to a comparable degree, typical inorganic salts tremendously differ in inducing γ-glycine. Therefore, it is strongly suggested that double layer formation alone is not sufficient for the salt-aided nucleation of γ-glycine.

It should be noted that the Na^+ and Cl^- ions which are strongly adsorbed at γ-glycine nucleus faces exerts opposing impacts. On the one hand, it reduces the interfacial energy, favouring nucleus growth[14] and nucleation. On the other hand, the removal of these adsorbed ions, a step similar to desolvation which is necessary for sustainable nucleation and nucleus growth, is likely difficult given their strong adsorption, tending to retard nucleus growth and nucleation. If interfacial energy reduction dominates the removal of adsorbed ions, then γ-glycine c-axis growth is also supposedly accelerated. However, it is not the case. In fact, a recent study[12] revealed that, at a comparable NaCl concentration, Na^+ and Cl^- ions do not promote but further impede the growth of the already water-retarded[13] γ-glycine polar c-axis. As a result, the NaCl-induced γ-glycine exhibits a short prismatic shape[1,10] and is not elongated along its c-axis. These findings therefore put additional doubt on the postulation that the NaCl-aided interfacial energy reduction effectively promotes the γ-glycine nucleation.

It is seen that the previous studies[1,10,11] presented different interpretations of the salt-induced formation of γ-glycine, and none of them is able to generally explain the observation that some salts (e.g., NaCl and Na_2SO_4) effectively induce γ-glycine while some other salts (e.g., $MgSO_4$, $Ca(NO_3)_2$ and $Mg(NO_3)_2$) hardly work. As such, why inorganic salts differ in inducing γ-glycine remains an open question.

It is known that the relative growth kinetics of polymorphs can play a significant role[13,14] in determining the outcome of polymorphic nucleation. Therefore, in this work, we investigated the effects of various typical inorganic salts (including non-sodium monovalent cation salts) on crystal growth kinetics of both the metastable α-glycine and the stable γ-glycine so as to assist elucidating the associated mechanisms. We found that the effects of salts on glycine growth are interesting and even unexpected. These effects and their implications for glycine polymorphic crystallization will be presented and discussed.

Experimental section

Materials

Both the α- and γ-glycine crystals (99%) were from Sigma-Aldrich and used as received.[13] Control experiments were performed by using a higher grade of glycine (>99.7%, Sigma-Aldrich) to prepare solutions. All the inorganic monovalent cation salts (NaCl, Na_2CO_3, Na_2SO_4, KCl, KNO_3,

NH_4NO_3, $(NH_4)_2SO_4$) and divalent cation salts ($MgSO_4$, $Ca(NO_3)_2*4H_2O$, $Mg(NO_3)_2*6H_2O$) employed as additives here were of analytical grade. These inorganic salts are representative, covering the very typical metal cations (K^+, Na^+, NH_4^+, Ca^{2+} and Mg^{2+}) and non-metal anions (Cl^-, NO_3^-, SO_4^{2-} and CO_3^{2-}). Ultrapure water (Millipore, resistivity 18.2 MΩcm and filtered with pore size 0.22 μm) was used for solution preparation.

Measurement of solubility

Solubilities of α- and γ-glycine in salt aqueous solutions at 23°C, required in performing experiments for crystal growth rates, were measured using a similar isothermal method as described in our previous studies.[9,28] Excess glycine crystals (either α-glycine or γ-glycine) were added to a solution containing certain amount of a given salt additive. The slurry was agitated continuously until the crystal-solution equilibrium was attained at the given temperature. The concentration of the glycine saturated solution (i.e., glycine solubility) was determined by solution density[9,28] (densitometer Anton Paar DMA5000 with a density resolution of 10^{-6} g/ml and a temperature resolution of 0.001°C).

Powder X-ray diffraction (Bruker D8 Advance Diffractometer) was employed to determine the polymorphic forms of the initial glycine crystals and the crystals harvested after the crystal-solution equilibration.

Preparation of seed crystals

The prismatic α-glycine seed crystals (Figure 2a) were prepared by evaporation of concentrated additive-free glycine aqueous solutions (~ 32 g/100g H_2O) at room temperature (~ 23°C). The needle-like γ-glycine seed crystals with identifiable +c and –c ends (Figure 2b) were grown from aqueous glycine solution in the presence of DL-aspartic acid. An α-glycine seed is readily differentiated from a γ-glycine seed. Nevertheless, Raman spectrometry (JY Horiba) was used to verify the polymorphic form of the seed crystals. The detailed method and procedure for the preparation and verification of glycine seed crystals had been elaborated in our previous work.[13]

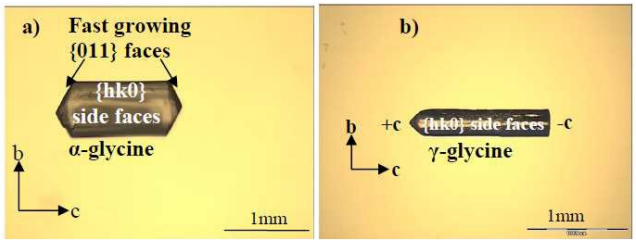


Figure 2. a) A typical prismatic α-glycine seed crystal formed from pure glycine aqueous solution, with the {011} faces being normally the fastest growing; b) A typical needle-like γ-glycine seed crystal formed from glycine aqueous solution in the presence of DL-aspartic acid, with a flat COO^--rich –c end and a pointed NH_3^+-rich +c end.

Measurement of crystal growth rates

The experiment was performed for the growth rate of a single glycine seed crystal (either α or γ form) in an aqueous glycine solution in the absence and in the presence of an inorganic salt at 23°C, at a given supersaturation σ = 1.51. The supersaturation σ is defined as the ratio C/C_{sat}, where C and C_{sat} are the actual glycine concentration and the solubility of γ-glycine respectively. Interestingly, for a given aqueous salt solution, γ-glycine supersaturation σ = 1.51 essentially corresponds to α-glycine supersaturation σ = 1.42. This offers an advantage in analysing and comparing α-glycine growth rates in various solutions at a given α-glycine supersaturation σ = 1.42.

The growing seed crystal was monitored using an optical polarizing microscope (Olympus, BX51, equipped with a CCD camera) at a magnification of 4X, with its images acquired at regular time intervals using Analysis (Soft Imaging Systems) image capture software. The dimensions along a given axis of the acquired images were measured and plotted against time. The slope of the plotted linear graph (R^2 > 0.99) gave the growth rate of the seed crystal. For a given growth experiment, at least three runs were performed to obtain the average growth rate, with a typical standard deviation of 20%. Such a reasonably good reproducibility was achieved given that the seed crystals were carefully prepared and the growth period was properly regulated for a seed crystal to develop to an appreciable extent. More details on the preparation and experiment for growth rate of a single seed crystal can be found elsewhere.[9,12,13]

Results and discussion

Solubility data

Solubilities of α- and γ-glycine in aqueous solutions in the presence of common inorganic salts at 23°C were measured in this study, with a standard deviation of typically 0.05 g/100g H_2O. These solubility data obtained in this work, together with those[12] from our previous study, are tabulated in Table 1. As expected, in a given salt solution, the solubility of the metastable α-glycine is always higher than that of the stable γ-glycine.

It is interesting to note that the solubility of each glycine polymorph increases with addition of each of the salts, indicating that all the salts examined in this study exert a salting-in effect on glycine solubility. The different extents to which various salts increase glycine solubility may be explained based on intermolecular interactions[12] (e.g., salt ion-glycine dipole interaction and salt ion solvation). In particular, the salting-in effects of these three salts, $Ca(NO_3)_2$, $Mg(NO_3)_2$ and $MgSO_4$, are more pronounced, largely due to a significantly stronger interaction[29] between a glycine zwitterion and a divalent salt cation. It should be noted that the highly solvated divalent anion SO_4^{2-} (e.g., from Na_2SO_4 and $(NH_4)_2SO_4$) exert a significantly less salting-in effect on glycine solubility than those divalent cations (e.g., Ca^{2+} and Mg^{2+}), which will be further discussed in next sections. As for the great effect of Na_2CO_3, it may be largely attributed to a

solution pH increase.[9]

Table 1. Solubilities (g/100g H_2O) of α- and γ-glycine in various aqueous salt solutions at 23°C

solution	α-glycine solubility	γ-glycine solubility	Solubility ratio (α:γ)
pure water	24.02	22.63	1.06
1.5m NaCl	26.30	24.8	1.06
1.5m KNO_3	28.23	26.49	1.07
1.5m KCl	25.46	23.99	1.06
1.5m NH_4NO_3	29.63	27.98	1.06
1m Na_2SO_4	27.67	26.17	1.06
1m $(NH_4)_2SO_4$	27.79	26.20	1.06
1m Na_2CO_3	33.63	32.08	1.05
1m $MgSO_4$	31.26	29.58	1.06
1m $Mg(NO_3)_2$	37.78	36.28	1.04
1m $Ca(NO_3)_2$	39.05	37.55	1.04

It should be pointed out that the solubility ratios of α-glycine to γ-glycine are nearly constant (approximately 1.055 ± 0.015) (Table 1), regardless of the salt additives. As discussed in our earlier study,[9] at a given temperature, a solubility ratio is determined by the solid-state activity ratio (a constant) and the activity coefficient ratio of the solutions saturated with α-glycine and γ-glycine respectively. Thus, these comparable solubility ratios indicate that the activity coefficient of a given glycine solution in the presence of a fixed salt additive remains nearly unchanged over a modest range of glycine concentrations (Table 1). However, this does not necessarily means that glycine solutions are ideal. In fact, a previous study[2] has revealed that, due to substantial solvation of glycine molecules, glycine aqueous solutions are significantly non-ideal. It is also reasonable to suggest that the strong salt-glycine interaction tends to cause glycine solutions to exhibit a further deviation from ideal behaviour.

Effect of divalent cation salts on glycine growth and its implication

Since, in the presence of these three divalent cation salts, ($Ca(NO_3)_2$, $Mg(NO_3)_2$ and $MgSO_4$), α-glycine remains to be the dominant polymorph[1] from glycine solution crystallization, one of the suggested postulations is that the crystal growth kinetics helps α-glycine dominate γ-glycine. In order to verify this postulation, the growth rates of α-glycine in the presence of these divalent cation salts were measured in this study so as to compare with the reported growth rates[12] of γ-glycine. The measured average growth rates at the given supersaturation are presented in Figure 3 (along the c-axes) and Figure 4 (along b-axes).

It is evident that all the three divalent cation salts examined exert an inhibiting effect on face growth rates of a glycine seed crystal, regardless of its polymorphic form. On the one hand, all the divalent cation salts considerably retard the growth along the c-axes (Figure 3) of both α-glycine and γ-glycine. On the other hand, the extents to which these divalent cation salts retard the b-axes (Figures 4) largely differ: they only slightly impede the growth of α-glycine b-axis but heavily hinder the growth of γ-glycine b-axis. This salt-mediated relatively severe c-axis growth inhibition is perhaps also well reflected by the observed reductions of the aspect ratio c-axis/b-axis of α-glycine crystals formed from batch crystallization in the presence of divalent cation salts (Figure 5).

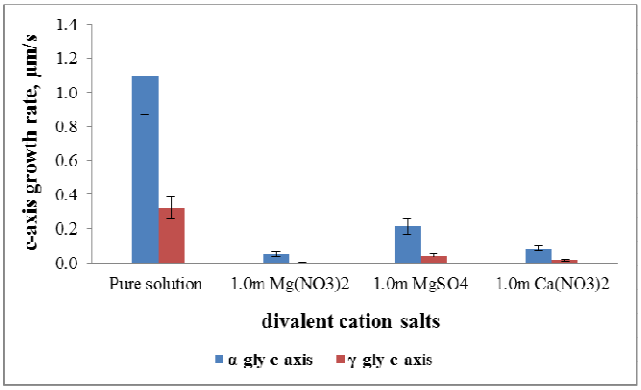


Figure 3. Growth rates of α-glycine and γ-glycine crystals along their c-axes at γ-glycine supersaturation σ = 1.51 at 23°C in the presence of divalent cation salts, showing that these salts considerably inhibits glycine c-axis growth. The error bar = 20%

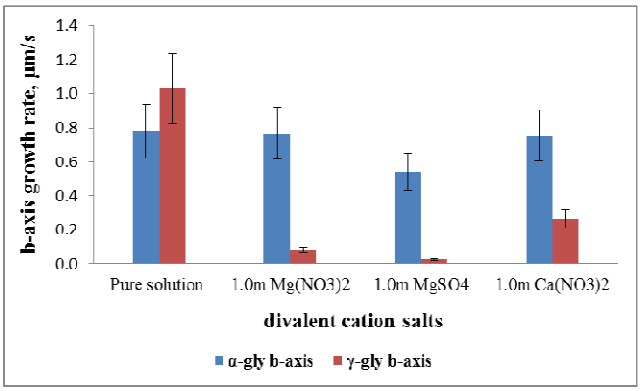


Figure 4. Growth rates of α-glycine and γ-glycine crystals along their b-axes at γ-glycine supersaturation σ = 1.51 at 23°C in the presence of divalent cation salts, showing that γ-glycine b-axis is inhibited far more severely than α-glycine b-axis. The error bar = 20%

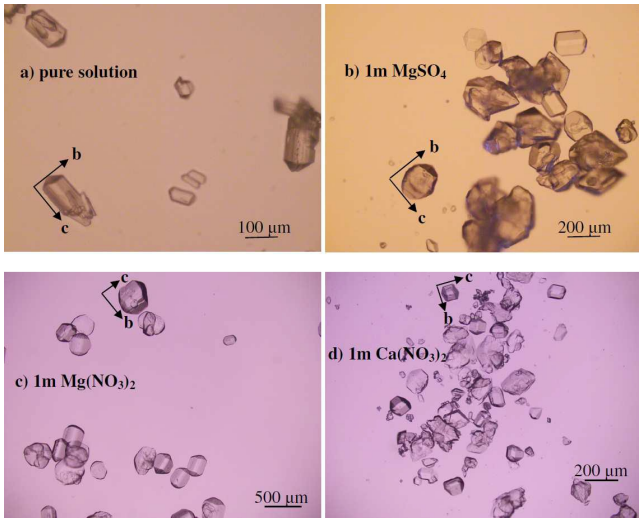


Figure 5. Typical prismatic α-glycine crystals formed from unseeded and unstirred batch crystallization of initial γ-glycine supersaturation σ = 1.51 at 23°C in the presence of divalent cation salts, showing that these salts cause α-glycine aspect ratio c-axis/b-axis to be reduced to a visible extent.

It should be noted that the growth rate along the b-axis of a given glycine polymorph is determined by some of the {hk0} side faces (Figure 2a and 2b). It practically represents the resulting growth rate of all the side faces, as our previous[9,13] and current studies show that all the {hk0} side faces of each of the two polymorphs largely exhibit an isotropic growth behaviour. In other words, for a given glycine seed crystal (either α-glycine or γ-glycine), the growth rates along its b-axis and a-axis are comparable.

Given the great difference of crystal growth rates of these two glycine polymorphs, the prevailing formation of α-glycine in the presence of these three divalent cation salts may be closely connected to the relative growth rates of α-glycine and γ-glycine. In order to provide insights into the salt-directed path of glycine polymorphic nucleation, the composite growth rates[9] were chosen as a reasonable measure of the comparative likelihood of formation of α- and γ-glycine polymorphs from point of view of their relative growth kinetics.[9,14] A composite growth rate of a given glycine seed crystal is defined as the summation of the growth rate along c-axis (Figure 3) and the growth rate along b-axis (Figure 4). For an easy comparison, it is further defined that a relative α-glycine composite growth rate is the ratio of α-glycine composite growth rate to γ-glycine composite growth. Using the c-axis data (Figure 3) and b-axis data (Figure 4), relative α-glycine composite growth rates are computed and presented in Figure 6 in the presence of divalent cation salts, indicating the enhancement of α-glycine growth over γ-glycine growth.

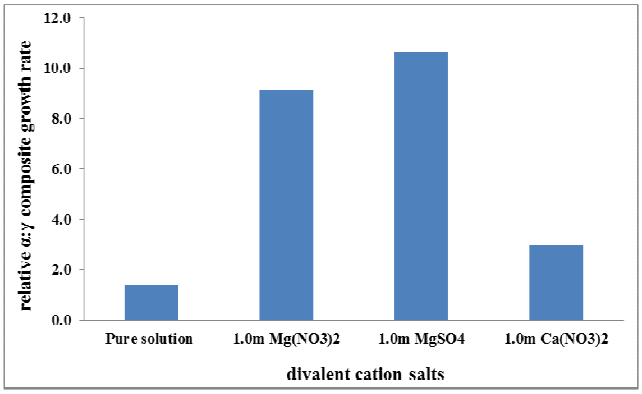


Figure 6. Relative α-glycine composite growth rates at γ-glycine supersaturation σ = 1.51 at 23°C in the absence and in the presence of divalent cation salts, showing that divalent cation inorganic salts favour α-glycine growth to a great extent.

The growth data in Figure 6 clearly shows that the divalent cation salts greatly enhance the relative growth rates of α-glycine. The enhancement factor ranges from 1.4 in pure solution to 3.0 in the presence of 1m $Ca(NO_3)_2$ and even up to 10.0 in the presence of 1m $MgSO_4$ and $Mg(NO_3)_2$. Interestingly, such a high enhancement factor of α-glycine growth in the presence of a divalent cation salt is the consequence of different extents of growth inhibitions exerted by these divalent cation salts, with γ-glycine growth inhibited far more severely than α-glycine growth.

It is reasonable to assume that the relative growth rates of these two mature polymorphic seed crystals largely reflect those of the corresponding initially formed subcritical-sized (unstable) polymorphic nuclei. As such, on a relative basis, it may be postulated that a divalent cation salt perhaps significantly reinforces the development of α-glycine nuclei hence the preferential crystallization of α-glycine. This postulation is consistent with the previous observation[1] that α-glycine remains the dominant polymorph when glycine nucleates from solutions in the presence of these divalent cation salts. It is therefore suggested that the largely salt-altered relative growth kinetics of these two glycine polymorphs plays an important part in favouring α-glycine formation, though other factors should not be ruled out.

In proposing the foregoing pathway to interpret the impacts of the relative growth kinetics on the outcome of polymorphic nucleation, the underlying hypothesis[30,31] is that unstable polymorphic nuclei, coexisting in a supersaturated solution, compete for their survival. In other words, only the nuclei growing faster and hence exceeding the so-called critical size earlier develop into the corresponding mature crystals, while other nuclei of subcritical sizes disintegrate into solution.

Effect of monovalent cation salts on glycine growth and its implication

Similarly, the growth rates along α-glycine c-axis and b-axis in the presence of monovalent cation salts were measured in this study. For comparison, the measured α-glycine growth rates and the reported γ-glycine growth rates[12] are presented

in Figures 7 and 8. It is seen that various monovalent cation salts inhibit the growth rates along the c-axes (Figure 7) of both γ-glycine and α-glycine, though the extent to which the crystal growth is inhibited appears to largely vary with the salts. On the other hand, in general, these salts tend to slightly promote the growth rates along the b-axes (Figure 8) of both polymorphs. The growth inhibition along the intrinsically fast growing γ-glycine c-axis is well reflected by the short prismatic shape[1,10] of γ-glycine crystals (Figure 9b) formed from a batch crystallization of a solution in the presence of a typical monovalent cation salt KNO_3. In contrast, γ-glycine crystals (Figure 9a) formed in the presence of DL-aspartic acid are needle-like, as DL-aspartic acid reduces the barrier[14] and thus accelerates γ-glycine c-axis growth.

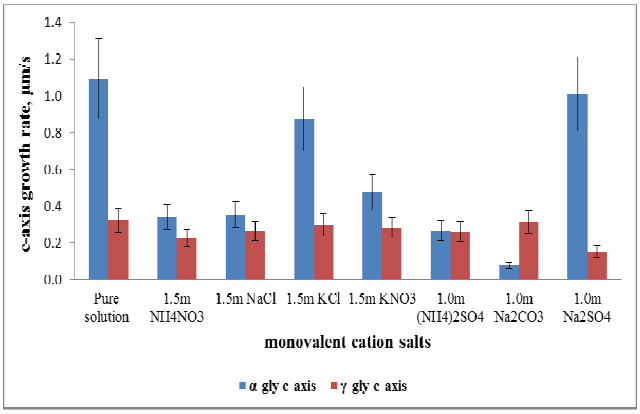


Figure 7. Growth rates of α-glycine and γ-glycine crystals along their c-axes at γ-glycine supersaturation σ = 1.51 at 23°C in the presence of monovalent cation salts, showing that these salts inhibits glycine c-axis growth. The error bar = 20%

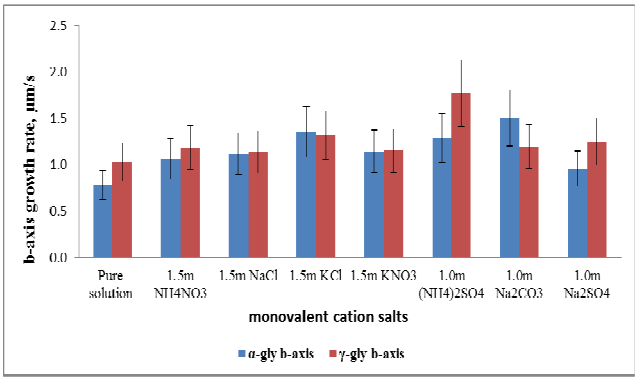


Figure 8. Growth rates of α-glycine and γ-glycine crystals along their b-axes at γ-glycine supersaturation σ = 1.51 at 23°C in the presence of monovalent cation salts, showing that these monovalent cation salts promote glycine b-axis growth but to a small (even insignificant) extent. The error bar = 20%

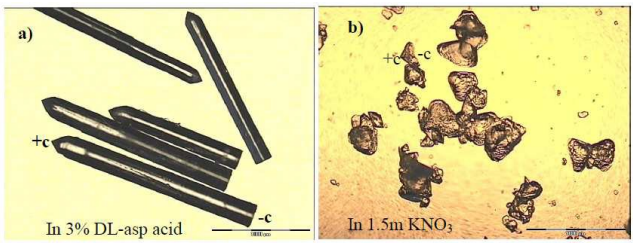


Figure 9. Comparison of needle-like and short prismatic γ-glycine crystals formed from batch crystallization in the presence of a) DL-aspartic acid and b) KNO_3 respectively.

The relative α-glycine composite growth rates in the presence of monovalent cation salts are similarly calculated and presented in Figure 10. From Figure 10, a few interesting observations can be made. In pure solution, α-glycine growth is favoured over γ-glycine growth to a factor of up to 1.4. In the presence of all the monovalent cation salts except for $(NH_4)_2SO_4$ which accelerates γ-glycine growth more than α-glycine growth, α-glycine growth remains faster than γ-glycine. In particular, in the presence of KCl and Na_2SO_4, the relative α-glycine composite growth rate is even as high as that (1.4) in pure solution.

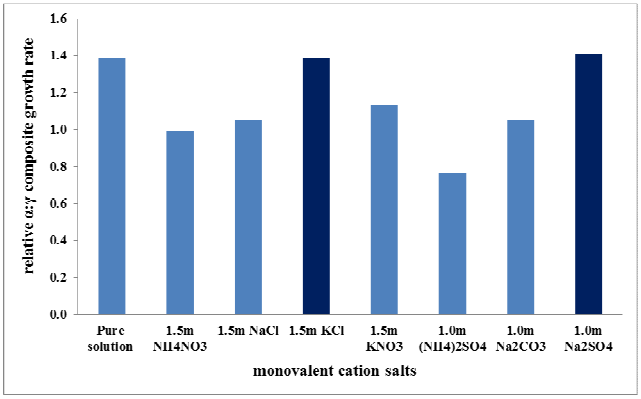


Figure 10. Relative α-glycine composite growth rates at γ-glycine supersaturation σ = 1.51 at 23°C, showing that, in general, monovalent cation inorganic salts still favour α-glycine growth.

From the point of view of growth kinetics, as in pure glycine solution where α-glycine formation is dominant, in the presence of monovalent cation salts especially KCl and Na_2SO_4, α-glycine is also supposed to form more readily than γ-glycine. However, previous experimental observation[1] showed that Na_2SO_4 (as well as other sodium salts) actually induces γ-glycine. In order to verify the influence of another particular salt KCl on polymorphic outcome of glycine crystallization, a similar method[1] was applied to perform an exploratory experiment for glycine nucleation. It was found that KCl (1.5m) effectively induces γ-glycine too. In fact, our further screening experiments showed that, besides KCl, all other examined non-sodium monovalent cation salts (KNO_3, NH_4NO_3 and $(NH_4)_2SO_4$)) at comparable salt concentrations also readily induce γ-glycine, broadening the horizon of the salt-dependent polymorph shift of glycine nucleation.

It is clear that, generally, α-glycine is still kinetically

favoured over γ-glycine in the presence of monovalent cation salts but γ-glycine rather than α-glycine is formed preferentially (even dominantly), indicating that growth kinetics of glycine polymorphs alone does not explain why monovalent cation salts favour the formation of γ-glycine. It is therefore inferred that, in the presence of monovalent cation salts, the salt-induced γ-glycine formation is not primarily governed by the relative growth kinetics of the polymorphs, strongly suggesting that nucleation steps[32,33] (e.g., clustering and ordering of solute molecules) play a great role.

Explanation of mixed effects of salts on glycine growth

The effects of various salts on the growth rates of glycine polymorphs are mixed, both inhibiting and promoting effects of the salts observed. This interesting phenomenon may be explained using the two opposing impacts, surface blocking (which inhibits face growth) and surface roughening[34-36] (which promotes face growth), both arising from the same additive-surface interaction.

All the three divalent cation salts examined in this study exert a great inhibiting effect on glycine growth, with one exception where the inhibiting effect on α-glycine b-axis growth is almost negligible. Such an inhibiting effect may be expected, since the coulombic interaction between the salt ions (especially the divalent ions) and the associated polar faces of glycine can be significant.

As pointed out earlier, the faces at the c ends of α-glycine[37] and γ-glycine[1] c-axes are highly polar because the polar COO^- and NH_3^+ groups are greatly exposed at these faces. The dissociated salt ions in solution strongly adsorb onto these polar faces of glycine seed crystals. The adsorption of the salt ions at these polar c ends is likely to be stronger than that of polar solvent water molecules due to greater coulombic interaction between charged salt ion (especially divalent ion) and the polar faces. As a result, the salt ions adsorbed on the polar faces are more difficult to be removed than the adsorbed solvent water molecules, blocking the active sites[38] and thus preventing glycine molecules from attaching onto the faces at the c ends. In other words, the significant surface blocking arising from the strong salt adsorption tends to retard the face growth[13,14] along the c-axis of a glycine seed crystal, despite the adsorption-caused surface roughening[34-36] which favours the face growth.

A similar analysis may be applied to explain the different extents of growth inhibition of glycine b-axes (Figures 4 and 8) in the presence of divalent cation salts. As discussed earlier, the growth along the b-axis of a given glycine polymorph is determined by the growth of the {hk0} side faces[9] (Figure 2a and 2b). In general, these side faces are far less hydrophilic than the corresponding faces at the polar c-ends where polar COO^- and/or NH_3^+ groups are largely exposed. In particular, the hydrophilicity of α-glycine {hk0} side faces seems appreciably low[8,37] due to the significant exposure of the hydrophobic H-C segments at these faces. Such a low hydrophilicity would greatly mitigate the coulombic interaction between ions (especially divalent ions) and α-glycine {hk0} side faces, therefore only causing a slight (even negligible) growth inhibition along α-glycine b-axis.

Different from the slight growth inhibition of α-glycine b-axis, the growth rate along γ-glycine b-axis is largely hindered by divalent cation salts, suggesting that the side faces of γ-glycine are significantly blocked by the salt ions. A simple examination of the structures of the {hk0} side faces of these two glycine polymorphs hardly reveals a visible difference in local polarities on the side faces. Nevertheless, it may be reasonable to suggest that, compared with α-glycine side faces, γ-glycine side faces exhibit local polarities which are great enough to attract divalent salt ions to an appreciable extent, thereby leading to significant growth inhibition along γ-glycine b-axis. This postulation has yet to be verified by probing interaction energies between salt ions and the delicate crystal faces using advanced computational tools (e.g., molecular dynamics simulations[39]).

Compared with the relatively strong adsorption of the divalent cation salts at the faces of glycine seed crystals, weak adsorption of monovalent cation salts is expected, leading to a lower extent of surface blocking, given that the monovalent cations have fewer charges. Supporting this, an earlier computational study[29] revealed that, in solution, monovalent cation-glycine interaction is significantly (even far) weaker than divalent cation-glycine interaction. In addition, the same adsorbed salt ions cause surface roughening,[34-36] mitigating and even overriding surface blocking. Overall, monovalent cation salts still generally inhibit the c-axes of glycine seed crystals but less severely than divalent cation salts; they promote the growth of glycine {hk0} side faces hence the growth of the b-axes, an outcome of the competition where surface roughening overrides surface blocking. Additive-aided growth acceleration of other crystals[36,40] was also reported.

It is interesting to note that the impact of divalent anions, SO_4^{2-} and CO_3^{2-}, seems significantly less pronounced than that of divalent cations Ca^{2+} and Mg^{2+} despite the same magnitude of the ionic charges. This is because an anion SO_4^{2-} is heavily hydrated with twelve water molecules in the first solvation shell[41] while a Ca^{2+} and a Mg^{2+} cation are surrounded by only eight and six water molecules[42] respectively. As a result, the impact of SO_4^{2-} is significantly weakened by these water molecules in the first solvation shell. As for CO_3^{2-}, it is active to react with water to produce OH^- and HCO_3^-, which is well supported by a significant increase of glycine solution pH from 6.2 of pure glycine solution up to 8.9 in the presence of 1m Na_2CO_3. (As a comparison, other associated salts only cause the glycine solution pH to change by ±0.5 unit). As such, a divalent anion CO_3^{2-} largely acts as a monovalent anion HCO_3^-. These analyses may explain the observation that the two sulphate salts (Na_2SO_4 and $(NH_4)_2SO_4$) and the one carbonate salt (Na_2CO_3) largely differ from divalent cation salts in their effects on the growth of glycine c-axes (Figures 3 and 7) and b-axes (Figures 4 and 8).

The above analyses of the salt ion-crystal face coulombic interaction seem consistent with the observations of the salting-in effects of salts on glycine solubility (Table 1). As observed, divalent cations (those from $Ca(NO_3)_2$, $Mg(NO_3)_2$ and $MgSO_4$) tend to exert more pronounced salting-in effects than monovalent cations, while the well-solvated divalent

SO_4^{2-} anions (e.g., those from Na_2SO_4 and $(NH_4)_2SO_4$) have weaker salting-in effects than those divalent cations.

It should be highlighted that the interaction between salt ion and glycine crystal surface is a complicated phenomenon as it is governed by many factors including the charges, size, shape and hydration of salt ions as well as the salt cation-anion self-interaction. As such, it should be cautious about a generalization that the charges of salt cations dominantly determine the ion-surface interaction at a given crystal face, despite the fact that both the divalent cations Ca^{2+} and Mg^{2+} examined here seemingly interact with glycine polar surfaces more strongly than the monovalent cations. For a higher level of analysis of salt ion-crystal surface interactions, a combination of various advanced computational methods[29,39] may be required.

Conclusions

Mechanisms of salt-dependent polymorphic outcome of glycine crystallization have been experimentally explored via measurements of the growth rates of α-glycine and γ-glycine in the presence of typical inorganic salts.

It is found that, on the relative basis of the growth rates of these two glycine polymorphs, the divalent cation salts examined here further reinforce the preferential formation of α-glycine to a significant extent. More interestingly, such a reinforcement of α-glycine formation is the consequence of more severe growth inhibition of γ-glycine than α-glycine in the presence of divalent cation salts. It is also observed that monovalent cation inorganic salts do not significantly alter the relative growth rates of these two glycine polymorphs but they do cause the polymorphic selectivity to shift from metastable α-glycine to stable γ-glycine.

Perusal of these interesting findings points toward a conclusion that both the growth kinetics and nucleation steps play important roles in directing the path of polymorphic nucleation, shedding lights on elucidating the mechanisms which govern the salt-dependent outcome of glycine polymorphic crystallization. It is therefore worth exploring the nucleation phenomena so as to eventually resolve the riddle of why inorganic salts differ in shifting polymorphic selectivity from metastable α-glycine to stable γ-glycine.

The observed inhibiting and promoting effects of inorganic salts on glycine face growth rates are explained on the basis of two opposing phenomena, surface roughening and surface blocking. The competition between these two phenomena determines whether a salt promotes or inhibits the face growth of a glycine crystal.

Acknowledgments

We are grateful to the Agency for Science, Technology and Research (A*STAR), Singapore, for financial support.

Notes and references

[a]*Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore 627833 Fax: 65 63166183; Tel: 65 67963841 ; E-mail: reginald_tan@ices.a-star.edu.sg; han_guangjun@ices.a-star.edu.sg*

[b]*Department of Chemical and Biomolecular Engineering, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260*

1. C. S. Towler, R. J. Davey , R. W. Lancaster, C. J. Price, J. Am. Chem. Soc., 2004, **126**, 13347–13353.
2. J. Huang, T. C. Stringfellow, L. Yu, J. Am. Chem. Soc., 2008, **130**, 13973–13980.
3. C. E. Hughes, K. D. M. Harris, Chem. Commun., 2010, **46**, 4982–4984.
4. G. Han, S. Thirunahari, P. S. Chow, R. B. H. Tan, CrystEngComm **2013**, 15, 1218–1224.
5. L. Dang, H. Yang, S. Black, H. Wei, Org. Process Res. Dev., 2009, **13**, 1301–1306.
6. B. D. Hamilton, I. Weissbuch, M. Lahav, M. A. Hillmyer, M. D. Ward, J. Am. Chem. Soc., 2009**, 131**, 2588–2596.
7. P. W. Carter, A. C. Hillier, M. D. Ward, J. Am. Chem. Soc., 1994, **116**, 944–953
8. D. Gidalevitz, R. Feidenhans, S. Matlis, D. M. Smilgies, M. J. Christensen, L. Leiserowitz, Angew. Chem. Int. Ed., 1997, **36**, 955–959.
9. G. Han, P. S. Chow, R. B. H. Tan, Cryst. Growth Des., 2012, **12**, 2212–2220.
10. X. Yang, J. Lu, X. J. Wang, C. B. Ching, J. Cryst. Growth 2008, **310**, 604–611.
11. N. Duff, Y. R. Dahal, J. D. Schmit, B. Peters, J. Chem. Phys. 2014, **140**, 014501.
12. G. Han, P. S. Chow, R. B. H. Tan, Cryst. Growth Des. 2015, **15**, 1082–1088.
13. G. Han, S. K. Poornachary, P. S. Chow, R. B. H. Tan, Cryst. Growth Des., 2010, **10**, 4883–4889.
14. R. Dowling, R. J. Davey, R. Curtis, G. Han, S. K. Poornachary, P. S. Chow, R. B. H. Tan, Chem. Commun., 2010, **46**, 5924–5926.
15. S. Hamad, C. R. A. Catlow, CrystEngComm 2011, **13**, 4391–4399.
16. M. Xu, K. D. M. Harris, J. Phys. Chem. B 2007, **111**, 8705–8707.
17. J. E. Aber, S. Arnold, B. A. Garetz, A. S. Myerson, Phys. Rev. Lett., 2005, **94**, 145503.
18. G. He, V. Bhamidi, S. R. Wilson, R. B. H. Tan, P. J. A. Kenis, C. F. Zukoski, Cryst. Growth Des. 2006, **6**, 1746–1749.
19. G. D. Profio, S. Tucci, E. Curcio, E. Drioli, Cryst. Growth Des. 2007, **7**, 526–530.
20. I. S. Lee, K. T. Kim, A. Y. Lee, A.S. Myerson, Cryst. Growth Des., 2008, **8**, 108–113.
21. J. W. Chew, S. N. Black, P. S. Chow, R. B. H. Tan and K. J. Carpenter, CrystEngComm, 2007, **9**, 128–130.
22. S. K. Poornachary, P. S. Chow, R. B. H. Tan, Cryst. Growth Des. 2008, **8**, 179–185.
23. J. Chen, B. L. Trout, J. Phys. Chem. B, 2010, **114**, 13764–13772.
24. I. Weissbuch, V. Y. Torbeev, L. Leiserowitz, M. Lahav, Angew. Chem. Int. Ed., 2005, **44**, 3226–3229.
25. P. Friant-Michel, M. F. Ruiz-Lopez, ChemPhysChem, 2010, **11**, 3499–3504.
26. S. Hamad, C. E. Hughes, C. R. A. Catlow, K. D. M Harris, J. Phys. Chem. B, 2008, **112**, 7280–7288.
27. Y. Yin, P. S. Chow, R. B. H. Tan, Cryst. Growth Des. 2012, **12**, 4771–4778.
28. G. Han, R. B. H. Tan, Chem. Eng. Sci. 2009, **64**, 3983–3995.
29. M. V. Fedotova, S. E. Kruchinin. Biophy. Chem. 2014, **190–191**, 25–31.
30. M. C. Etter, J. Phys. Chem. 1991, **95**, 4601–4610.
31. I. Weissbuch, L. Leisorowitz, M. Lahav, Adv. Mater., 1994, **6**, 952–956.
32. D. Erdemir, A. Y. Lee, A. S. Myerson, Acc. Chem. Res., 2009, **42**, 621–629.
33. R. J. Davey, K. R. Back, R. A. Sullivan, Faraday Discuss., 2015, **179**, 9–26.
34. J. R. Bourne, R. J. Davey, J. Cryst. Growth 1976, **36**, 278–286.
35. L. J. W. Shimon, M. Addadi, L. Vaida, M. Lahav, L. Leiserowitz, J. Am. Chem. Soc. 1990, **112**, 6215–6220.
36. G. Han, P. S. Chow, R. B. H. Tan, Cryst. Growth Des. 2012, **12**, 5555–5560.
37. L. Li, N. Rodriguez-Hornedo, J. Cryst. Growth, 1992, **121**, 33–38.

38. N. Kubota, Cryst. Res. Technol. 2001, **36**, 749–769.
39. C. Stoica, P. Verwer, H. Meekes, P. J. C. M. van Hoof, F. M. Kaspersen, E., Vlieg, Cryst. Growth Des. 2004, **4**, 765−768.
40. A. Baynton, B. D. Chandler, F. Jones, G. Nealon, M. I. Ogden, T. Radomirovic, G. K. H. Shimizub, J. M. Taylorb, CrystEngComm, 2011, **13**, 1090–1095.
41. X. B. Wang, X. Yang, J. B. Nicholas, L. S. Wang, Science 2001, **294**, 1322−1325.
42. D. Jiao, C. King, A. Grossfield, A. Thomas, T. A. Darden, P. Ren, J. Phys. Chem. B 2006, **110**, 18553–18559.

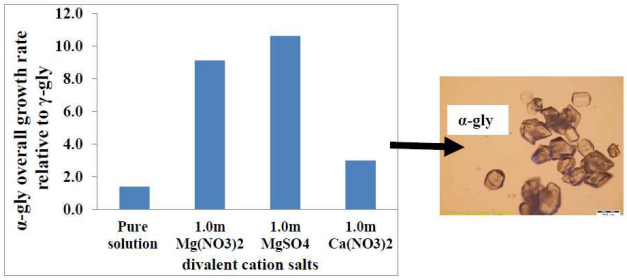
ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Salt-Dependent Growth Kinetics in Glycine Polymorphic Crystallization

Guangjun Han[a,*], Pui Shan Chow[a] and Reginald B. H. Tan[a,b,*]

[a]*Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore 627833 Fax: 65 63166183; Tel: 65 67963841 ; E-mail: reginald_tan@ices.a-star.edu.sg; han_guangjun@ices.a-star.edu.sg*
[b]*Department of Chemical and Biomolecular Engineering, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260*

Graphical Abstract



Divalent cation salts inhibit the growth of α-glycine far less severely than that of γ-glycine, causing α-glycine to have a greater competitive advantage over γ-glycine and thereby further reinforcing the preferential formation of α-glycine on a relative basis.