Solubility of Form α and Form γ of Glycine in Aqueous Solutions

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The solubilities of two polymorphs of glycine (α-form and γ-form) in different aqueous solvent mixtures were measured by using the analytical gravimetric method. Based on the measured solubility data in pure water, the relative stability and the enthalpy and entropy of dissolution of the two forms were determined using van't Hoff plots. The solubilities of forms α and γ were also investigated in aqueous solutions containing methanol or polyethylene glycol (PEG200) at 20 °C. It was shown that the solubilities of both forms decreased with increasing concentration of methanol and PEG200. The pH dependence of solubility of the γ-form was measured in the pH range of (0.35 to 13.7) at temperatures of (20 and 25) °C. The solubility profiles show a U-shape with pronounced changes at pH below 3.0 or above 10.0.

Introduction

The study on physical and chemical properties of biochemicals is very important in chemical, pharmaceutical, and food industries. Amino acids are often chosen as model compounds to understand the nature and behavior of more complex biomolecules such as proteins, nucleic acids, and peptides.[1,2]

It is well-known that most amino acids exhibit polymorphism in the solid state. Polymorphs differ in their physicochemical properties, including crystal morphology, hygroscopicity, color, melting point, solubility, and dissolution rates, which affect the product effectiveness. Therefore, polymorphism is a crucial issue in the development of the separation and purification process of amino acids by crystallization. The solubility data of different polymorphs of an amino acid are indispensable to crystallization from solution. The knowledge of solubility of different polymorphs not only is a matter of theoretical interest but also allows one to carry out polymorphic crystallization in a more rational manner than happens at random.

In the past decades, considerable efforts have been devoted to the investigation of phase behavior and molar properties of amino acids in aqueous electrolyte[3–8] or nonelectrolyte[9–12] solutions. It has been recognized that the presence of an alkanol or an electrolyte in amino acid solutions greatly affects their solubility,[13,14] activity coefficient,[15,16] density,[17] and enthalpy of the solutions.[18–20] A variety of thermodynamic models have been utilized to describe physical and chemical properties of amino acids in various aqueous media.[21–24] These investigations have given considerable quantitative predictions of solubility of amino acids with emphasis on both theoretical understanding of the behavior of amino acids in different solvents and experimental design of optimal separation and purification processes. However, these predictions ultimately depend on the detailed experimental solubility data. Also, the thermodynamic properties of amino acids in electrolyte and nonelectrolyte aqueous systems are much less well understood due to the complexity of amino acid−solvent interactions.

In this work, the detailed solubility of glycine in water and in aqueous solutions with various pH values and concentrations of methanol or PEG200 was determined using the isothermal analytical gravimetric method. Compared with the previous work mentioned above, the present study took into account more comprehensive experimental measurements of different polymorphs (α- and γ-forms) of glycine in aqueous solutions. The two pure forms were prepared and identified using powder X-ray diffraction patterns and solid state FTIR spectra. Utilizing the van't Hoff relationship, the enthalpy and entropy of dissolution of the two forms in pure water were estimated based on regression of the solubility data. These results will be helpful to establish the strategy for rational design of separation and purification processes of glycine by crystallization.

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Experimental Section

Material. Glycine (99 mass %) and sodium chloride (99.5 mass %) were purchased from Sigma-Aldrich (Singapore). Methanol (> 99.8 mol %), PEG200 (> 99.8 mol %), hydrochloric acid (37 %), and sodium hydroxide (99 mass %) were obtained from Merck and used to prepare the buffer solutions. The ultrapure deionized water was obtained through a Millipore ultrapure water system (Milli-Q Gradient A10 System).

Preparation of α- and γ-Forms of Glycine Crystals. The α-form of glycine was recrystallized from aqueous solution. The γ-form crystals were obtained by melting the quench-cooled glycine−NaCl solution. A saturated glycine solution was prepared at 60 °C in the presence of NaCl. The resulting solution was filtered and then quench-cooled in a refrigerator at −18 °C. Once the sample was frozen, it was allowed to anneal at room temperature. Then the slurry was filtered, and the solids were dried in a vacuum oven at 60 °C for 12 h.

Characterization of Glycine Crystals. Powder XRD patterns of glycine crystals were determined at room temperature using a Bruker D8 Advance diffractometer with Cu Kα radiation at 40 mA, 40 kV. The characteristic peaks (Figure 1) at 19.5° and 25.3° (2θ) corresponding to form α and form γ, respectively, were chosen to identify the two polymorphs, as previously reported.[25]

FTIR spectra were obtained with a Digilab FTS-3100 FTIR spectrometer by using KBr in a palletized form. The scans were performed with a resolution of 4 cm^{-1}. All spectra were collected at ambient temperature in the range of wavenumber

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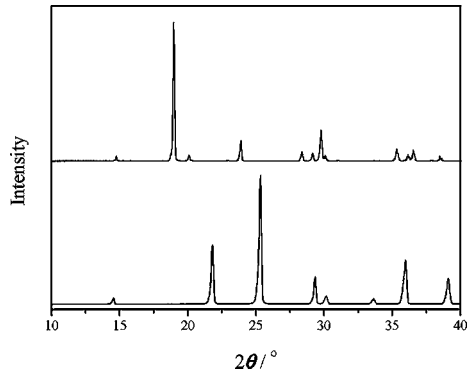

Figure 1. PXRD patterns of the α-form (upper curve) and γ-form (lower curve) of glycine crystals.

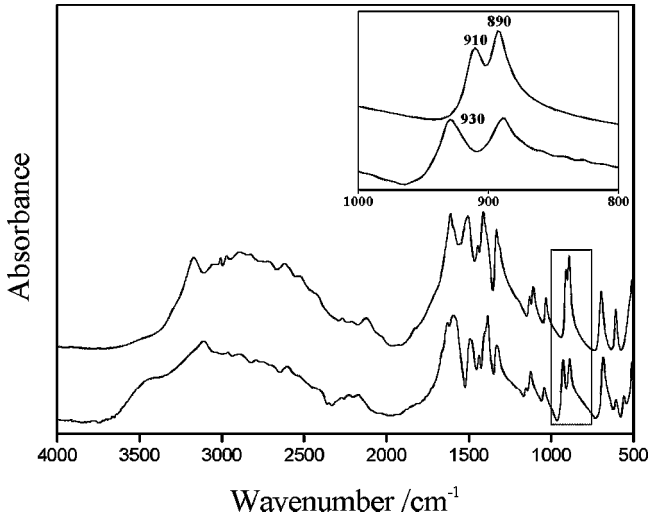

Figure 2. FTIR spectra of the α-form (upper curve) and γ-form (lower curve) of glycine crystals.

from (500 to 4000) cm^{-1}. IR spectra of the forms α and γ are shown in Figure 2. The characteristic peaks at 910 cm^{-1} for the α-form and 930 cm^{-1} for the γ-form and a common peak at 890 cm^{-1} for both forms (highlighted by a dashed rectangle) were selected for the identification.

Solubility Measurements. The solubilities were measured by a gravimetric method. The experiments were carried out in 50 mL jacketed crystallizers equipped with a magnetic stirrer bar. The temperature was controlled by circulating water from a Julabo programmable circulator FP50-ME.

For each measurement, a certain amount of solvent or solvent mixtures was added into the crystallizer and stabilized at a measured temperature. An excess amount of α-form or γ-form crystals was then added into the prepared stirred solvent. The solution was kept stirring at least 10 h to establish equilibrium at the constant temperature. Equilibrium between solids and solution was determined by measuring the variation in solution concentration. Then the equilibrium suspension was settled down ca. 4 h, and aliquots of 5 mL were withdrawn by using a syringe and filtered through a 0.2 μm PTFE filter (Whatman). The filtered clear solution was placed into a glass Petri dish (100 × 15 mm, previously weighed) and weighed. Then the solution was completely dried in a drying oven at 60 °C for ca. three days. The solubility was calculated by determining the weight of dried solid and evaporated solvent. The pH values of the solutions were adjusted by adding HCl or NaOH buffer and measured by a Mettler Toledo 320 digital pH meter. The mass of additives in the solution was taken into account in calculating the solubility. Considering the solution-mediated transformation between the two forms, the polymorph of solids after each measurement was checked and analyzed by XRD. The mass of glycine solid was measured by using a precise balance (Metller Toledo, AB203-S) with a resolution of ± 0.1 mg. The temperature was controlled by a Julabo programmable circulator FP-50 ME with a precision of ± 0.1 °C. All experiments were repeated at least five times. The estimated accuracy of the solubility values based on error analysis and repeated observations was within 2.0 % for each measurement.

Table 1. Solubility of the α-Form and γ-Form in Water

α-form		γ-form	
this work		this work	
T/°C	*S*/(g·kg^{-1} of water)	*T*/°C	*S*/(g·kg^{-1} of water)
5.0	141.1 ± 1.8	5.0	127.2 ± 1.1
12.5	166.7 ± 1.5	14.0	154.8 ± 0.6
20.0	198.9 ± 0.7	20.0	177.0 ± 1.0
25.0	226.8 ± 1.5	25.0	202.1 ± 0.9
28.5	241.7 ± 0.2	30.0	225.6 ± 0.5
33.0	259.6 ± 0.5	37.0	260.7 ± 0.6
36.0	283.1 ± 1.2	42.0	286.1 ± 0.8
46.0	334.5 ± 1.1	50.0	336.2 ± 1.3
50.0	354.2 ± 1.2	57.0	375.6 ± 1.9
55.0	384.8 ± 1.5	61.0	399.5 ± 1.6

Results and Discussion

Solubility of α- and γ-Forms of Glycine in Water. According to our previous work,[26] the polymorphic transformation of the α-form to the γ-form in water took more than 20 h. Therefore, the solid−liquid equilibrium could be well attained before polymorphic transformation. Table 1 lists the solubility of the two polymorphs of glycine in water at different temperatures along with their standard deviation (numbers after the ± signs). It can be seen that the solubility of both forms increases with temperature, and the α-form has a higher solubility than the γ-form over the entire studied temperature range of (5 to 60) °C, which indicates that the γ-form is the thermodynamically stable form and the α-form is the metastable form at ambient temperature.

The solubilities of the α-form in water at different temperatures are also plotted in Figure 3. For comparison, the corresponding solubility data of the previous work[6–8,27] are also shown in the same Figure 3. It can be seen that the solubility values of this work are close to those reported by Ramasami[6] and Ferreira et al.[7,8] However, there is an obvious discrepancy

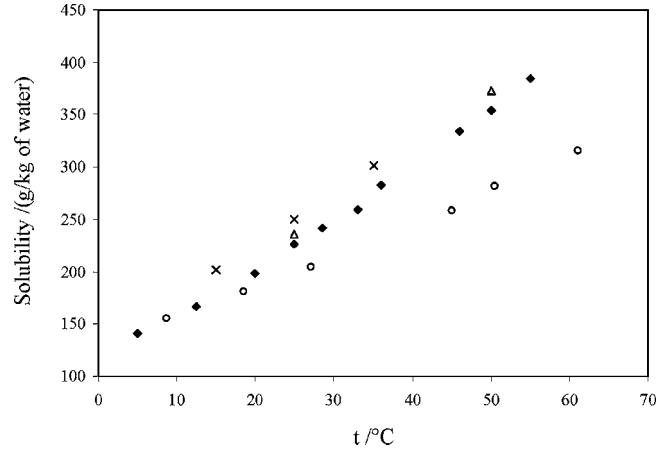

Figure 3. Comparison of solubility data for the α-form in water: ♦, this work; ×, Ramasami; Δ, Ferreira et al.; ○, Park et al.

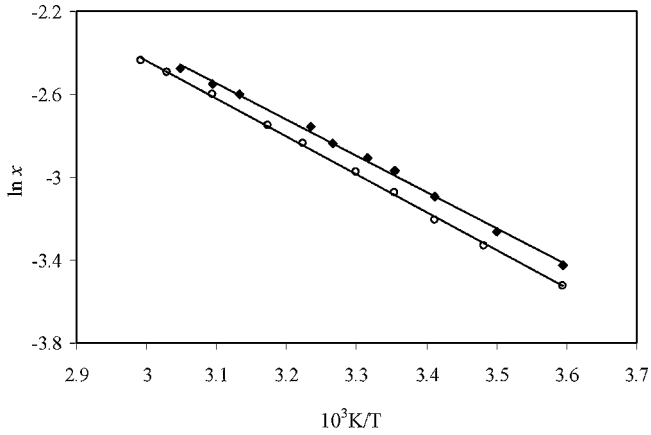

Figure 4. van't Hoff plot of logarithm mole fraction solubility of the ♦, α-form and ○, γ-form in water.

with those of Park and co-workers,[27] measured with differential scanning calorimetery (DSC), at the relatively high temperature range. A similar discrepancy was also observed in the comparison of γ-form solubility. In the DSC solubility measurement, the heat flow due to the dissolution of a given amount of solute is recorded as a function of temperature. The saturated temperature is determined with the help of the intersection point of two tangents drawn on the DSC curve. Prior to the solubility measurement, a pretreatment including dissolution and recrystallization cycles is usually applied for identification of the appropriate temperature range as well as sample homogenization. For some polymorphic systems, conversion from one polymorph to another could occur in the pretreatment step especially at high temperatures, thus leading to unreliable solubility data. On the other hand, the sensitivity of the heat flow signal with the dissolution could be dramatically affected by various parameters, such as the amount of solute, solvent, the heat of solution, heating rate, mixing, and dissolution rate of a solute, etc.[28] In our work, the solubility was determined by the classical gravimetric method. The mixture had been stirred long enough to establish equilibrium between crystals and solution. This method is highly reliable for solubility measurement due to the precise temperature and weight measurements. To minimize the human error, the measurements were repeated at least five times. The maximal error of the solubility data was estimated to be less than 2.0 % by means of repeatability measurements.

Enthalpy and Entropy of Dissolution of α- and γ-Forms of Glycine in Water. The van't Hoff equation relates the logarithm of mole fraction of a solute in an ideal solution as a linear function of the reciprocal of the absolute temperature

$$\ln x = -\left(\frac{\Delta_{diss}H}{RT}\right) + \left(\frac{\Delta_{diss}S}{R}\right) \quad (1)$$

where x is the mole fraction of solute in the solvent; $\Delta_{diss}H$ and $\Delta_{diss}S$ are the enthalpy and the entropy of dissolution; T is the corresponding absolute temperature; and R is the universal gas constant. By linear least-squares fitting of the van't Hoff equation to the experimentally obtained solubility data, the enthalpy and entropy of dissolution can be obtained from the slope of the solubility curve and the intercept with the y axis, respectively. The values of $\Delta_{diss}H$ can be regarded as a reflection of the nature of intermolecular interactions. Figure 4 shows the van't Hoff plot of the logarithm of mole fraction solubility of the two forms versus reciprocal absolute temperature, and the

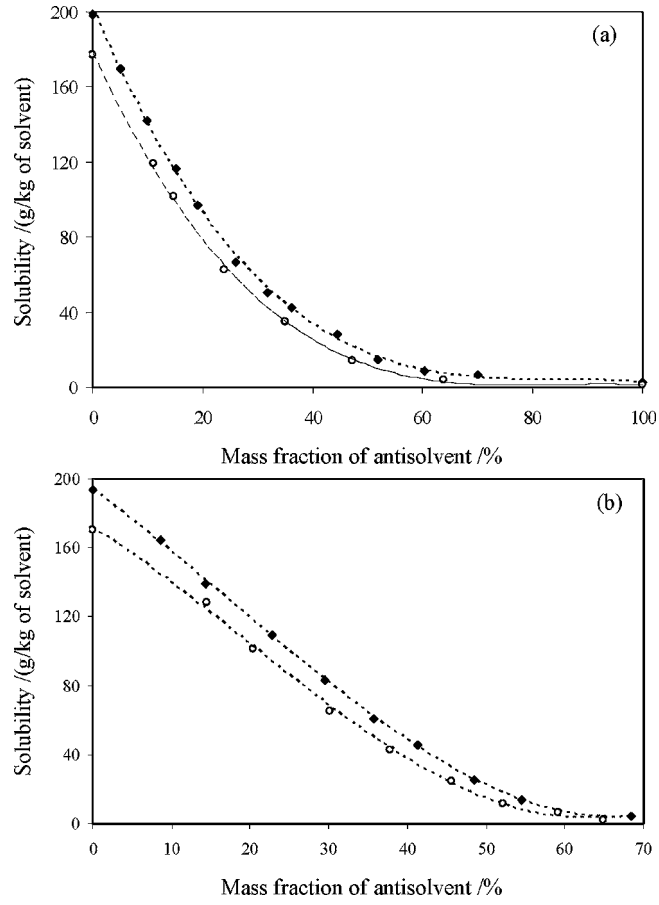

Figure 5. Solubility of ♦, α-form and ○, γ-form of glycine in (a) methanol + water and (b) PEG200 + water solutions at 20 °C; ---, calculated from eq 2.

dissolution enthalpies of the α-form and γ-form are therefore calculated to be [(14.50 ± 1.1) and (15.22 ± 0.9)] kJ·mol^{-1}, respectively. The dissolution entropies of the α-form and γ-form are determined to be [(23.77 ± 0.6) and (25.38 ± 0.2)] J·mol^{-1}·K^{-1}, respectively.

Solubility of α- and γ-Forms Glycine in the Mixture of Methanol and Water As Well As in the Mixture of PEG200 and Water. Organic solvents have been widely used as antisolvents to precipitate and crystallize amino acids from aqueous solutions. In this work, methanol and PEG200 were chosen as antisolvents for glycine crystallization from water. As mentioned in the Experimental Section, similarly, the equilibrium of solid−liquid in these solvent mixtures could be well obtained before polymorphic transformation. The solubilities of the α- and γ-forms of glycine in the mixtures of water with methanol and PEG200 as a function of antisolvent composition at 20 °C are presented in Figure 5 and also listed in Table 2. It can be seen that the solubilities of both forms significantly decreased with increasing concentration of methanol or PEG200. Generally, hydrophilic amino acids (e.g., glycine and DL-serine) have poor solubility in alcohol or other organic solvents. It has been recognized that two major forces, electrostatic and hydrophobic interactions, may usually affect the solubility behavior of amino acids.[29] With an increase in the alcohol composition, the hydrophobic interactions between glycine and alcohol could be promoted, which leads to decreased solubility of glycine. Even though the increased electrostatic repulsion among glycine molecules could also contribute to solubility, it is offset by the promoted hydrophobicity of glycine molecules and therefore results in a decrease of the solubility.

Table 2. Solubility of α-Form and γ-Form in Aqueous Methanol (1) or PEG200 (2) at 20 °C

α-form				γ-form			
methanol		PEG200		methanol		PEG200	
w_1/%	S/(g·kg^{-1} of solvent)	w_2/%	S/(g·kg^{-1} of solvent)	w_1/%	S/(g·kg^{-1} of solvent)	w_2/%	S/(g·kg^{-1} of solvent)
0	198.9 ± 0.7	0	198.9 ± 0.7	0	177.0 ± 1.0	0	177.0 ± 1.0
5.0	169.9 ± 0.3	8.58	164.8 ± 0.9	11.0	119.5 ± 0.4	14.5	128.6 ± 1.3
10.0	142.1 ± 0.6	14.4	139.5 ± 0.5	14.7	102.0 ± 0.6	20.5	101.8 ± 1.4
15.2	116.2 ± 1.1	22.9	109.9 ± 1.1	23.9	62.76 ± 1.1	30.1	65.75 ± 1.7
19.1	96.9 ± 1.2	29.6	83.47 ± 0.8	35.0	34.93 ± 1.6	37.7	43.42 ± 1.6
26.1	66.50 ± 0.9	35.8	61.52 ± 1.3	47.2	14.46 ± 1.4	45.6	25.16 ± 1.6
31.7	50.57 ± 1.4	41.3	46.04 ± 1.7	63.8	4.02 ± 1.9	52.2	11.62 ± 1.5
36.2	42.55 ± 1.3	48.4	25.45 ± 1.8	100	1.1 ± 1.8	59.2	6.62 ± 1.7
44.4	28.02 ± 0.8	54.6	13.86 ± 1.8			64.9	2.35 ± 1.9
51.9	14.79 ± 1.1	68.4	4.33 ± 1.6				
60.4	8.82 ± 1.3						
70.0	6.61 ± 1.5						
100	2.4 ± 1.7						

Table 3. Parameters of the Model Equation2

	α-form		γ-form	
	methanol	PEG200	methanol	PEG200
$A\cdot10^{-2}$	2.02	1.98	1.79	1.78
B	−6.95	−3.80	−6.39	−3.40
$C\cdot10^{2}$	8.17	−1.64	7.60	−2.43
$D\cdot10^{4}$	−3.21	4.44	−2.99	5.46
rmsd	0.0153	0.0049	0.0196	0.0076

For practical application, the experimental solubility data of glycine and solvent compositions are correlated as the following polynomial equation

$$S_c = A + Bw + Cw^2 + Dw^3 \quad (2)$$

where S_c is the solubility (g of solute/kg of solvent) of glycine; w refers to the initial mass fraction of the antisolvent in the total solvent (i.e., water + methanol); and A, B, C, and D denote the regression curve coefficients. The regression curve coefficients and the root-mean square deviations (rmsd) defined by eq 3 are listed in Table 3.

$$\sigma = \left[\sum_{i=1}^{n} \frac{(S_c - S_i)^2}{n-1}\right]^{1/2} \quad (3)$$

where S_c stands for the calculated values by eq 2 and n is the number of experimental points.

Effect of pH Values on the Solubility of the γ-Form of Glycine. Generally, amino acids appear in three ionic forms (cationic, zwitterions, and anionic) according to different pH values of the solution. At the isoelectric point, the amino acids exist in the form of zwitterions ($NH_3^+-R-COO^-$), which is the most stable at the isoelectric point (pI) value. As the pH is varied, the relative concentration of the charged amino acid molecules rises. This results in an increase in solubility with increasing or decreasing pH values. Due to the relatively fast solution-mediated transformation of the metastable form α to the stable form γ in the presence of electrolytes, it is difficult to measure the reliable solubility of the α-form over the entire pH value range. The solubilities of the γ-form in water as a function of pH value at temperatures of (20 and 25) °C are listed in Table 4. Carta and Tola[3] also reported solubility of glycine at different pH using the gravimetric method. However, they did not mention the polymorphic form. In the literature, the solubility data were expressed as mol·dm^{-3}. To be convenient for further comparison, our solubility unit has been converted to mg·mL^{-1} by assuming a constant water density of 0.997 g·mL^{-1} at the selected temperatures. The solubility data are depicted as a function of pH values in Figure 6. At temperatures

Table 4. Solubility of Form γ at Various pH Values and Temperatures

S/(g·kg^{-1} of water)			
pH	20 °C	pH	25 °C
0.35	302.7	0.35	319.0
1.04	221.6	1.04	246.9
2.11	203.8	2.11	229.1
2.78	187.0	3.11	213.4
4.50	181.7	4.42	208.7
5.50	178.1	6.04	201.4
7.40	177.0	7.40	202.1
8.50	184.3	8.89	203.5
9.90	190.5	10.73	211.8
10.73	198.2	11.37	217.8
11.37	201.4	12.53	232.8
12.59	215.5	12.89	246.8
13.60	251.8	13.37	263.5
		13.70	284.1

of (20 and 25) °C, a similar trend of solubilities with varying pH values is observed. The pH−solubility profiles show a U-shape characteristic with a minimum solubility occurring at the pH value near the pI of glycine (pH 5.9). In the pH range of (3 to 10), the pH effect on the glycine solubility is relatively small, and the comparison with Carta and Tola data shows reasonable agreement. However, some discrepancies between our data and literature values are observed at lower and higher pH values.

In the reported polymorphic system of glycine, the γ-form is the most stable and least soluble form at ambient conditions.[14]

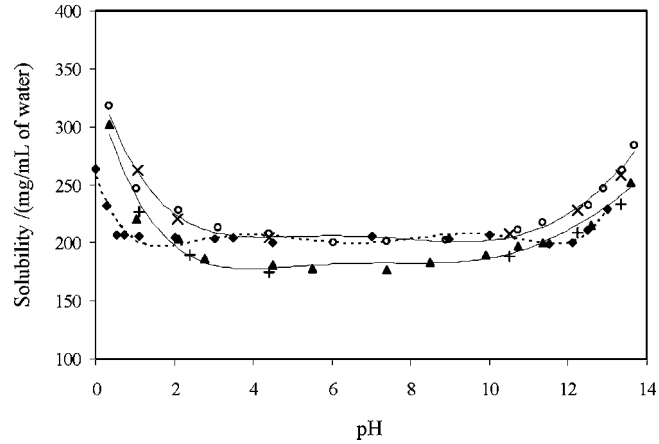

Figure 6. Solubility of the γ-form at various pH values and temperatures: ▲, 20 °C (gravimetric method); +, 20 °C (crystal disappearance method); ○, 25 °C (gravimetric method); ×, 25 °C (crystal disappearance method); ♦, Carta et al., 25 °C.

Therefore, we verified our experimental data at lower and higher pH values by the crystal disappearance method to avoid the possible oversaturation. This method is based on sequentially adding required acidic and basic buffer solutions to the stirred slurry at a certain temperature. The solubility is determined by detecting the disappearance point of the particles suspended in the solution. A Lasentec S400A focused beam reflectance measurement (FBRM) was used to detect the onset of dissolution of particles. In Figure 6, these results are compared with those previously measured by the gravimetric method. A good agreement of these experimental data is observed.

Conclusions

The solubilities of two polymorphs of glycine (α-form and γ-form) were measured in various aqueous solutions. The enthalpy and entropy of dissolution of both forms were determined by plotting the measured solubility data in water according to the van't Hoff equation. Compared with the α-form, the γ-form exhibits a lower solubility and a higher energy of dissolution, indicating that the γ-form is the stable form and the α-form is the metastable form at the studied temperature range of (5 to 60) °C. The solubilities of the γ-form were again lower than the α-form in the solvent mixtures of methanol with water as well as of PEG200 with water. The solubilities of both forms decrease with the addition of methanol and PEG200, suggesting that methanol and PEG200 can be used as antisolvents to precipitate and crystallize glycine from an aqueous solution. The effect of pH values on the solubility of the γ-form in water at (20 and 25) °C was investigated in the pH region of (0.35 to 13.7). The solubility curve shows a U-shape characteristic with the minimum solubility at the isoelectric point (pH 5.9).

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