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Determination of the Nucleation and Growth Kinetics for Aqueous L-glycine Solutions from the Turbidity Induction Time Data

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Abstract: As the turbidity induction time measurements are influenced by the size distribution of the nuclei at the detection point, these data should provide important information on both nucleation and growth. A model is developed in this work to determine the nucleation and growth kinetics of aqueous L-glycine solutions using the turbidity induction time data for various supersaturations from 293.15 K to 313.15 K. The photomicroscopic growth experiments of aqueous L-glycine solutions are also conducted to determine the growth kinetics of nuclei under the same conditions for comparison. The results indicate that the interfacial energy obtained from this model is consistent with that obtained based on the traditional method by assuming $t_i^{-1} \propto J$. The growth kinetics, including the growth activation energy and the kinetic growth parameter, obtained from this model using the induction time data are close to those obtained from the photomicroscopic growth experiments performed in this work.

Keywords: crystallization; nucleation; induction time; interfacial energy

1. Introduction

According to classical nucleation theory (CNT), only nuclei greater than a critical nucleus size are thermodynamically stable and can continue to grow to a detectable size [1–3]. The formation of critical nuclei is closely related to the interfacial energy of the crystallized substance, which is usually calculated from the induction time data in the literature [4–10].

The induction time is defined as the elapsed time between the creation of the supersaturation and the appearance of detectable nuclei at a constant temperature. Although the induction time can be detected by visual observation of the crystal's appearance [7,11], turbidity measurements have been commonly adopted in recent years to determine the induction time by detecting the change in the intensity of transmitted light in solution at the onset of nucleation [12–17]. Traditionally, determination of the interfacial energy from the induction time data is often simplified by assuming $t_i^{-1} \propto J$ [1,4–10]. Thus, it is implicitly assumed that at the detection of the nucleation point, only the number of the nuclei is accounted for regarding the change in the intensity of transmitted light in solution.

The detection of nucleation point based on turbidity measurements should be influenced by both the number and the size of the nuclei [18] as the change in the intensity of transmitted light in solution is proportional to the size distribution of the nuclei instead of the number of the nuclei. To incorporate the effect of the nuclei size distribution on the detection of nucleation, Shiau and coworkers [18,19] have developed a model to examine the turbidity induction time data of aqueous L-glutamic acid solutions using the L-glutamic acid growth kinetics reported by Scholl et al. [20]. It is found that the obtained interfacial energy and growth activation energy of L-glutamic acid [19] are consistent with

the literature data. L-glycine is the simplest amino acid and is often used as a model compound in the study of solution nucleation [21–25]. The objective of this work is to develop a model to study the nucleation and growth of aqueous L-glycine solutions based on the turbidity induction time data. To validate the obtained L-glycine growth kinetics from this model, the photomicroscopic growth experiments of aqueous L-glycine solutions are also conducted to determine the growth kinetics of nuclei at the same conditions for comparison.

2. Theory

The nucleation rate based on CNT [1–3] is expressed as:

$$J = A_J \exp\left(-\frac{16\pi v^2 \gamma^3}{3k_B^3 T^3 \ln^2 S}\right), \quad (1)$$

where $v = \frac{M_W}{\rho_C N_A}$ and $S = \frac{C}{C_{eq}}$. For simplicity, the nucleation event is assumed to correspond to a point at which the total number density of the nuclei has reached a fixed (but unknown) value, f_N [26,27]. One obtains at the induction time t_i using:

$$f_N = J t_i, \quad (2)$$

Thus, it is implicitly assumed that the detection of the nucleation point is related to the number of nuclei. Substituting Equation (1) into Equation (2) yields:

$$\ln\left(\frac{1}{t_i}\right) = \ln\left(\frac{A_J}{f_N}\right) - \frac{16\pi v^2 \gamma^3}{3k_B^3 T^3 \ln^2 S}, \quad (3)$$

This is consistent with the common method adopted in the literature to calculate γ from induction time data [1,4–10].

The turbidity induction time measurements are based on the change in intensity of transmitted or scattered light along the detector direction, which should be related to the size distribution of the nuclei instead of the number of the nuclei at the detection point [18,19]. As nuclei are progressively generated during the induction time period ($t = 0$ – t_i), the nuclei born in the earlier stage will grow to a greater size than those born in the later stage at t_i . To incorporate the effect of crystal growth at the nucleation point, Shiau and Lu [18] proposed a model to correlate the nucleation and growth with the turbidity induction time data using the predetermined growth kinetics. However, as it is often difficult to experimentally measure the growth kinetics of small nuclei, the application of this model is restricted.

As the turbidity induction time measurements are influenced by the size distribution of the nuclei, these data should provide important information on both nucleation and growth. A model is developed in the following to investigate the nucleation and growth of nuclei based on the turbidity induction time data without the predetermined growth kinetics. In the derivation, a simple empirical power-law growth rate is proposed as:

$$G = k_G (S - 1)^g, \quad (4)$$

where the value of g mostly falls between 1 and 2. Based on Burton–Cabrera–Frank (BCF) growth theory [28–30], the value of g is found close to 2 for low supersaturations [31]. Mohan and Myerson [32] indicated for aqueous L-glycine solutions at 293.15 K that Equation (4) with $g = 2$ is consistent with the BCF growth kinetics reported by Li and Rodriguez-Hornedo [33].

In the induction time study, nuclei born at any time t ($0 < t < t_i$) can grow from t to t_i and their size at time t_i is:

$$L(t) = G(t_i - t) \quad (5)$$

The corresponding volume of nuclei with size L at time t_i is

$$V(t) = k_V L(t)^3 = k_V G^3 (t_i - t)^3, \quad (6)$$

As nuclei are progressively generated from $t = 0$ to t_i , the total volume of all the nuclei per unit solution volume at time t_i is given by:

$$f_V = \int_0^{t_i} JV(t)dt, \quad (7)$$

Substituting Equation (6) into Equation (7) yields:

$$f_V = Jk_V G^3 \int_0^{t_i} (t_i - t)^3 dt = \frac{Jk_V G^3 t_i^4}{4}, \quad (8)$$

Note that J and G remain unchanged as S is kept at a particular supersaturation during each induction time experiment.

Substituting Equations (1) and (4) into Equation (8) with $g = 2$ leads to:

$$f_V = \frac{A_J k_V k_G^3 (S - 1)^6 t_i^4}{4} \exp\left(-\frac{16\pi v^2 \gamma^3}{3k_B^3 T^3 \ln^2 S}\right), \quad (9)$$

Rearranging Equation (9) yields:

$$\ln\left[\frac{4}{k_V t_i^4 (S - 1)^6}\right] = \ln\left(\frac{A_J k_G^3}{f_V}\right) - \frac{16\pi v^2 \gamma^3}{3k_B^3 T^3 \ln^2 S}, \quad (10)$$

A plot of $\ln\left[\frac{4}{k_V t_i^4 (S - 1)^6}\right]$ versus $\frac{1}{\ln^2 S}$ at a given temperature should give a straight line, the slope and intercept of which permit determination of γ and $\frac{A_J k_G^3}{f_V}$, respectively.

The temperature dependence of k_G can be expressed in terms of the Arrhenius equation as:

$$k_G = A_G \exp\left(-\frac{E_G}{RT}\right), \quad (11)$$

Once $\frac{A_J k_G^3}{f_V}$ is determined at different temperatures, substitution of Equation (11) yields:

$$\ln\left(\frac{A_J k_G^3}{f_V}\right) = \ln\left(\frac{A_J A_G^3}{f_V}\right) - \frac{3E_G}{RT}, \quad (12)$$

Thus, a plot of $\ln\left(\frac{A_J k_G^3}{f_V}\right)$ versus $\frac{1}{T}$ should give a straight line, the slope and intercept of which permit determination of E_G and $\frac{A_J A_G^3}{f_V}$, respectively. It should be noted that $A_J A_G^3$ can be determined if f_V is known.

3. Experimental

3.1. Induction Time Measurements

The experimental apparatus of a 250 mL crystallizer was the same as that used by Shiao and Lu [18]. Deionized water and L-glycine (>99%, Alfa Aesar, Haverhill, MA, USA) were used to prepare the supersaturated solution. In each experiment, a 200 mL aqueous L-glycine solution with the desired supersaturation was loaded into the crystallizer. The solution was stirred with a magnetic stirrer at a constant stirring rate of 350 rpm. A turbidity probe with a Near-Infrared source (Crystal Eyes

manufactured by HEL limited, Hertford, UK) was used to detect the nucleation event during the induction time study. The solution is held at 3 K above the saturated temperature for 5–10 min to ensure a complete dissolution at the beginning of the experiment, which was also confirmed using the turbidity measurement. As the cooling rate to reach a particular supersaturation influences the nucleation induction time [34], the solution was rapidly cooled at 25 °C/min to the desired constant temperature. Thus, the lag time was usually less than 60 s, which was much smaller than the measured induction times listed in Table 1. Figure 1 shows the variation of measured turbidity with time for $S = 1.15$ and a temperature of 293.15 K. The percentage threshold for the turbidity data was defined as the change in turbidity to determine whether a nucleation event had occurred [35]. A setting of 20% for the threshold was employed for all the turbidity induction time data in this work.

Table 1. The average induction times and the corresponding standard deviations (SD) for L-Glycine.

$T(K)$	$S(-)$	$t_i (SD)(s)$
293.15	1.10	2120 (471)
	1.12	1090 (242)
	1.13	936 (253)
	1.16	563 (157)
303.15	1.07	2672 (588)
	1.08	1390 (276)
	1.10	831 (247)
	1.12	442 (198)
313.15	1.06	2327 (534)
	1.07	953 (273)
	1.08	737 (201)
	1.10	429 (175)

Figure 1. The variation of measured turbidity with time for $S = 1.15$ and 293.15 K.

3.2. Growth Rate Measurements

The photomicroscopic experiments shown are performed to investigate the growth rates of L-glycine in water. This growth cell shown in Figure 2 [36] has a solution chamber of 20 mL in the upper part and a chamber for temperature-controlled water in the lower part. The growth rates of

aqueous L-glycine solutions for various supersaturations from 293.15 K to 313.15 K were studied isothermally in the upper stagnant solution.

Figure 2. The photomicroscopic growth apparatus (a) the real picture of growth cell; (b) schematic diagram of growth cell with the features: (1) solution chamber; (2) thermistor; (3) solution inlet and outlet; (4) constant-temperature water chamber; (5) water inlet and outlet.

The growth of crystals was monitored photographically through a microscope and analyzed using an image analyzer (Imaging Software, NIS-Elements, Nikon, Japan) to determine the area of each crystal. For simplicity, the characteristic size of the small crystal is taken as the equivalent circular diameter, i.e., $A = \pi L^2/4$, leading to $L = \sqrt{4A/\pi}$. The sizes were then plotted against time for each crystal with the slope equal to the growth rate. In each run, 8–10 crystals were analyzed to calculate the mean growth rate among these crystals under each condition. Figure 3 shows the photograph of the needle-like α -form crystals in solution taken in an experimental run for $S = 1.12$ at $T = 303.15$ K. It was found for various supersaturations from 293.15 K to 313.15 K that the needle-like α -form crystals were nucleated in the photomicroscopic experiments.

Figure 3. The photograph of the needle-like α -form L-glycine crystals in solution taken in the photomicroscopic experiment at $S = 1.12$ and 303.15 K.

4. Results and Discussion

The induction time data for aqueous L-glycine solutions were measured for various supersaturations from 293.15 K to 313.15 K. Each run was carried out at least three times to determine the average induction time under each condition. The average induction times and the corresponding standard deviations (SD) are listed in Table 1. The equilibrium concentration of the α -form L-glycine in water was given by $C_{eq}(T) = 5.4397 \times 10^{-3}T^2 - 3.2022 \times 10^{-1}T - 188.2$ (C_{eq} in kg/m³, and T in K) [37]. Note that $M_W = 0.075$ kg/mol, $\rho_C = 1607$ kg/m³, and $v = 7.757 \times 10^{-29}$ m³ for L-glycine.

Although L-glycine can be crystallized in different polymorphs, the α -form is usually achieved from nucleation of pure aqueous solutions [21–25]. To validate the polymorph of the L-glycine crystals, the final dried crystals at the end of the induction time experiments were analyzed using both optical microscopy and Raman spectroscopy (P/N LSI-DP2-785 Dimension-P2 System, 785 nm, manufactured by Lambda Solutions, INC., Seattle, WA, USA). The results all indicated that the needle-like α -form crystals were obtained from aqueous L-glycine solutions for various supersaturations from 293.15 K to 313.15 K. Figure 4 shows the Raman spectra of pure α -form crystals and product crystals obtained at various supersaturations. As compared with the Raman spectra of pure α -form crystals reported by Murli et al. [38], it was confirmed that α -form crystals were produced for various supersaturations at 303.15 K. The section of the Raman spectra of α -, β -, and γ -glycine used for characterization are also depicted by Bouchard et al. [39].

Figure 5 shows the measured induction time data from 293.15 K to 313.15 K fitted to Equation (3) based on f_N . The fitted results are listed in Table 2, where γ was in the range 1.93–2.37 mJ/m² and $\frac{A_I}{f_N}$ was in the range 4.35×10^{-3} – 6.42×10^{-3} s^{−1}. Although the exact value of A_I could only be determined with a known value of f_N , γ was not influenced by the chosen value of f_N .

Table 2. The fitted results of the induction time data to Equation (3) based on f_N .

$T(K)$	$\gamma(mJ/m^2)$	$\frac{A_I}{f_N}(s^{-1})$	$A_I(m^{-3}s^{-1})$
293.15	2.37	4.35×10^{-3}	3.32×10^9
303.15	2.07	5.29×10^{-3}	4.04×10^9
313.15	1.93	6.42×10^{-3}	4.91×10^9

Figure 4. The Raman spectra of pure α -form crystals and product crystals obtained in the induction time experiments for various supersaturations at 303.15 K.

Figure 5. The induction time data of L-glycine at 293.15–313.15 K fitted to Equation (3) based on f_N .

As the induction time data are measured by the intensity change of the transmitted light, Figure 6 shows the measured induction time data from 293.15 K to 313.15 K fitted to Equation (10) based on f_V . Note that g was assumed to be 2 due to low supersaturations ($S = 1.4$ – 2.4) in the induction time experiments. The fitted results are listed in Table 3, where γ was in the range 2.49 – 2.93 mJ/m² and $\frac{A_J k_G^3}{f_V}$ was in the range 2.78×10^{-5} – 2.58×10^{-3} s⁻⁴. It should be noted that γ was not influenced by the chosen value of f_V .

Figure 6. The induction time data of L-glycine at 293.15–313.15 K fitted to Equation (10) based on f_V .

Table 3. The fitted results of the induction time data to Equation (10) based on f_V .

$T(K)$	$\gamma(mJ/m^2)$	$\frac{A_I k_G^3}{f_V} (s^{-4})$
293.15	2.93	2.78×10^{-5}
303.15	2.66	4.15×10^{-4}
313.15	2.49	2.58×10^{-3}

The turbidity induction time measurements in the current experiments were based on the intensity change of the transmitted light, which is related to f_V . Thus, compared to γ based on f_N , γ based on f_V should more accurately represent the actual interfacial energy of L-glycine. Shiau [40] reported $\gamma = 1.35$ – 2.02 mJ/m² for aqueous α -form L-glycine solutions using the turbidity metastable zone width measurements at the saturation temperature between 308.15 K and 328.15 K. Using the visual observation of the induction time data, Devi and Srinivasan [25] reported $\gamma = 5$ mJ/m² for aqueous α -form L-glycine solutions at 303.15 K.

Figure 7 shows the plot of $\frac{A_I k_G^3}{f_V}$ versus $\frac{1}{T}$ fitted to Equation (12). The fitted results are listed in Table 4, which indicates $E_G = 58$ kJ/mol and $\frac{A_I A_G^3}{f_V} = 2.30 \times 10^{26} s^{-4}$. Although the exact value of $A_I A_G^3$ could only be determined with a known value of f_V , E_G was not influenced by the chosen value of f_V . Because activation energy is usually 10–20 kJ/mol for diffusion and 40–60 kJ/mol for surface integration [1], $E_G = 58$ kJ/mol obtained for the growth of L-glycine in the induction time experiments should be integration controlled.

Table 4. The fitted results of E_G and A_G using Equation (12).

$E_G (kJ/mol)$	$\frac{A_I A_G^3}{f_V} (s^{-4})$	$A_I A_G^3 (s^{-4})$	$A_G (m/s)$		
			293.15 K	303.15 K	313.15 K
58	2.30×10^{26}	9.18×10^{22}	3.02×10^4	2.83×10^4	2.66×10^4

Figure 7. The plot of $\frac{A_J k_G^3}{f_V}$ versus $\frac{1}{T}$ fitted to Equation (12).

Based on the study of 28 inorganic systems, Mersmann and Bartosch [41] estimated $f_V = 10^{-4}$ – 10^{-3} with a detectable size of 10 μm . In the calculations here, the intermediate value, $f_V = 4 \times 10^{-4}$, for spherical nuclei with $k_V = \frac{\pi}{6}$ was assumed, leading to $f_N = 7.64 \times 10^{11} \text{ m}^{-3}$. Consequently, as indicated in Table 2, A_J was in the range 3.32×10^9 – $4.91 \times 10^9 \text{ m}^{-3} \cdot \text{s}^{-1}$ based on $f_N = 7.64 \times 10^{11} \text{ m}^{-3}$. Table 4 indicates $A_J A_G^3 = 9.18 \times 10^{22} \text{ s}^{-4}$ based on $f_V = 4 \times 10^{-4}$. For simplicity, if A_J obtained based on f_N was adopted to find A_G , one obtains $A_G = 2.66 \times 10^4$ – $3.02 \times 10^4 \text{ m/s}$.

The average growth rates and the corresponding standard deviations (SD) obtained from the photomicroscopic growth experiments are listed in Table 5. Figure 8 displays the growth rate data for various supersaturation from 303.15 K to 323.15 K. The growth rate obtained here is consistent with that reported by Han et al. [23] for aqueous α -form L-glycine solutions at $S = 1.35$ and $T = 303.15 \text{ K}$. Substituting Equation (11) into Equation (4) for $g = 2$ yields:

$$G = A_G \exp\left(-\frac{E_G}{RT}\right)(S-1)^2, \quad (13)$$

Rearranging Equation (13) leads to:

$$\ln\left[\frac{G}{(S-1)^2}\right] = \ln A_G - \frac{E_G}{RT}, \quad (14)$$

As shown in Figure 9, a plot of $\ln\left[\frac{G}{(S-1)^2}\right]$ versus $\frac{1}{T}$ should give a straight line, leading to $E_G = 57 \text{ kJ/mol}$ and $A_G = 6.05 \times 10^4 \text{ m/s}$.

Table 5. The average growth rates and the corresponding standard deviations (SD) for L-Glycine.

<i>T</i> (K)	<i>S</i> (–)	<i>G</i> (SD) ($\times 10^{-7}$) (m/s)
303.15	1.08	0.42 (0.17)
	1.10	0.67 (0.29)
	1.12	1.09 (0.36)
	1.14	1.35 (0.55)
313.15	1.08	1.03 (0.42)
	1.10	1.67 (0.85)
	1.12	1.87 (0.64)
	1.14	3.21 (1.37)
323.15	1.08	2.13 (0.73)
	1.10	2.55 (0.82)
	1.12	3.88 (1.03)
	1.14	5.62 (2.14)

Figure 8. The growth rate data of L-glycine for various supersaturations at 303.15–323.15 K. The lines represent the fitted values to Equation (13) using $g = 2$, $E_G = 57$ kJ/mol and $A_G = 6.05 \times 10^4$ m/s.

Figure 8 shows the growth rate data fitted well to Equation (14) using $g = 2$ and the fitted values of E_G and A_G . Thus, it was reasonable to adopt the power-law growth rate of Equation (4) with $g = 2$ in derivation of Equation (10). It should be noted that the turbidity induction time data were measured for nuclei of near-zero size (<10 μm , as assumed here for $f_V = 4 \times 10^{-4}$ and $f_N = 7.64 \times 10^{11} \text{ m}^{-3}$) in the 200 mL stirred solution while the photomicroscopic growth data were measured for nuclei of size $L = 50\text{--}100$ μm in the 20 mL stagnant solution. Nevertheless, E_G obtained from the growth rate data was close to that obtained from the induction time data while A_G obtained from the growth rate data was still quite consistent with that obtained from the induction time data.

Figure 9. The growth rate data of L-glycine for various supersaturations at 303.15–323.15 K fitted to Equation (14).

5. Conclusions

In practical applications, the turbidity induction time measurements should be more related to the volume fraction of the nuclei than to the number density of the nuclei. A model is developed in this work to determine the interfacial energy and growth activation energy of aqueous L-glycine solutions from the turbidity induction time data without the knowledge of the actual growth kinetics. The results reveal that the interfacial energy of L-glycine obtained in this work is close to that calculated based on the traditional method by assuming $t_i^{-1} \propto J$, and the growth activation energy of L-glycine obtained from the induction time data was close to that obtained from the photomicroscopic growth experiments. The kinetic growth parameter of L-glycine obtained from the photomicroscopic growth experiments was consistent with that obtained from the induction time data. Thus, the proposed model in this work provides an efficient method to determine the nucleation and growth kinetics of nuclei using the induction time data.

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Notation

A_G	growth kinetic parameter (m/s)
A_J	nucleation kinetic parameter ($\text{m}^{-3}\text{s}^{-1}$)
C	concentration of solutes (kg solute/kg solution)
C_{eq}	saturated concentration of solutes (kg solute/kg solution)
E_G	growth activation energy (J/mol)
f_N	minimum detectable number density of nuclei for a detector (m^{-3})
f_V	minimum detectable volume density of nuclei for a detector (—)
G	growth rate (m/s)
g	growth rate order (—)
J	nucleation rate ($\text{m}^{-3}\text{s}^{-1}$)
k_B	Boltzmann constant ($= 1.38 \times 10^{-23} \text{ J K}^{-1}$)
k_G	growth rate constant (m/s)
k_V	volume shape factor (—)
L	size of a nucleus (m)
M_W	molar mass (kg mol^{-1})
N_A	Avogadro number ($= 6.02 \times 10^{23} \text{ mol}^{-1}$)
R	ideal gas constant ($= 8.314 \frac{\text{J}}{\text{mol K}}$)
S	supersaturation ratio (—)
T	temperature (K)
t	time (s)
t_i	induction time (s)
V	volume of a nucleus (m^3)

Greek letters

γ	interfacial energy (J/m^2)
ρ_C	crystal density (kg m^{-3})
v	volume of the solute molecule (m^3)

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