Comparison of the Nucleation Parameters of Aqueous L-glycine Solutions in the Presence of L-arginine from Induction Time and Metastable-Zone-Width Data

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Abstract: Induction time and metastable-zone-width (MSZW) data for aqueous L-glycine solutions in the presence of L-arginine impurity were experimentally measured using a turbidity probe in this study. The nucleation parameters, including the interfacial free energy and pre-exponential nucleation factor, obtained from induction time data, were compared with those obtained from MSZW data. The influences of lag time on the nucleation parameters were examined for the induction time data. The effects of L-arginine impurity concentration on the nucleation parameters based on both the induction time and MSZW data were investigated in detail.

Keywords: crystallites; impurities; induction time; metastable zone width; nucleation parameters

1. Introduction

In crystal growth, the induction time is defined as the time interval between the establishment of the supersaturated state and the formation of detectable nuclei. The metastable-zone-width (MSZW) limit is defined as the time taken at a given cooling rate between the establishment of the supersaturated state and the formation of detectable nuclei. Nucleation is the initial process for the formation of crystals in liquid solutions. Thus, both the induction time and MSZW data are related to the nucleation rate of the crystallized substance in solutions. In classical nucleation theory (CNT) [1–3], the nucleation rate is expressed in the Arrhenius form, governed by two nucleation parameters, including the interfacial free energy and pre-exponential nucleation factor. The interfacial free energy is the energy required to create a new solid/liquid interface for the formation of crystals in liquid solutions, while the pre-exponential factor is related to the attachment rate of solute molecules to a cluster in the formation of crystals. The influences of impurities on the nucleation parameters have long been investigated using induction time or MSZW data with the addition of different impurities in solutions for a variety of compounds [4–14].

The nucleation parameters of a crystallized substance have been traditionally determined from induction time data by assuming $t^{-1} \propto J$, where $J$ is nucleation rate [1]. Recently, various methods have been proposed to calculate the nucleation parameters from MSZW data [15–21]. Although the induction time and MSZW processes are two different temperature-controlling methods for determination of the nucleation parameters in a crystallization system, a model should be available to relate the induction time and MSZW data with the nucleation parameters. Furthermore, as a cooling process is applied first to reach the desired operating temperature and then a constant temperature is adopted in the induction time measurements, there always exists a lag time between the prepared supersaturated solution being at a higher temperature and it being cooled to the desired lower constant temperature. For simplicity, the lag time is usually neglected in determining the nucleation parameters from the induction time data.

The nucleation process can behave differently. For certain systems, induction time cannot even be considered due to sharp phase transition, while for some cases there is
induction time governed by different material properties. For example, by evaporating a cellulose nanocrystal-based cholesteric drop, the drop edges are pinned to the substrate, which leads to nonequilibrium sliding of the individual cholesteric fragment with active ordering [22]; following the induction period of cholesteric collagen tactoids, phase separation goes through the nucleation process during which multiple chiral nuclei spontaneously emerge and grow throughout the continuous isotropic phase [23]. In the present work, a model was proposed based on CNT to relate the induction time and MSZW data with the nucleation parameters for the systems with an experimentally measurable nucleation point. The proposed model was then applied to determine the nucleation parameters for the aqueous $L$-glycine solutions in the presence of $L$-arginine impurity from the induction time and MSZW data. The effects of lag time on the nucleation parameters within the induction time data were investigated.

$L$-glycine was adopted in this work as it is the simplest amino acid and is often used as a model compound in the study of solution nucleation [24–30]. $L$-arginine is another amino acid which was randomly chosen as impurity in the aqueous $L$-glycine solutions.

2. Theory

The nucleation rate according to CNT is expressed as [1–3]

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

where $A$ is the nucleation pre-exponential factor, $\gamma$ is the interfacial free energy, $k_B$ is the Boltzmann constant, $v = M_w / \rho c N_A$ is the molecular volume, $T$ is the temperature, and $S$ is the supersaturation.

A model is derived based on CNT to determine $\gamma$ and $A$ by relating the induction time and MSZW data with $J$ as follows. If a solution saturated at $T_0$ is cooled to $T_m$ at a constant cooling rate $b$ within the time period $t = 0$ to $t_m$ and then the temperature is kept at $T_m$ within the time period $t_m$ to $t_m + t_i$, the nucleation event for this combined process is assumed to be detected at $t = t_m + t_i$. If $t_m$ is small compared to $t_i$, this combined process can be regard as the induction time process with consideration of the lag time $t_m$, which is the time required for the solution saturated at $T_0$ to cool to $T_m$ at cooling rate $b$. Thus, $\Delta T_m = T_0 - T_m$ and the lag time is given by $t_m = \Delta T_m / b$. This combined process for $t_m = 0$ corresponds to the induction time process without consideration of the lag time. On the other hand, this combined process for $t_i = 0$ corresponds to the MSZW process.

Figure 1 depicts the MSZW process for a saturated solution of $C_0$ cooled at a constant cooling rate $b$, where $T_0$ is the initial saturated temperature at $t = 0$, $T_m$ is the nucleation temperature at $t_m$, $C_0$ is the saturated concentration at $T_0$, $C_m$ is the saturated concentration at $T_m$, $C_{eq}(T)$ is the solubility, and $S(T) = C_0 / C_{eq}(T)$ is the supersaturation. As $C_{eq}(T)$ generally decreases with decreasing temperature, $S(T)$ increases and subsequently $J$ increases with time. For the nucleation point at $t_m$, $S_m$ is the supersaturation at $T_m$ defined as $S_m = C_0 / C_{eq}(T_m) = C_0 / C_m$. The nucleation rate at $T_m$ is given by

$$J_m = A \exp \left[ -\frac{16 \pi v^2 \gamma^3}{3 k_B T_m^3 \ln^2 S_m} \right]. \quad (2)$$
Note that both $S_m$ and $\Delta T_m$ are measures of the MSZW.

As the first appearance of nuclei can be regarded as a random process, the stochastic process of nucleation can be described by the Poisson’s law [32–34]. For the combined process described above, as the temperature is cooled from $T_0$ to $T_m$ within the time period $t = 0$ to $t_m$, $S(T)$ increases and $J$ increases with time; and as the temperature is kept at $T_m$ within the time period $t_m$ to $t_m + t_i$, the supersaturation remains the same at $S_m$ and $J$ remains the same at $J_m$. Based on the given reasoning, the average number of expected nuclei $N$ in a solution volume $V$ within the time period $t = 0$ to $t_m + t_i$ is proposed in this study as

$$N = \left( \int_{0}^{t_m} JV dt \right) + J_m V t_i. \tag{3}$$

where the first term on the right-hand side represents the average number of expected nuclei generated within the time period $t = 0$ to $t_m$ and the second term on the right-hand side represents the average number of expected nuclei generated within the time period $t_m$ to $t_m + t_i$.

Based on the two-point trapezoidal rule for computing the value of a definite integral, one can derive [35]

$$\int_{0}^{t_m} JV dt = \frac{1}{2} (J_0 + J_m) V t_m = \frac{J_m V \Delta T_m}{2b}, \tag{4}$$

where $J_0$ and $J_m$ represent the nucleation rate at $t = 0$ and $t = t_m$, respectively. Note that $J_0 = 0$ at $t = 0$ when $S(T_0) = 1$ and $t_m = \Delta T_m / b$.

According to the single nucleus mechanism (SNM) proposed by some researchers through experimental validation [32–34], a single primary nucleus is formed in a supersaturated solution, which grows out to a particular size and undergoes secondary nucleation by

Figure 1. A schematic diagram showing the increasing of supersaturation during the cooling process reproduced from Shiau [31], where $C_{eq}(T)$ is the temperature-dependent solubility ($\bigcirc$ represents the starting point and $\bullet$ represents the nucleation point).
crystal-stirring-impeller or crystal-wall collision. Based on the assumptions that the growth time between the formation of nucleus and growth to the minimum size for secondary nucleation is negligible, and one secondary nucleation is enough to generate detectable crystal volume increase in a negligible amount of time, the nucleation event is detected after the secondary nucleation of the single primary nucleus. Thus, the nucleation event for the combined process occurs at \( t = t_m + t_i \) when the first nucleus is formed. By substituting \( N = 1 \) in Equation (3), combining Equations (2)–(4) leads to

\[
\ln \left( \frac{\Delta T_m}{2b} + t_i \right) = -\ln(AV) + \frac{16\pi v^2 \gamma^3}{3k_B^3 T_m^3 \ln^2 S_m}.
\]

Thus, Equation (5) can be applied to determine the nucleation parameters from the induction time data, \( t_i \), with consideration of the lag time, \( \Delta T_m/b \). A plot of \( \ln(\Delta T_m/2b + t_i) \) versus \( \ln^2 S_m \) should give a straight line, the slope and intercept of which permit determination of \( \gamma \) and \( A \), respectively.

Equation (5) for \( \Delta T_m/b = 0 \) reduces to

\[
\ln t_i = -\ln(AV) + \frac{16\pi v^2 \gamma^3}{3k_B^3 T_m^3 \ln^2 S_m},
\]

which corresponds to the conventional method adopted in determination of \( \gamma \) and \( A \) from the induction time data without consideration of the lag time. Equation (5) for \( t_i = 0 \) reduces to

\[
\ln \left( \frac{\Delta T_m}{2b} \right) = -\ln(AV) + \frac{16\pi v^2 \gamma^3}{3k_B^3 T_m^3 \ln^2 S_m},
\]

which can be applied to determine \( \gamma \) and \( A \) from the MSZW measurements, where a solution saturated at \( T_0 \) is cooled at a constant rate \( b \) from \( t = 0 \) to \( t_m \) and the nucleation event is detected at \( T_m \).

If the temperature-dependent solubility is described in terms of the van’t Hoff Equation (1), one obtains

\[
\ln S_m = \ln \left( \frac{C_0}{C_m} \right) = -\frac{\Delta H_d}{R_G} \left( \frac{1}{T_0} - \frac{1}{T_m} \right) = \left( \frac{\Delta H_d}{R_G T_0} \right) \left( \frac{\Delta T_m}{T_m} \right),
\]

where \( \Delta H_d \) is the heat of dissolution and \( R_G \) is the gas constant. Substituting \( \ln S_m \) in Equation (8) into Equation (7) yields

\[
\left( \frac{T_0}{\Delta T_m} \right)^2 = \frac{3}{16\pi} \left( \frac{k_B T_0}{v^2/3\gamma} \right)^3 \left( \frac{\Delta H_d}{R_G T_0} \right)^2 \left[ \ln \left( \frac{\Delta T_m}{b} \right) + \ln \left( \frac{AV}{2} \right) \right].
\]

A plot of \( (T_0/\Delta T_m)^2 \) versus \( \ln(\Delta T_m/b) \) based on the MSZW data should give a straight line, the slope and intercept of which permit determination of \( \gamma \) and \( A \), respectively. Equation (9) is consistent with the result developed by Shiau and Wu [21] in determination of \( \gamma \) and \( A \) from the MSZW data.

3. Experimental Methods

Deionized water, L-glycine (>99%, Alfa Aesar) and L-arginine (>98%, ACROS) were used to prepare the desired supersaturated solution for the specified impurity concentration. The experimental apparatus adopted by Shiau and Lu [18] was used in the study of nucleation, which consists of a 250 mL crystallizer equipped with a magnetic stirrer at a constant stirring rate of 350 rpm, immersed in programmable thermostatic water. A turbidity probe with a near-infrared source (Crystal Eyes manufactured by HEL limited, Hertford, UK) was used to detect the nucleation event.

The solubility of L-glycine in water from 303 K to 318 K was measured in this work. The solubility measurements indicated that the solubility of L-glycine in water was nearly not
influenced by the presence of L-arginine ranging from $C_{im} = 0$ to 10 kg arginine/m$^3$ solution, which corresponds to 0–0.02 mol arginine/mol glycine. The measured solubility of L-glycine in water was consistent with the solubility data reported by Park et al. [36]. In terms of the van’t Hoff equation for the measured solubility, one obtains $\Delta H_d = 10.2$ kJ/mol with $C_{eq}(303 \, K) = 215 \, \text{kg/m}^3$ and $C_{eq}(318 \, K) = 261 \, \text{kg/m}^3$ in this work.

For the induction time and MSZW experiments, a 200 mL aqueous L-glycine solution ($V = 2 \times 10^{-4} \, \text{m}^3$) at the desired concentration was held at 5 K above the saturated temperature for 20 min to ensure a complete dissolution at the beginning of the experiments, which was also confirmed by the turbidity measurement. In the induction time experiments, the induction time and lag time data were measured by rapidly cooling the supersaturated solution at various supersaturations to 303 K. In the MSZW experiments, MSZW data were measured by cooling the solution saturated at 318 K with different constant cooling rates. Each run was carried out at least three times at each condition for the solubility, the induction time, and the MSZW measurements.

Although L-glycine can be crystallized in different polymorphs, including $\alpha$-form, $\beta$-form and $\gamma$-form, $\alpha$-form is usually obtained from pure aqueous L-glycine solutions [24–30]. In this work, the final dried crystals at the end of the experiments were analyzed using Raman spectroscopy (P/N LSI-DP2-785 Dimension-P2 System, 785 nm, manufactured by Lambda Solutions, INC., Seattle, WA, USA) to validate the polymorph of the L-glycine crystals. By comparing with the Raman spectra of $\alpha$-form crystals reported by Murli et al. [37], it was found that $\alpha$-form L-glycine crystals were formed from aqueous L-glycine solutions in this work for various supersaturations without and with the presence of L-arginine impurity. Figure 2 shows some Raman spectra of the L-glycine crystals obtained in this work at $S = 1.07$ and $S = 1.12$ for $C_{im} = 0$ and $C_{im} = 10 \, \text{kg/m}^3$, respectively.

![Figure 2](cont)
4. Results and Discussion

The induction time data of aqueous L-glycine solutions were measured for various supersaturations at 303 K in the presence of L-arginine for various impurity concentrations, \( C_{im} \). The average induction times are listed in Table 2, which were measured based on \( b \approx 0.038 \text{ K/s} \) adopted for cooling the heated supersaturated solution to the desired constant temperature. The lag time corresponds to the time required for the heated solution to be lowered to 303 K. Thus, as the temperature range \( \Delta T_m \) increases, the lag time increases. The MSZW data of aqueous L-glycine solutions saturated at 303 K were measured for various \( b \) in the presence of L-arginine for \( C_{im} = 0-10 \text{ kg/m}^3 \). The average MSZWs are listed in Table 3. Note that \( M_w = 0.075 \text{ kg/mol, } \rho_c = 1607 \text{ kg/m}^3, \text{ and } v = 7.757 \times 10^{-20} \text{ m}^3 \) for L-glycine.

Table 1. The average induction times, \( t_i \), in the induction time measurements for various impurity concentrations, \( C_{im} \), and supersaturations, \( S \), at 303 K. The standard deviations in the least significant digits are given in parentheses.

| \( C_{im} \text{ (kg/m}^3) \) | \( S = 1.07 \) | \( S = 1.08 \) | \( S = 1.10 \) | \( S = 1.12 \) |
|----------------|-------------|-------------|-------------|-------------|
| 0              | 27 (5.9)    | 14 (2.8)    | 8.3 (2.5)   | 4.4 (2.0)   |
| 2              | 62 (15)     | 33 (7.3)    | 16 (4.6)    | 8.2 (2.5)   |
| 5              | 107 (17)    | 48 (8.9)    | 23 (5.1)    | 12 (3.0)    |
| 10             | 154 (21)    | 62 (11)     | 31 (8.8)    | 16 (4.7)    |

Figure 2. The Raman spectra of the produced L-glycine crystals at \( S = 1.07 \) and \( S = 1.12 \) for (a) \( C_{im} = 0 \) and (b) \( C_{im} = 10 \text{ kg/m}^3 \), respectively.
Table 2. The average lag time, $\Delta T_m/b$, based on $b \approx 0.038$ K/s in the induction time measurements for various impurity concentrations, $C_{im}$, and supersaturations, $S$, at 303 K, where $\Delta T_m$ corresponds to the temperature range for a solution with concentration $C_0$ saturated at $T_0$ and cooled to 303 K. Note that $\Delta T_m = T_0 - 303$ K and $S = C_0/C_{eq}(303$ K). The standard deviations in the least significant digits are given in parentheses.

| $C_{im}$ (kg/m³) | $\Delta T_m/b$ (s) | $\Delta T_m$ (K) |
|------------------|---------------------|------------------|
|                  | $S = 1.07$          | $S = 1.08$       | $S = 1.10$       | $S = 1.12$       |
|                  | ($\Delta T_m = 5.1$ K) | ($\Delta T_m = 5.8$ K) | ($\Delta T_m = 7.2$ K) | ($\Delta T_m = 8.7$ K) |
| 0                | 135 (14)            | 153 (16)         | 177 (16)         | 236 (19)         |
| 2                | 127 (12)            | 144 (13)         | 195 (17)         | 221 (17)         |
| 5                | 141 (13)            | 159 (15)         | 182 (16)         | 232 (17)         |
| 10               | 146 (15)            | 163 (14)         | 188 (18)         | 241 (22)         |

Table 3. The average MSZWs, $\Delta T_m$, in the MSZW measurements for a solution saturated at $T_0 = 318$ K cooled at various impurity concentrations, $C_{im}$, and cooling rates. The standard deviations in the least significant digits are given in parentheses.

| $C_{im}$ (kg/m³) | $\Delta T_m$ (K) |
|------------------|------------------|
|                  | $b = 0.00417$ K/s | $b = 0.00833$ K/s | $b = 0.01111$ K/s | $b = 0.01389$ K/s |
| 0                | 6.9 (1.6)         | 8.5 (1.7)         | 9.1 (2.1)         | 9.9 (2.2)         |
| 2                | 8.4 (1.8)         | 10.3 (2.0)        | 11.7 (2.3)        | 12.2 (2.3)        |
| 5                | 9.7 (2.1)         | 12.2 (2.5)        | 13.8 (2.9)        | 14.4 (3.1)        |
| 10               | 11.5 (2.3)        | 13.9 (2.4)        | 16.1 (2.7)        | 18.8 (3.3)        |

Table 1 indicates that $t_i$ increases significantly with increasing $C_{im}$ for each $S$ and decreases with increasing $S$ for each $C_{im}$. Thus, L-arginine exerts a nucleation inhibition effect in aqueous L-glycine solutions, which increases with increasing $C_{im}$ and remains nearly independent of $C_{im}$. Note that $\Delta T_m$ corresponds to the temperature range for a solution saturated at $T_0$ cooled to 303 K, where $T_0$ increases with increasing $S$ and remains nearly independent of $C_{im}$. For example, $\Delta T_m/b = 236$ s is quite significant compared with $t_i = 442$ s at $S = 1.12$ ($\Delta T_m = 8.7$ K) for $C_{im} = 0$. On the other hand, $\Delta T_m/b = 135$ s is negligible compared with $t_i = 2672$ s at $S = 1.07$ ($\Delta T_m = 5.1$ K) for $C_{im} = 0$.

Figure 3 shows plots of $\ln t_i$ against $\ln^2 S_m$ for each $C_{im}$ according to Equation (6) based on the induction time data without consideration of the lag time. Figure 4 shows plots of $\ln(\Delta T_m/2b + t_i)$ against $\ln^2 S_m$ for each $C_{im}$ according to Equation (5) based on the induction time data with consideration of the lag time. Calculated values of $\gamma$ and $A$ from the slope and intercept of the best-fit plots for each $C_{im}$ are listed in Table 4. Note that the regression coefficient, $R^2$, with the lag time is generally greater than that without the lag time for each $C_{im}$, which indicates that Equation (5) with the lag time fits the induction time data better than Equation (6) without the lag time.
Figure 3. Plots of \( \ln t_i \) against \( \ln^2 S_{im} \) for various impurity concentrations, \( C_{im} \), according to Equation (6) based on the induction time data without consideration of the lag time.

Figure 4. Plots of \( \ln(\Delta T_{im}/2b + t_j) \) against \( \ln^3 S_{im} \) for various impurity concentrations, \( C_{im} \), according to Equation (5) based on the induction time data with consideration of the lag time.

Table 4. Calculated values of \( \gamma \) and \( A \) with the regression coefficients, \( R^2 \), based on the induction time data. The number before the slash represents the value without consideration of the lag time and the number after the slash represents the value with consideration of the lag time.

| \( C_{im} \) (kg/m\(^3\)) | \( \gamma \) (mJ/m\(^3\)) | \( A \) (m\(^{-3}\)s\(^{-1}\)) | \( R^2 \) |
|----------------|----------------|----------------|---------|
| 0       | 2.07/1.99 | 26.5/19.7 | 0.981/0.987 |
| 2       | 2.17/2.13 | 16.9/14.3 | 0.991/0.994 |
| 5       | 2.22/2.20 | 12.7/11.6 | 0.993/0.997 |
| 10      | 2.24/2.22 | 10.0/9.1  | 0.989/0.990 |

As indicated in Table 4, one can note that the value of \( \gamma \) with the lag time, \( \gamma_{lag} \), is lower by about 2% than that without the lag time, \( \gamma \), while the value of \( A \) with the lag time,


$A_{lag}$ is lower by about 15% than that without the lag time, $A$. These findings are consistent with $\gamma_{lag} < \gamma$ and $A_{lag} < A$ derived in Supplementary Materials.

Table 3 indicates that $\Delta T_m$ increases with increasing $C_{im}$ for each $b$ and increases with increasing $b$ for each $C_{im}$. Thus, as similar to the results from the induction time data, l-arginine exerts a nucleation inhibition effect in aqueous l-glycine solutions, which increases with increasing $C_{im}$. Figure 5 shows plots of $(T_0/\Delta T_m)^2$ against $\ln(\Delta T_m/b)$ for various $C_{im}$ according to Equation (9) based on the MSZW data. Calculated values of $\gamma$ and $A$ from the slope and intercept of the best-fit plots for each $C_{im}$ are listed in Table 5.

![Graph](image_url)

**Figure 5.** Plots of $(T_0/\Delta T_m)^2$ against $\ln(\Delta T_m/b)$ for various impurity concentrations, $C_{im}$, according to Equation (9) based on the MSZW data.

| $C_{im}$ (kg/m$^3$) | $\gamma$ (ml/m$^2$) | $A$ (m$^{-3}$s$^{-1}$) | $R^2$ |
|---------------------|---------------------|----------------------|-------|
| 0                   | 2.13                | 30.9                 | 0.990 |
| 2                   | 2.36                | 22.1                 | 0.981 |
| 5                   | 2.54                | 17.2                 | 0.975 |
| 10                  | 2.71                | 12.6                 | 0.953 |

The values of $\gamma$ and $A$ obtained from the MSZW data in Table 5 are consistent with those obtained from the induction time data in Table 4. They all indicate that, as $C_{im}$ increases, $\gamma$ increases slightly while $A$ decreases quite significantly. For example, as $C_{im}$ increases from 0 to 10 kg/m$^3$, $\gamma$ only increases slightly in the range of 10% to 30%, while $A$ decreases significantly in the range of 50% to 60%. It is speculated that the presence of l-arginine in the aqueous l-glycine solution leads to some l-arginine molecules adsorbed on the nucleus surface of l-glycine, which suppresses nucleation and results in a higher $\gamma$ compared to that without l-arginine adsorbed on the nucleus surface of l-glycine. On the other hand, the presence of l-arginine in the aqueous l-glycine solution suppresses nucleation and results in a lower $A$ compared to that without l-arginine in the aqueous l-glycine solution. As the effects of l-arginine impurity on $\gamma$ and $A$ become more profound at a greater concentration of l-arginine impurity, a greater $C_{im}$ results in a higher $\gamma$ and a lower $A$. This trend is consistent with the finding reported by Heffernan et al. [8] for the
nucleation of curcumin in propan-2-ol due to the presence of demethoxycurcumin and bisdemethoxycurcumin.

5. Conclusions

A model was proposed based on CNT to determine the nucleation parameters from both the induction and MSZW data. The unique feature is that the derivation of this model for both the induction and MSZW data is based on the same assumption that the nucleation point corresponds to the formation of a single primary nucleus in a supersaturated solution. This model results in two different equations. One is derived for the induction data while the other is derived for the MESZW data. The proposed model was applied to calculate the interfacial free energy and pre-exponential nucleation factor from both the induction time data and the MSZW data for the aqueous L-glycine solutions in the presence of L-arginine impurity. The results indicated that the values of interfacial free energy and pre-exponential nucleation factor obtained from the MSZW data are consistent with those obtained from the induction time data. The induction time data with consideration of the lag time lead to a lower interfacial free energy and a lower pre-exponential nucleation factor than those for the induction time data without consideration of the lag time. As the impurity concentration increases, the interfacial free energy increases slightly while the pre-exponential nucleation factor decreases quite significantly based on both the induction time and MSZW data.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cryst11101226/s1, The derivation of $\gamma_{\text{lag}} < \gamma$ and $A_{\text{lag}} < A$.

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Notation

\[ A = \text{pre-exponential nucleation factor (m}^{-3}\text{s}^{-1}) \]
\[ b = \text{cooling rate (K/s)} \]
\[ C_0 = \text{initial saturated concentration at } T_0 \text{ (kg/m}^3\text{)} \]
\[ C_e(T) = \text{saturated concentration at } T \text{ (kg/m}^3\text{)} \]
\[ C_m = \text{saturated concentration at } T_m \text{ (kg/m}^3\text{)} \]
\[ C_{\text{im}} = \text{concentration of impurity (kg/m}^3\text{)} \]
\[ J = \text{nucleation rate (m}^{-3}\text{s}^{-1}) \]
\[ J_0 = \text{nucleation rate at } t = 0 \text{ (m}^{-3}\text{s}^{-1}) \]
\[ J_m = \text{nucleation rate at } t_m \text{ (m}^{-3}\text{s}^{-1}) \]
\[ k_B = \text{Boltzmann constant (}= 1.38 \times 10^{-23} \text{ J/K}) \]
\[ M_W = \text{molar mass (kg/mol)} \]
\[ N = \text{average number of expected nuclei (–)} \]
\[ N_A = \text{Avogadro number (}= 6.02 \times 10^{23} \text{ mol}^{-1}\text{)} \]
\[ R_G = \text{gas constant (}= 8.314 \text{ J mol}^{-1}\text{K}^{-1}) \]
\[ S = \text{supersaturation (–)} \]
\[ S_m = \text{supersaturation at } t_m \text{ (–)} \]
\[ T = \text{temperature (K)} \]
\[ T_0 = \text{initial saturated temperature (K)} \]
\[ T_m = \text{temperature at } t_m \text{ (K)} \]
\[ t = \text{time (s)} \]
$t_i =$ induction time (s)  
$t_m =$ time at the MSZW limit (s)  
$V =$ solution volume (m$^3$)

**Greek Letters**
- $\rho_c =$ crystal density (kg/m$^3$)
- $v =$ volume of the solute molecule (m$^3$)
- $\gamma =$ interfacial free energy (J/m$^2$)
- $\Delta H_f =$ heat of dissolution (J/mole)
- $\Delta T_m =$ MSZW (K)

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