Investigations into the Influence of Solvents on the Nucleation Kinetics for Isonicotinamide, Lovastatin, and Phenacetin

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ABSTRACT: A new method of data interpretation based on classical nucleation theory is proposed in this work to elucidate the influence of solvents on the pre-exponential nucleation factor and interfacial energy using the induction time data for three crystallization systems, including isonicotinamide, lovastatin, and phenacetin. In this method, the pre-exponential nucleation factor is replaced by the intrinsic nucleation factor multiplied by temperature and divided by solution viscosity. The proposed method is applied to study the nucleation kinetics of isonicotinamide, lovastatin, and phenacetin among various solvents using the induction time data measured in this work. The results indicate that the intrinsic nucleation factor increases linearly with increasing square root of interfacial energy in various solvents for each system.

■ INTRODUCTION

Nucleation is the initial process for the formation of crystals in solutions. In classical nucleation theory (CNT),1−3 the nucleation rate is expressed in the thermally activated Arrhenius form governed by the pre-exponential nucleation factor and interfacial energy. The interfacial energy is the energy required to create a new solid liquid interface for the formation of crystals in solutions. Traditionally, the interfacial energy is determined from the induction time measurements by assuming \( J \propto t_i^{-1} \).1,4−7 Generally, the higher the value of interfacial energy, the more difficult it is for the solute to crystallize.

As the nucleation behavior of the same solute is greatly influenced by the choice of solvent, the study of nucleation in various solvents has long been an important research subject.8−14 Recent studies have indicated an increasing trend of the interfacial energy with the increasing corresponding solute–solvent interaction for the same solute in various solvents.15−18 Apart from the interfacial energy, nucleation should also be influenced by the pre-exponential factor based on CNT. However, few studies have been published regarding to the influence of the solvent type on the pre-exponential factor for nucleation.

Although the pre-exponential factor is related to the solute mobility in solutions, it is also implicitly dependent on the interfacial energy of a crystalline solid according to the derivation of CNT2,3,19 which nevertheless has not been experimentally validated in the literature. Nucleation in various solvents for a system can provide important information for nucleation rate parameters. In this work, the influence of the solvent type on nucleation will be investigated based on CNT to examine the implicit relationship between the pre-exponential factor and interfacial energy in various solvents using the induction time data for three common model compounds widely studied in crystal engineering, including isonicotinamide, lovastatin, and phenacetin. The chemical structures of these compounds are given in Figure 1. Various

Figure 1. Chemical structures of (a) isonicotinamide, (b) lovastatin, and (c) phenacetin.

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THEORY

The nucleation rate based on CNT is expressed as:

\[
J = A_0 \exp \left[ -\frac{16\pi a_m^3 \gamma^3}{3k_B T^3 \ln^2 S} \right]
\]

(1)

where \( A_0 \) is the nucleation pre-exponential factor, \( \gamma \) is the interfacial energy, \( k_B \) is the Boltzmann constant, \( a_m = \frac{8v_{m}}{3S} \) is the molecular volume, and \( S = C_p / C_{eq} \) is the supersaturation ratio. As the solute attachment for small critical nucleus in a stirred solution should be interface-transfer control, it yields based on CNT:

\[
A_j \propto \gamma^{1/2} D_{AB}
\]

(2)

where \( D_{AB} \) is the solute diffusivity in the solution.

For simplicity, the solute diffusivity is usually estimated based on the Stokes–Einstein equation as:

\[
D_{AB} = \frac{k_B T}{6\pi \eta r}
\]

(3)

where \( r \) is the molecular radius of solute and \( \eta \) is the solution viscosity. As \( D_{AB} \) is generally assumed to be proportional to \( T/\eta (T, S) \) for the same solute among various solvents, the intrinsic nucleation factor \( A_0 \) is introduced in this work as:

\[
A_j = A_0 \frac{T}{\eta (T, S)}
\]

(4)

To differentiate between the effects of \( \gamma^{1/2} \) and \( T/\eta (T, S) \) on \( A_0 \), the intrinsic nucleation factor \( A_0 \) is introduced in this work as:

\[
A_j = A_0 \frac{T}{\eta (T, S)}
\]

(5)

Substituting eq 5 into eq 4 yields

\[
A_0 \propto \gamma^{1/2}
\]

(6)

Consequently, although \( A_j \) in eq 2 is dependent on \( D_{AB} \) among various solvents, \( A_0 \) is not related to the dependence of \( D_{AB} \) on \( T/\eta (T, S) \) among various solvents. Substituting eq 5 into eq 1 yields

\[
J = \frac{A_0 T}{\eta (T, S)} \exp \left[ -\frac{16\pi a_m^3 \gamma^3}{3k_B T^3 \ln^2 S} \right]
\]

(7)

Thus, \( J \) is expressed in terms of \( A_0 \) and \( \gamma \) as opposed to \( J \) commonly adopted in terms of \( A_j \) and \( \gamma \) in eq 1.

In the induction time study, the nucleation event is usually assumed to correspond to a point at which the total number density of accumulated crystals in a vessel has reached a fixed (but unknown) value, \( f_N \). Thus, one obtains at the nucleation time \( t_i \)

\[
f_N = J t_i
\]

(8)

where \( f_N \) depends on the measurement device and on the substance. Note that eq 8 is consistent with \( J \propto t_i^{-1} \) reported in the literature. Based on the study of 28 systems, Mersmann and Bartosch estimated \( f_N = 10^{-4} \) to \( 10^{-3} \) with a detectable size of 10 \( \mu \)m. If the intermediate value, \( f_N = 4 \times 10^{-4} \), for spherical nuclei with \( k_v = \pi/6 \) is assumed, it leads to \( f_N = 7.64 \times 10^{11} \) m \(^{-3} \) proposed by Shiu.

Substituting eq 1 into eq 8 yields

\[
\ln \left( \frac{1}{t_i} \right) = \ln \left( \frac{A_0}{f_N} \right) - \frac{16\pi a_m^3 \gamma^3}{3k_B T^3 \ln^2 S}
\]

(9)

Experimental induction time data can be evaluated by plotting \( \ln(1/t_i) \) versus \( 1/T^3 \ln^2 S \) for determination of \( \gamma \) from the slope and \( A_0 \) from the intercept, respectively. Substituting eq 7 into eq 8 yields

\[
\ln \left[ \frac{\eta (T, S)}{t_i T} \right] = \ln \left( \frac{A_0}{f_N} \right) - \frac{16\pi a_m^3 \gamma^3}{3k_B T^3 \ln^2 S}
\]

(10)

Experimental induction time data can be evaluated by plotting \( \ln[\eta(T,S)/t_iT] \) versus \( 1/T^3 \ln^2 S \) for determination of \( \gamma \) from the slope and \( A_0 \) from the intercept, respectively.

RESULTS AND DISCUSSION

Tables 1–3 list the experimental average induction time data of each solute in various solvents measured for various \( S \) at the

### Table 1. Experimental Induction Time Data of Isonicotinamide in Each Solvent for Various \( S \) at 303 K

| solute             | solvent   | \( S \) (×) | \( t_i \) (s) |
|--------------------|-----------|-------------|--------------|
| isonicotinamide    | methanol  | 1.43        | 664          |
|                    |           | 1.45        | 564          |
|                    |           | 1.50        | 400          |
|                    |           | 1.55        | 370          |
| acetone            |           | 1.20        | 1077         |
|                    |           | 1.25        | 330          |
|                    |           | 1.30        | 186          |
|                    |           | 1.40        | 122          |
| acetonitrile       |           | 1.10        | 2879         |
|                    |           | 1.13        | 1338         |
|                    |           | 1.14        | 787          |
|                    |           | 1.20        | 206          |
| ethyl acetate      |           | 1.05        | 1156         |
|                    |           | 1.07        | 605          |
|                    |           | 1.10        | 589          |
|                    |           | 1.15        | 341          |

### Table 2. Experimental Induction Time Data of Lovastatin in Each Solvent for Various \( S \) at 303 K

| solute   | solvent       | \( S \) (×) | \( t_i \) (s) |
|----------|---------------|-------------|--------------|
|lovastatin| ethyl acetate | 1.45        | 1139         |
|          |               | 1.50        | 970          |
|          |               | 1.60        | 573          |
|          |               | 1.70        | 275          |
|ethanol   |               | 1.40        | 1998         |
|          |               | 1.50        | 1240         |
|          |               | 1.70        | 633          |
|          |               | 1.90        | 357          |
|butyl acetate|            | 1.40        | 1156         |
|          |               | 1.45        | 788          |
|          |               | 1.50        | 531          |
|          |               | 1.70        | 363          |
|methanol  |               | 1.30        | 1389         |
|          |               | 1.40        | 889          |
|          |               | 1.50        | 378          |
|          |               | 1.70        | 278          |
|acetone   |               | 1.25        | 846          |
|          |               | 1.30        | 545          |
|          |               | 1.40        | 447          |
|          |               | 1.50        | 321          |
and the deviation of the induction time is generally less than 15%. In the following, eqs 9 and 10 are applied to determine the nucleation kinetics in various solvents using the induction time data for each system.

In the application of eq 10, the solution viscosities \( \eta(T,S) \) in various solvents for each system are experimentally measured in this work using a rotational viscometer (Brookfield DV2T). The measurements under each condition are repeated three times, and the deviation of the viscosity value is generally less than 6%.

Figure 2a shows the measured supersaturation dependence of solution viscosity for isonicotinamide in various solvents at 303 K, where \( C_{eq} \) for isonicotinamide in each solvent at 303 K is taken from a report by Hansen et al.22 (\( C_{eq} = 210 \text{ mg solute/g solvent} \) for methanol, \( C_{eq} = 11 \text{ mg solute/g solvent} \) for ethyl acetate, \( C_{eq} = 23 \text{ mg solute/g solvent} \) for acetonitrile, and \( C_{eq} = 37 \text{ mg solute/g solvent} \) for acetone). Figure 2b shows the measured induction time data fitted to eq 10 for isonicotinamide in various solvents at 303 K, where the induction time data are experimentally obtained in this work for various initial concentrations cooled to 303 K. Figure 2c shows that \( A_0 \) increases linearly with increasing \( \gamma^{1/2} \) for isonicotinamide in various solvents at 303 K, where \( A_0 \) and \( \gamma \) in each solvent are determined using the corresponding induction time data fitted.
to eq 10. On the other hand, Figure 2d shows that no clear relationship is observed between $A_J$ and $\gamma^{1/2}$ for isonicotinamide in various solvents at 303 K, where $A_J$ and $\gamma$ in each solvent are determined using the corresponding induction time data fitted to eq 9.

As shown in Figure 2a, $\eta$ increases in the order: acetone < acetonitrile < ethyl acetate < methanol. Although Figure 2c shows that $A_0$ increases in the order: ethyl acetate < acetonitrile < acetone < methanol, $A_J$ in Figure 2d increases in the order: ethyl acetate < methanol < acetonitrile < acetone, which is different from the increasing order of $A_0$. It should be noted that $\eta$ in methanol is significantly greater than that in other solvents. Consequently, although $A_0$ in methanol is the greatest among various solvents, $A_J$ in methanol becomes smaller than that in acetone or acetonitrile because of eq 5.

As shown in Figure 3a, $\eta$ increases in the order: acetone < acetonitrile < ethyl acetate < methanol. Although Figure 2c shows that $A_0$ increases in the order: ethyl acetate < acetonitrile < acetone < methanol, $A_J$ in Figure 2d increases in the order: ethyl acetate < methanol < acetonitrile < acetone, which is different from the increasing order of $A_0$. It should be noted that $\eta$ in methanol is significantly greater than that in other solvents. Consequently, although $A_0$ in methanol is the greatest among various solvents, $A_J$ in methanol becomes smaller than that in acetone or acetonitrile because of eq 5.

Figure 3a shows the measured supersaturation dependence of solution viscosity for lovastatin in various solvents at 303 K, where $C_{eq}$ for lovastatin in each solvent at 303 K is taken from a report by Sun et al.$^{30}$ ($C_{eq} = 38$ mg solute/g solvent for ethanol, $C_{eq} = 22$ mg solute/g solvent for butyl acetate, $C_{eq} = 52$ mg solute/g solvent for methanol, $C_{eq} = 31$ mg solute/g solvent for ethyl acetate, and $C_{eq} = 105$ mg solute/g solvent for acetone). Figure 3b shows the measured induction time data fitted to eq 10 for lovastatin in various solvents at 303 K, where the induction time data are experimentally obtained in this work for various initial concentrations cooled to 303 K. Figure 3c shows that $A_0$ increases linearly with increasing $\gamma^{1/2}$ for lovastatin in various solvents at 303 K, where $A_0$ and $\gamma$ in each solvent are determined using the corresponding induction time data fitted to eq 10. On the other hand, Figure 3d shows that no clear relationship is observed between $A_J$ and $\gamma^{1/2}$ for lovastatin in various solvents at 303 K, where $A_J$ and $\gamma$ in each solvent are determined using the corresponding induction time data fitted to eq 9.

Figure 4a shows the measured supersaturation dependence of solution viscosity for phenacetin in various solvents at 298 K, where $C_{eq}$ for phenacetin in each solvent at 298 K is taken from a report by Croker et al.$^{21}$ ($C_{eq} = 72$ mg solute/g solvent for ethanol, $C_{eq} = 24$ mg solute/g solvent for ethyl acetate, and $C_{eq} = 48$ mg solute/g solvent for acetonitrile).
Figure 4b shows the measured induction time data fitted to eq 10 for phenacetin in various solvents at 298 K, where the induction time data are experimentally obtained in this work for various initial concentrations cooled to 298 K. Figure 4c shows that $A_0$ increases linearly with increasing $\gamma^{1/2}$ for phenacetin in various solvents at 298 K, where $A_0$ and $\gamma$ in each solvent are determined using the corresponding induction time data fitted to eq 10. On the other hand, Figure 4d shows that no clear relationship is observed between $A_J$ and $\gamma^{1/2}$ for phenacetin in various solvents at 298 K, where $A_J$ and $\gamma$ in each solvent are determined using the corresponding induction time data fitted to eq 9.

As shown in Figures 2a, 3a, and 4a, the supersaturation dependence of solution viscosity in these systems is nearly negligible because of the narrow concentration range associated with the varied supersaturations. Table 4 lists the value of $\gamma$ and the correlation coefficient $R^2$ for each line in Figures 2b, 3b, and 4b. The value of $\gamma$ in each solvent for these systems agrees with the reported literature value.\textsuperscript{27,28} Note that the correlation coefficient in each solvent for these systems exceeds the critical value of 0.900 for the 90% confidence interval and 4 points (i.e., degree of freedom = 2).

Table 5 lists comparison between the correlation coefficient for each line in Figures 2c, 3c, and 4c and the corresponding critical value based on the 95% confidence interval. As the correlation coefficient for these systems exceeds the corresponding critical value based on the 95% confidence interval, it is concluded that $A_0$ increases linearly with increasing $\gamma^{1/2}$ in various solvents for each system. As an increasing trend of the interfacial energy with the increasing corresponding solute—solvent

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**Table 4. Value of $\gamma$ and the Correlation Coefficient for Each Line in Figures 2b, 3b, and 4b**

| solute     | solvent       | $\gamma$ (mJ/m^2) | $R^2$  |
|------------|---------------|-------------------|--------|
| isonicotinamide | methanol     | 3.32              | 0.973  |
|             | acetone       | 2.53              | 0.992  |
|             | acetonitrile  | 1.72              | 0.951  |
|             | ethyl acetate | 0.77              | 0.900  |
| lovastatin  | ethyl acetate | 1.94              | 0.915  |
|             | ethanol       | 1.72              | 0.959  |
|             | butyl acetate | 1.62              | 0.974  |
|             | methanol      | 1.44              | 0.926  |
|             | acetone       | 1.08              | 0.965  |
| phenacetin  | ethanol       | 1.17              | 0.964  |
|             | acetonitrile  | 0.674             | 0.960  |
|             | ethyl acetate | 0.632             | 0.943  |
interaction for the same solute in various solvents has been reported in the literature, it is speculated that the effect of this interaction on $\gamma$ is also strongly correlated with that on $A_0$, for the same system. Consequently, if the choice of solvent results in a smaller $\gamma$ because of a weaker solute–solvent interaction, it simultaneously results in a smaller $A_0$. On the other hand, if the choice of solvent results in a larger $\gamma$ because of a stronger solute–solvent interaction, it simultaneously results in a smaller $A_0$.

## CONCLUSIONS

According to CNT, $A_1 = A_0 \frac{T}{\eta}$ is proposed in this work.

Equation 10 is derived to investigate the nucleation kinetics in various solvents using the induction time data for isonicotinamide, lovastatin, and phenacetin. Although no clear relationship is observed between $A_1$ and $\gamma^{1/2}$ among various solvents for each system, $A_1$ increases linearly with increasing $\gamma^{1/2}$ among various solvents for each system, which is consistent with eq 6 derived based on CNT. Based on the analyzed results of nucleation kinetics in these systems, it is proposed that $A_1$ consists of two parts: the first part $T/\eta$ is proportional to $D_{AB}$, and the other part $A_0$ is proportional to $\gamma^{1/2}$. Although $A_1$ is dependent on $D_{AB}$ among various solvents, $A_0$ is not related to the dependence of $D_{AB}$ on $T/\eta(T,S)$ among various solvents. It is speculated that both $\gamma$ and $A_0$ are proportional to the solute–solvent interaction for the corresponding solvent.

## EXPERIMENTAL SECTION

The experimental apparatus consists of a 250 mL crystallizer immersed in a programmable thermostatic water bath shown in Figure 5. The crystallizer is equipped with a magnetic stirrer at a constant stirring rate 350 rpm. The turbidity probe (Crystal Eyes manufactured by HEL limited) is used to detect the nucleation event during the induction time study.

The induction times for three crystallization systems, including isonicotinamide (Alfa Aesar, purity 99%), lovastatin (Acros, purity 98%), and phenacetin (Acros, purity 78%) are measured in this work. Analytical grade solvents (purity 99.9%) are used to prepare the supersaturated solution. In each experiment, a 200 mL solution with the desired supersaturation is loaded into the crystallizer. The solution is held at 3 °C above the saturated temperature for 5–10 min to ensure a complete dissolution at the beginning of the experiment, which is also confirmed by the turbidity measurement. Then, the supersaturated solution is rapidly cooled to the desired temperature for the induction time measurements.

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**Notes**

The author declares no competing financial interest.

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**NOTATION**

$A_B$, pre-exponential nucleation factor (m$^{-3}$ s$^{-1}$)

$A_0$, intrinsic nucleation factor (Pa m$^{-6/2}$ s$^{-3}$)

$C_p$, initial concentration of solute molecules (m$^{-3}$)

$C_{eq}$, equilibrium concentration of solute molecules (m$^{-3}$)

$D_{AB}$, solute diffusivity (m$^2$/s)

$f_{MN}$, minimum detectable number density of accumulated crystals (m$^{-3}$)

$f_{V}$, minimum detectable volume fraction of accumulated crystals (-)

$f_i$, nucleation rate (m$^{-3}$ s$^{-1}$)

$k_B$, Boltzmann constant (=1.38 × 10$^{-23}$ J/K)

$k_v$, volume shape factor (-)

$M$, molar mass (kg/mol)

$N_A$, Avogadro number (=6.02 × 10$^{23}$ mol$^{-1}$)

$r_m$, molecular radius of solute (m)

$S$, supersaturation ratio (-)

$T$, temperature (K)

$i$, time (s)

$t_i$, induction time (s)

$V_m$, volume of the solute molecule (m$^3$)

**GREEK LETTERS**

$\gamma$, interfacial energy (J/m$^2$); $\rho$, crystal density (kg/m$^3$); $\eta$, solution viscosity (Pa s)

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