

GROWTH AND SOLVENT-MEDIATED PHASE TRANSITION OF CIMETIDINE POLYMORPHIC FORMS A AND B

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For the organic compound cimetidine, which has seven polymorphic forms, the growth rates of form A (metastable) and B (stable) and the solvent-mediated phase transition rates from A to B were measured in 2-propanol solvent. At high supersaturation ratio ($S_{C,A}=3.6$), with form-A seed, agglomerated crystals of form A were obtained without an induction period. With form-B seed, by contrast, form A nucleated heterogeneously on B seed's surface and then grew to single-like crystals after the induction period. At low supersaturation ratio ($S_A \leq 1.3$, $S_B \leq 1.7$), the growth rate of form A was higher than that of form B at the same supersaturation ratio, S_i , based on their respective solubilities, but at the same solute concentration this tendency was reversed. At $S_A=1.0$, a solvent-mediated phase transition took place, being controlled by the growth rate of form B. The growth rates of both forms at low supersaturation were proportional to the surface area of crystal and $(S_i - 1)^2$.

Introduction

Previously⁷⁾, the solubilities and crystallization behavior of cimetidine¹⁾, *N*-cyano-*N'*-methyl-*N''*-[2-[(5-methyl-1*H*-imidazol-4-yl)-methyl-thio]-ethyl]-guanidine, were studied, and it was found that form A is more soluble than form B in H₂O, 2-propanol (IPA) and H₂O-IPA mixed solvent, and that, using IPA as a solvent, only form A is crystallized regardless of the presence or absence of seeds at $S_A \geq 4.5$, or of the kinds of seed form at $S_A \geq 3.6$. On the other hand, at low supersaturation ratio ($S_A \leq 2.0$) the same form as that of seed is crystallized.

In this work, growth of form A at high supersaturation ratio ($S_{C,A}=3.6$) with different kinds of seed and growth rates of forms A and B at low supersaturation ratio ($S_A \leq 1.3$, $S_B \leq 1.7$) were studied. Further, the rates of solvent-mediated phase transition from form A to B were measured at $S_A=1.0$.

1. Experimentals

All crystallization experiments were carried out in a jacketed cylindrical glass vessel of 553 ml volume ($\phi 80 \times 110$ mm) with a stirrer consisting of a glass rod with two paddles of 40 mm length and 10 mm width at 45° angle, using IPA as a solvent.

Exp. 1 (growth of form A at high S [—] ($= C/C_s$, where C_s : equilibrium solubility)) and Exp. 2 (growth of forms A and B at low S): A solution of a given concentration C_0 , which was perfiltered through a

0.45- μ m milipore membrane, was added to the vessel. Then the solution was cooled to a given temperature, T_c , as quickly as possible (at a rate of about 10 K/min), followed by the addition of seed crystals. Exp. 3 (solvent-mediated phase transition ($S_A=1.0$): Growth rate of form B: Admitting a mixture of forms A and B seed crystals into 500 ml of solution with $C_0=0.152$ mol/l (equal to the solubility of form A, i.e., $S_A=1.0$), under agitation, and then the solution concentration and the content ratio of forms A and B in the crystals were measured. Solid samples were obtained by filtration of aliquots of the suspended solution.

All the seed crystals were used after washing by unsaturated solution. The seed crystals used for the growth experiments of form A at high supersaturation ratio (Exp. 1) are shown in **Table 1**. The seed crystals used in the other experiments were commercial ones, with sieving between 35 and 100 mesh (Exp. 2) and without sieving (Exp. 3).

The concentration of cimetidine in solution was determined from the intensity of UV absorption at

Table 1. Seed crystal used in Exp. 1 (Sec. 2.1)

| Key | Form | Preparation of seed | Weight [g] |
|----------------|------|---------------------|------------|
| A1 | A | commercial | 0.2 |
| A2 | A | crushed | 0.2 |
| A3 | A | recrystallized | 0.2 |
| B ₁ | B | commercial | 0.2 |
| B ₂ | B | commercial | 0.05 |
| B ₃ | B | commercial | 0.01 |

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218 nm, using a Shimadzu UV-140. Identification of polymorphic crystal forms was made by their characteristic infrared band peaks⁵ [cm^{-1}]; A: 1204, 1156, B: 1184, using a Shimadzu FTIR-4300. The content ratio of forms A to B in a mixed crystal was determined in the range of 0–100% by using the following characteristic peaks of the X-ray diffraction pattern: A: $2\theta=16.4^\circ$, B: $2\theta=21.1^\circ$, using a Shimadzu XD-610. Observations by optical microscope (OLYMPUS IMT-2) and scanning electron microscope (Shimadzu EPM-810) were also carried out.

Cimetidine powder (supplied by Fujimoto Pharmaceutical Co.) and guaranteed reagent-grade 2-propanol (Wako Chemicals Co.) were used without further purification.

Experimental conditions were as follows; Exp. 1: growth of form A at high S [—] ($=C/C_s$, where C_s : equilibrium solubility): initial concentration, C_0 [mol/l]=0.137, S at initial crystallization $S_{C,A}=3.6$, $S_{C,B}=4.8$, crystallization temperature T_c [K]=293.2, agitation rate N_r [min^{-1}]=600, seed: see Table 1; Exp. 2: growth of form A or B at low S : $C_0=0.053$ –0.214, $S_{C,A}=1.41$ for the growth experiments of form A, $S_{C,B}=1.70$ –1.88, for the growth experiments of form B, $T_c=293.2, 303.2, 323.2$, $N_r=600$; seed: A or B 1.5 g (35/100 mesh); Exp. 3: solvent-mediated phase transition: $C_0=0.152$, $S_{C,B}=1.0$, $S_{C,A}=1.25$, $T_c=323.2$, $N_r=400,600$; seed: total initial weight $W_0=W_{A0}+W_{B0}=6.0$ g, initial content ratio of form B $\Gamma_0=W_{B0}/(W_{A0}+W_{B0})=0.22, 0.25, 0.50$.

The physical properties of cimetidine are as follows: MW [g/mol]=252, ρ_s [g/cm^3]=1.3², v_m [cm^3]=193.8, d [nm] ($= (v_m/N_A)^{1/3}$)=0.69, a [nm^2] ($=d^2$)=0.47, m_p [K]⁶=414–416 (form A), 415–418 (form B), 418–419 (form C).

2. Results and Discussion

2.1 Exp. 1: Growth of form A at high initial supersaturation ratio ($S_{C,A}=3.6$)

In this experimental condition, only form A was crystallized regardless of the form of seed crystals, in a similar manner as shown in the previous report⁷. **Figure 1** shows the time course of solute concentration in the presence of different kinds of seed, accompanying the crystallization of form A. Observation by FTIR and optical microscope showed that nucleation and growth of form B did not occur. From Fig. 1, crystallization with form-A seed took place without an induction period. With form B-seed, however, there is apparently an induction period (waiting time), and it increased with decrease in the weight of seed. No crystallization occurred without seed. Previously, secondary nucleation of form A was found to take place at a detectable rate at 1000 min of processing

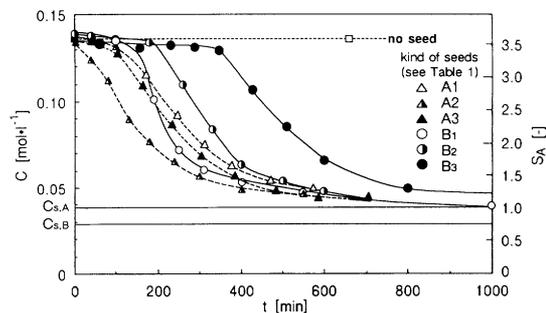


Fig. 1. Time course of solute concentration with different kinds of seed. $T_c=293.2$, $N_r=600$

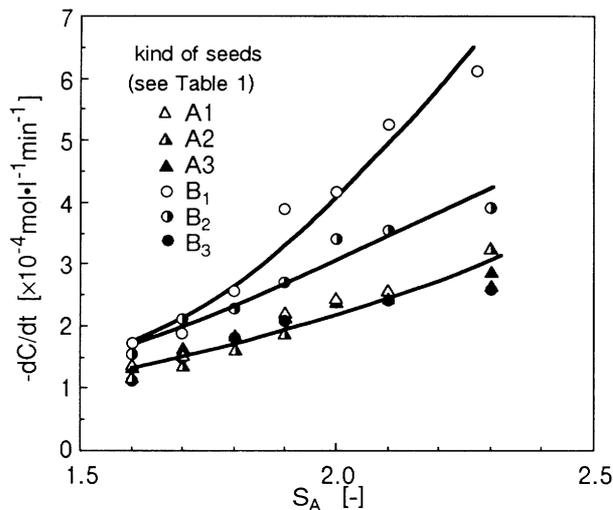


Fig. 2. $-(dC/dt)$ vs. S_A . $T_c=293.2$, $N_r=600$

time, $S_A=2.2$, with $A1=0.1$ g⁷). Therefore, it was considered that in this experimental condition, the secondary nucleation of form A takes place vigorously at the initial stage, and then the crystals thus produced are grown. **Figure 2** shows the slopes ($-dC/dt$) of the curves in Fig. 1 in the $S_A=1.6$ to 2.3 region as determined by the mirror method⁴, which corresponds to the crystallization rate, vs. the dimensionless solute concentration (S_A). As can be seen from Fig. 2, the rates obtained with form-A seeds are almost the same for different seeds, A1, A2 and A3. As to form-B seeds, the rates become higher with increase in seed weight.

Figure 3 shows photographs of seeds (A1, A2, A3, B, see Table 1) and typical examples of form-A crystals finally obtained (a, b, see Table 1), and **Fig. 4** shows SEM photographs of crystals in the progress of crystallization with form-B seed. Regardless of the type of form-A seed (A1, A2, A3), the final product crystals were always obtained as agglomerated crystals as shown in Fig. 3a. As mentioned above, in the case of adding the form-A seed, it was considered that secondary nucleation takes place vigorously at the initial stage.

As to form-B seed, single like crystals of form A

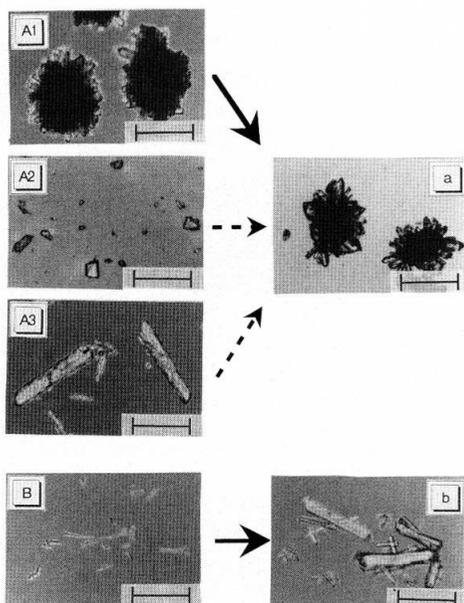


Fig. 3. Photographs of seed crystals (A1, A2, A3, B) and crystals obtained (a, b) a, obtained with seed A1, at 1205 min; b, with seed B₃, at 1055 min; scale, 100 μm

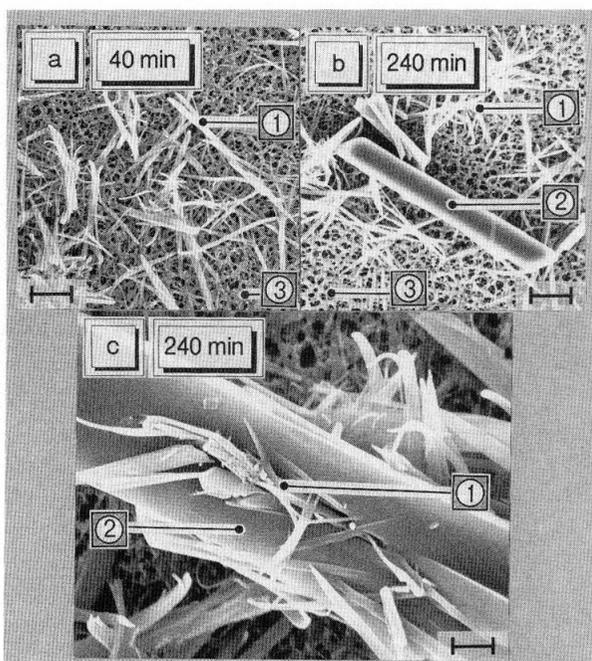


Fig. 4. SEMs of form A crystal, during crystallization with form-B seed (B₃)
1, form-B seed; 2, form-A crystal; 3, fiber of filter paper scale,
(a), (b) 20 μm; (c) 4 μm

were obtained and no growth of the seed was observed, as shown in Fig. 3b and Fig. 4. Occasionally, partial incorporation of seed into newly produced form-A crystal was observed, as shown in Fig. 4c. From these facts, form A is considered to nucleate heterogeneously on the surface of form-B seed and then to grow preferentially.

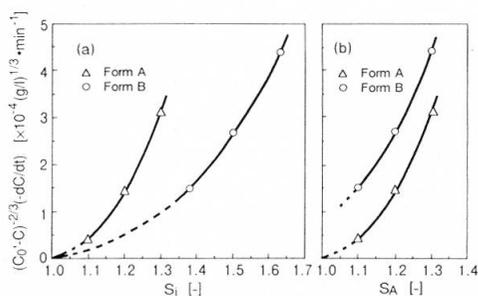


Fig. 5. Growth rates of forms A and B at low S
 $T_c = 323.2$; $N_r = 600$; Seeds, A or B 1.5 g (35/100 mesh)

2.2 Exp. 2: Growth of forms A and B at low initial supersaturation ratios ($S_{C,A} = 1.4$ and $S_{C,B} = 1.7$)

Under these experimental conditions, only the growth of the seed crystals took place⁷⁾. Therefore, the data of C vs. t were arranged, on the assumption that the growth rate is proportional to the total surface area of crystals. Figure 5 shows the relation between $(C_0' - C)^{-2/3} (-dC/dt)$ and the supersaturation ratio, where $C_0' = C_0 + w_i/MW$, w_i is the weight of seed crystals per 1000 cm³ of suspended solution expressed in grams and MW is the molecular weight of cimetidine. The supersaturation ratio based on the respective solubilities of each form are different at the same solute concentration, because of the difference in solubility between forms A and B ($C_{s,A} > C_{s,B}$). Therefore, in Fig. 5a the ratio based on their own solubilities was taken as the abscissa, denoted by S_i ; i.e., for form A, $S_i = C/C_{s,A} = S_A$ and for form B, $S_i = C/C_{s,B} = S_B$.

From Fig. 5, The growth rate of form A is higher than that of form B at the same supersaturation ratio for the respective form (Fig. 5a), however, at the same solute concentration this tendency is reversed (Fig. 5b). This may be the reason why the same form as that of seed was crystallized at low supersaturation, contrary to the crystallization behavior at high supersaturation (see 2.1). That is, even if the form-A crystals are born via heterogeneous nucleation on the surface of form-B seed in the same manner as at high supersaturation, form B grows at a more sufficient rate than form A.

Figure 6 shows the growth rate data rearranged by taking $(S_i - 1)$ as the driving force, where the slope of the straight line was estimated to be 2.0. Thus the growth rates of both crystals forms at this low supersaturation ratio probably obey the following relation, based on BCF theory.

$$-dC/dt = k_1(C_0' - C)^{2/3}(S_i - 1)^2; \quad C_0' = C_0 + w_i/MW \quad (1)$$

2.3 Exp. 3: Solvent-mediated phase transition ($S_A = 1.0$): Growth rate of form B.

Figure 7 shows the data obtained with unsieved crystals at $N_r = 600$. Though the solute concentration was at a constant value, ($C = 0.152 \text{ mol/l}$, $S_A = 1.0$,

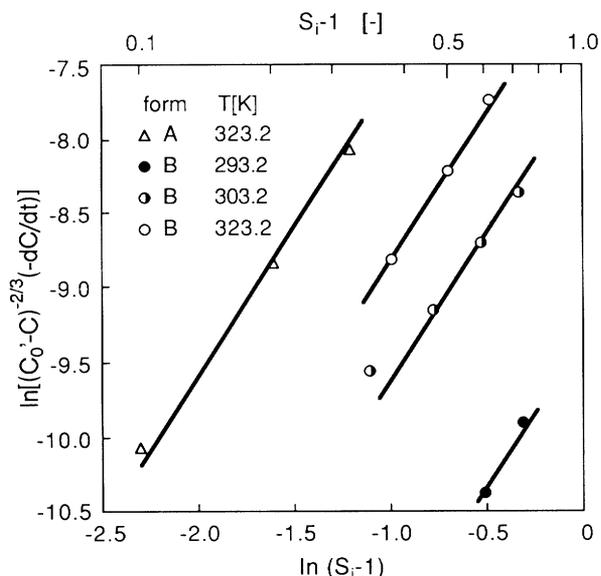


Fig. 6. Growth rates of forms A and B at low S
 $N_r=600$; Seed, A or B 1.5 g (35/100 mesh)

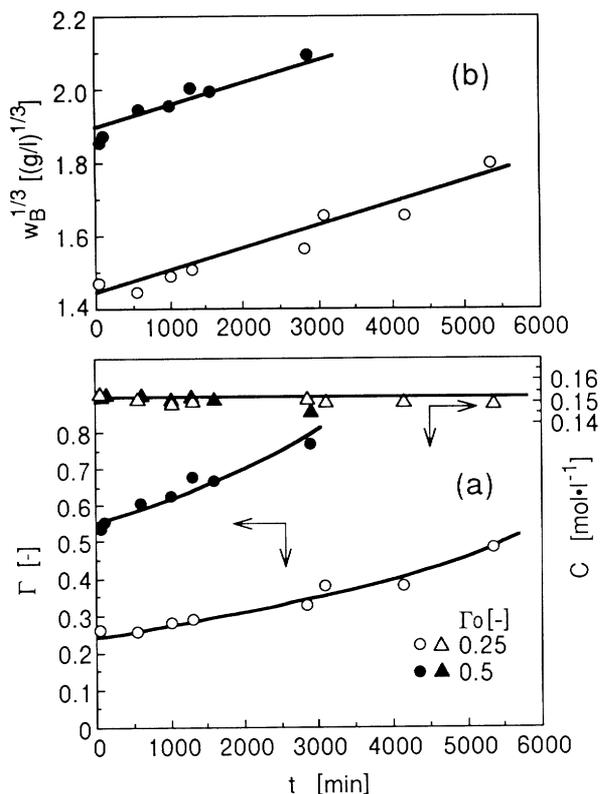


Fig. 7. Solvent-mediated phase transition from form A to form B
 $T_c=323.2$; $N_r=600$

$S_B=1.25$), the content ratio of form B, Γ , increased (Fig. 7a). This means that the solvent-mediated phase transition from form A to form B proceeds at constant weight of total crystals, under the condition that the growth rate of form B is the rate determining step³⁾. Since the growth rate of crystals is proportional to the crystal surface, the rate is expressed by

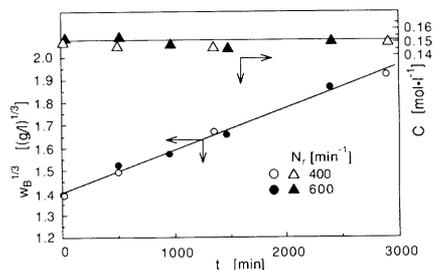


Fig. 8. C and $w_B^{1/3}$ vs. time
 $T_c=323.2$; Seed, 35/100 mesh; $\Gamma_0=0.22$

$$dw_B/dt = k_2 w_B^{2/3} f(X) \quad (2)$$

or

$$w_B^{1/3} - w_{B,0}^{1/3} = k_2' f(X) t, \quad k_2' = k_2/3 \quad (3)$$

where w is the weight of crystals in 100 cm^3 of suspended solution and X is the driving force for crystal growth. In this experiment, the solute concentration was constant and hence $f(X)$ was constant in progress of the growth of form B. Therefore, $w_B^{1/3}$ increases linearly with transition time, proving Eq. (2). This was the case, as shown in Fig. 7b. Figure 8 shows the time course of the solute concentration and the weight of form B expressed by $w_B^{1/3}$ obtained under the same conditions as those of "O" in Fig. 6. From Fig. 8, the linear relation between $w_B^{1/3}$ and t were independent of the agitation rate, meaning that the growth rate is not controlled by the mass transfer rate of solute.

In Section 2.2, the growth rate at low supersaturation ratio was found to be expressed by Eq. (1). Therefore, assuming $f(X)$ in Eq. (2) to be $(S_B - 1)^2$,

$$dw_B/dt = k_2 \cdot w_B^{2/3} \cdot (S_B - 1)^2 \quad (4)$$

In what follows, the growth rates in Figs. 6 and 8 were compared. From the slope of the straight line between $w_B^{1/3}$ and $t (= k_2' \cdot (S_B - 1)^2)$ and $S_B = 1.25$ (Fig. 8), $k_2 = 3 \cdot k_2'$ was estimated to be $9.0 \times 10^{-3} (\text{g/l})^{1/3}/\text{min}$. From Eq. (1) and the data at 323.2 K in Fig. 6, k_1 was evaluated to be $1.14 \times 10^{-3} (\text{mol/l})^{1/3}/\text{min}$. Comparing Eqs. (1) and (4), $k_2 = k_1 (\text{MW})^{1/3} = 6.32 \cdot k_1 [(\text{g/l})^{1/3}/\text{min}]$. Putting the value of k_1 , the value estimated from the data in Fig. 6 was $7.2 \times 10^{-3} (\text{g/l})^{1/3}/\text{min}$. These two values are almost the same. Therefore, the growth rates of both forms were found to be represented by Eqs. (1) or (4) in the range of $S_A = 1.3-1.1$, $S_B = 1.7-1.2$.

Conclusion

The growth and solvent-mediated phase transition have been measured in IPA solvent and the following results were obtained.

1) At high supersaturation ratio of $S_{C,A} = 3.6$, only form A was crystallized regardless of the form of seed. With form-A seed, the crystals were obtained as

agglomerated ones, without an induction period. With form-B seed, single like crystals were obtained with an induction period at higher growth rate than that for crystals obtained with form-A seed.

2) At low supersaturation ratio of $S_A \leq 1.3$, $S_B \leq 1.7$, only the growth of seed crystals proceeded, obeying Eq. (1). The growth rate of form A was higher than that of form B at the same supersaturation based on their own solubilities, but this tendency was reversed at the same solute concentration.

3) As $S_A = 1.0$, a solvent-mediated phase transition from A to B took place, being controlled by the growth rate of form B. The latter rate was expressed by Eq. (4), which was found to be equivalent to Eq. (1).

Acknowledgement

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Nomenclature

| | | |
|------------------|---|----------------------|
| a | = area occupied by unit solute in surface, $= d^2$ | [nm ²] |
| C | = solute concentration | [mol/l] |
| C_0 | = initial concentration | [mol/l] |
| C_0' | = $C_0 + w_i/MW$ | [mol/l] |
| C_s | = equilibrium solubility | [mol/l] |
| d | = solute diameter | [nm] |
| $f(X)$ | = function of X | |
| k | = Boltzmann constant | [J/m ²] |
| k_1, k_2, k_2' | = growth rate constant defined in Eqs. (1), (2) and (3), respectively | [—] |
| MW | = molecular weight | [g/mol] |
| N_r | = agitation rate | [min ⁻¹] |
| S | = supersaturation ratio ($= C/C_s$) | [—] |
| S_c | = S at initial crystallization | [—] |

| | | |
|----------|--|----------------------|
| S_i | = supersaturation ratio based on respective forms in the same solute concentration, $i=A$ or B | [—] |
| T | = absolute temperature | [K] |
| T_c | = T at crystallization | [K] |
| v_m | = molar volume of crystal | [cm ³] |
| w | = total weight of suspended crystals per 1000 cm ³ of suspended solution | [g/l] |
| w_i | = weight of seed crystals per 1000 cm ³ of suspended solution, $i=A$ or B | [g/l] |
| W | = total weight of seed crystals per 1000 cm ³ of suspended solution | [g/l] |
| W_i | = weight of form- i crystals in mixed crystals, $i=A$ or B | [g] |
| X | = function of supersaturation corresponding to driving force for crystal growth | |
| Γ | = content ratio of form B in mixed crystal | [—] |
| ρ_s | = density of crystal | [g/cm ³] |

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