

Kinetics of Cross-Nucleation between Polymorphs

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We report the first kinetic measurement of cross-nucleation between polymorphs, a newly discovered phenomenon important to the theory and control of crystallization. D-Mannitol crystallized from its melt first as the least stable δ polymorph and then as the second least stable α polymorph, with α nucleating on δ . The kinetics of cross-nucleation was determined from the frequencies of α nuclei appearing on δ spherulites, the distances between α and δ nuclei, and the growth rate of the δ spherulite. The presence of poly(vinylpyrrolidone), a noncrystallizing, melt-miscible additive, increased the rate of cross-nucleation.

How does nucleation occur in a polymorphic system (a system able to crystallize in different structures of the same chemical composition)? The question is important to the makers of drugs and specialty chemicals and to the basic understanding of nucleation.¹ Ostwald postulated that the least stable polymorph should crystallize first, followed by the conversion to the second least stable polymorph, and so on to the most stable.² Other theories hold that different polymorphs nucleate independently.^{3–5} Recently, cross-nucleation between polymorphs has been identified as a viable mechanism of crystallization in polymorphic systems.^{6–8} By this mechanism, an early nucleating polymorph does not consume the entire liquid or undergo solid-state transformation, but nucleates another polymorph of higher or lower thermodynamic stability and of faster or comparable growth rate. This phenomenon indicates that the pathway of crystallization is not controlled solely by the initial nucleation, but also by the cross-nucleation between polymorphs and the relative growth rates of polymorphs.

Herein we report the first kinetic measurement of cross-nucleation between polymorphs. We used as model systems D-mannitol and 10% w/w poly(vinylpyrrolidone) (PVP) in D-mannitol, which enable identification and counting of cross-nucleation sites.⁶ The PVP (GAF Chemicals) was K15 (mw \approx 8000) and K30 (mw \approx 50000). 0.8 ± 0.1 mg of D-mannitol (99+%, Aldrich) or 10% PVP in D-mannitol was melted at 180 °C between two cover glasses on a microscope hot stage (Linkam THMS 600) and cooled at 20 °C/min to desired temperatures of crystallization (103–120 °C). The PVP, a noncrystallizing, melt-miscible additive, slowed the crystallization of D-mannitol and helped identify phase boundaries and cross-nucleation sites. To ensure good mixing, a cryogenic impact mill (SPEX CertiPrep model 6750) was used to prepare the D-mannitol/PVP mixtures.⁹ D-Mannitol, which has three polymorphs (α , β , and δ),¹⁰ crystallized first as δ and then as α , with α nucleating on δ (Figure 1).⁶ Once an α nucleus formed on a δ spherulite, the two polymorphs grew simultaneously and competed for the remaining liquid. Because the new polymorph

grew faster (see later), an “angle of spread” θ resulted (Figure 1a). In the presence of PVP, the spherulites of both polymorphs were banded when viewed between crossed polarizers. The banding of the δ spherulite was narrower and fainter than that of the α spherulite. Such banding is generally attributed to the periodic twisting of crystal fibrils. The polymorphs were identified by melting point¹¹ and Raman microscopy (Renishaw System 1000 with HeNe laser). X-ray diffraction (Bruker D8 Advance) showed that the crystals of each polymorph grew along the c axis (the shortest unit-cell dimension). Thus the growth front of the spherulite was likely the (001) face. As the temperature decreased, the frequency of cross-nucleation increased and the distance from the center of a δ spherulite to the site of α nucleation (R_δ) decreased. Below 110 °C, spontaneous nucleation of α was occasionally observed; but above 110 °C, δ always nucleated first and α could not nucleate without the aid of δ . On rare occasions, the β polymorph crystallized first (instead of δ), and on its surface the α polymorph also nucleated.

We define the rate of cross-nucleation, $J_{\alpha/\delta}$, as the number of α nuclei formed on one m^2 of the δ surface in one second. For a δ spherulite of radius R_δ and thickness h on which no prior cross-nucleation has occurred, the surface area available for cross-nucleation is $A = 2\pi R_\delta h$ [the area of the growth front] and the number of α nuclei formed during time dt is $dn(t) = J_{\alpha/\delta} A dt = 2\pi J_{\alpha/\delta} R_\delta h dt$. Integrating the last equation and using $R_\delta = v_\delta t$, where v_δ is the growth rate of the δ spherulite, we obtain

$$n = \left(\frac{J_{\alpha/\delta} \pi h}{v_\delta} \right) R_\delta^2 \quad (1)$$

Equation 1 shows that $J_{\alpha/\delta}$ can be calculated from the slope of the $n - R_\delta^2$ plot, h , and v_δ . h was estimated to be 2.7 ± 0.2 μm , from the sample's mass, area, and density (≈ 1.5 g/cm^3). We measured v_δ from the advance speed of a growth front by video microscopy (Figure 2). The same measurement yielded the growth rate of the α polymorph, v_α , and on the rare occasions when the β polymorph nucleated first, that of the β polymorph, v_β . Whenever measurable, v_β was found to be

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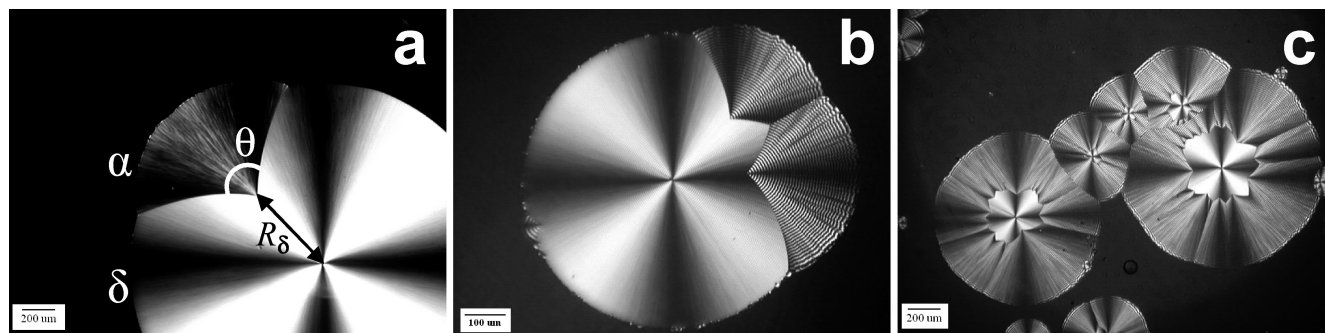


Figure 1. Crystallization of D-mannitol containing 10% w/w PVP (K30) at 115 °C (a), 110 °C (b), and 105 °C (c). The δ polymorph crystallized first and the α polymorph next, with α nucleating on δ . For each polymorph, the growth direction is c and the growth front is (001).

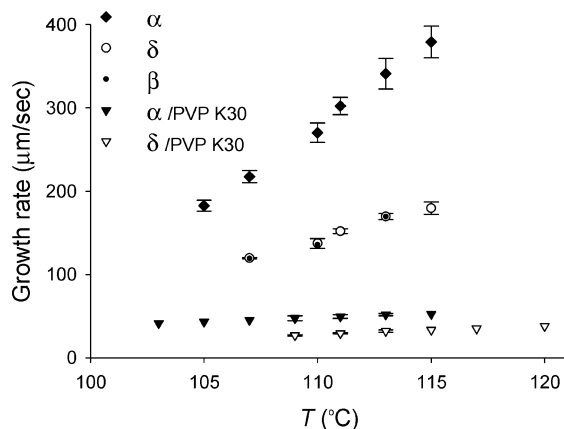


Figure 2. Growth rates of D-mannitol polymorphs in pure liquid and in the presence of 10% w/w PVP. Error bars are shown unless only single measurements were made because crystallization might occur before a low target temperature was reached or spontaneous crystallization rarely occurred at high temperature.

similar to v_δ . Both v_δ and v_β were significantly smaller than v_α . The ratio v_α/v_δ was 2.02 ± 0.08 and 1.67 ± 0.10 in pure D-mannitol and in D-mannitol containing 10% PVP, respectively. The addition of 10% PVP reduced the growth rate of D-mannitol by 5–10-fold; the reduction by PVP K30 was slightly larger (by 1–5 $\mu\text{m/s}$) than by PVP K15. The ratio v_α/v_δ was also estimated from the angle of spread θ (Figure 1). θ increases with v_α/v_δ according to $\cos \theta/2 = v_\delta/v_\alpha - (v_\alpha^2 - v_\delta^2)/2R_\delta v_\alpha t$, where t is the time elapsed from the moment of cross-nucleation.¹² At $t = 0$, $\cos \theta/2 = v_\delta/v_\alpha$. v_α/v_δ calculated from θ agreed with those directly measured (Figure 2). Because it grew faster, the α polymorph could dominate the crystallization product, despite its slow spontaneous nucleation. This result agrees with the previous finding that to be observable, a cross-nucleated polymorph needs to grow faster than or as fast as the initial one.⁷

To obtain the $n - R_\delta^2$ relation, we analyzed at each temperature of interest, a total of 40–80 δ spherulites from 4 to 20 crystallization experiments. For each δ spherulite, we recorded the R_δ values of all cross-nucleation sites (see Figure 1 for examples). The results from all the δ spherulites analyzed were combined into a single list $\{R_{\delta i}, i = 1, 2, \dots\}$ and sorted in ascending order ($R_{\delta 1} < R_{\delta 2} < \dots$). From this list, the average number of α nuclei on one δ spherulite within $R_{\delta i}$ could be calculated from $n = i/n_\delta$, where n_δ is the total number of δ spherulites analyzed. Figure 3 shows the $n - R_\delta^2$ relation thus obtained at 105, 107, and 110 °C for D-mannitol and 109, 111, and 113 °C for D-mannitol containing 10% w/w PVP K30. Except for steeper slopes, the plots for 10% PVP K15 in D-mannitol were similar to those in Figure 3b and not shown.

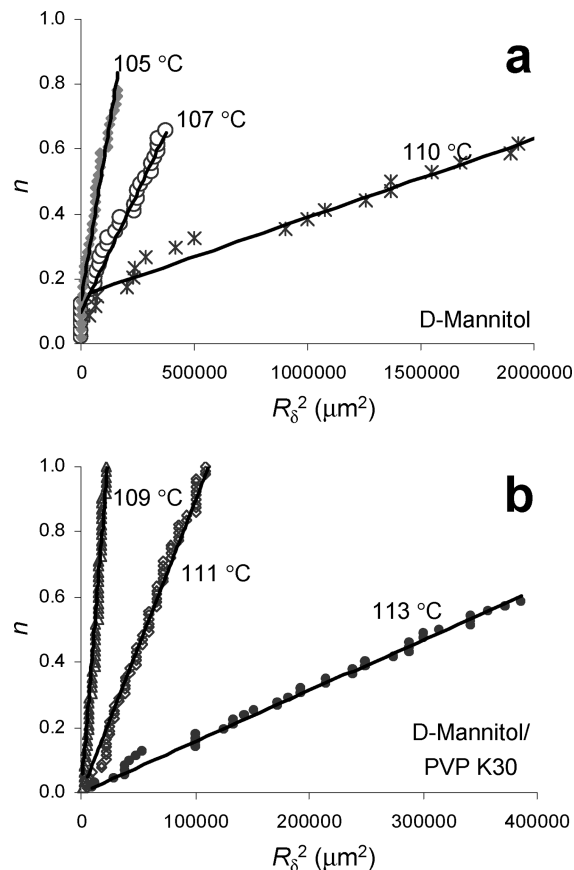


Figure 3. The $n - R_\delta^2$ plots used for calculating rates of cross-nucleation. (a) D-mannitol. (b) 10% PVP K30 in D-mannitol.

The temperature range was limited at the low end by the minimal separation between individual α nuclei that must exist for reliable counting, and at the high end by the minimal rate of cross-nucleation that must be reached to observe events of cross-nucleation. Under our experimental conditions, most δ spherulites (> 95%) were covered by α crystals before they grew to contact with each other or with the edge of the sample. Thus, the $n - R_\delta^2$ data characterized the cross-nucleation on an average isolated δ spherulite.

Figure 3 shows only the early data corresponding to the first appearance of an α nucleus on a δ spherulite. For each line, the R_δ value at $n = 1$ was that size of the δ spherulite at which, on average, every δ spherulite surveyed contained one α nucleus. Thus, each line described the frequency of cross-nucleation on an average δ spherulite on which events of cross-nucleation did not affect each other. This fulfills the condition under which eq 1 is derived. In later stages of crystallization, the surface of a δ spherulite was partially covered by α crystals,

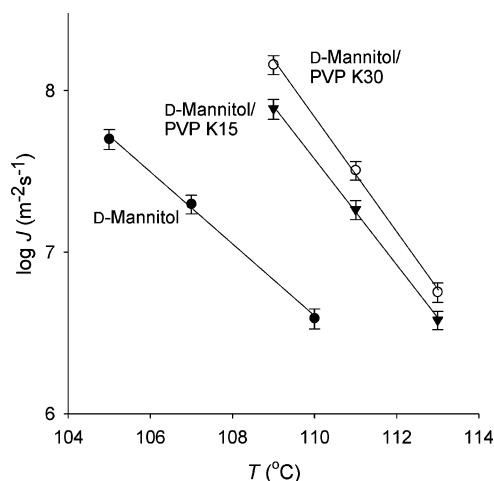


Figure 4. Kinetics of cross-nucleation between polymorphs.

which caused the $n - R_\delta^2$ plot to deviate from linearity. It is noteworthy that the lines in Figure 3a have nonzero intercepts. This perhaps resulted from the faster cross-nucleation on non-(001) faces of the δ polymorph, which were still exposed when the δ spherulite was small. As it grew larger, only the (001) face was exposed and the subsequent data characterized the cross-nucleation rate on that face.

Figure 4 shows the cross-nucleation rate $J_{\alpha/\delta}$ in D-mannitol and D-mannitol containing 10% w/w PVP calculated from h , v_δ , and the slope of the $n - R_\delta^2$ plot. v_δ in D-mannitol at 105 °C was obtained by extrapolating high-temperature data because the δ polymorph did not grow large enough to be measured at 105 °C before cross-nucleation occurred. The error bar is one standard deviation.¹³ In all three systems, $J_{\alpha/\delta}$ increased with decreasing temperature. The presence of 10% PVP increased $J_{\alpha/\delta}$ by about 1 order of magnitude at the same temperature. The increase was greater by PVP K30 than by PVP K15. The increase of $J_{\alpha/\delta}$ in the presence of PVP might have resulted because (i) the reduced v_δ provided a “more stable” surface and longer time for cross-nucleation; (ii) PVP introduced imperfections in the δ crystals and made them more effective substrates for cross-nucleation.

According to Volmer’s theory of heterogeneous nucleation,¹⁴ the activation energy of the α polymorph nucleating on δ is given by $\Delta G = \phi 16\pi\sigma^3 T_f^2 V_m^2 / 3\Delta H_f^2 \Delta T^2$, where σ is the surface energy of the α /liquid (L) interface, T_f and ΔH_f the temperature and enthalpy of melting of α , V_m the molar volume, ΔT the undercooling ($= 166\text{ °C} - T$, where 166 °C is the mp of α), and ϕ a function between 0 and 1 of the surface energies of the α /L, δ /L, and α / δ interfaces. The rate equation is $J_{\alpha/\delta}(T) = J_0 \exp(-\Delta G/RT) = J_0 \exp(-A/RT\Delta T^2)$, where A includes all the temperature-insensitive terms in ΔG . The slope of the $\ln J_{\alpha/\delta} - 1/T\Delta T^2$ plot yielded A (in $\text{K}^2 \text{ kJ/mol}$) = 1.75×10^5 for D-mannitol, 2.14×10^5 for 10% PVP K15 in D-mannitol, and 2.31×10^5 for 10% PVP K30 in D-mannitol. From A , ΔG can be calculated: $\Delta G = A/\Delta T^2$. The intercept of the same plot yielded J_0 (in $\text{m}^{-2}\text{s}^{-1}$) = 1.6×10^{14} for D-mannitol, 8.4×10^{16} for 10% PVP K15 in D-mannitol, and 8.0×10^{17} for 10% PVP K30 in D-mannitol. In this analysis we neglected the slight depression of the melting point of D-mannitol by 10% PVP. According to this theory, the higher activation energy of cross-nucleation in the presence of PVP results from the effect of PVP on the relevant interfacial energies.

We have attributed the observation of α crystals on a δ spherulite to the heterogeneous nucleation of one polymorph on another. Because δ is metastable to α , another explanation

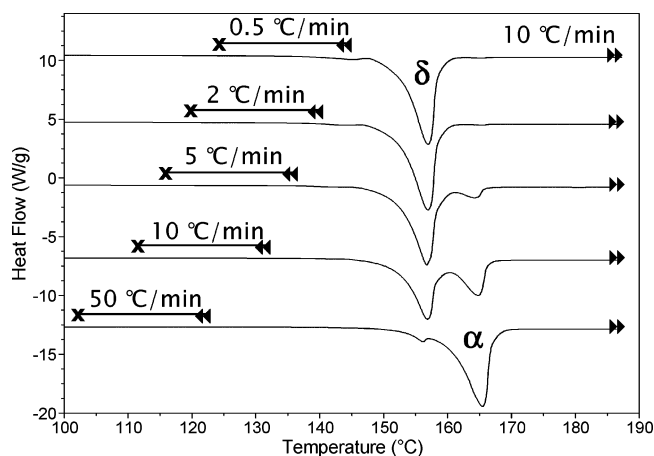


Figure 5. DSC data showing the melting peaks of α and δ after crystallization at different cooling rates. ‘x’ marks the onset temperature of crystallization. Double arrow indicates the direction of temperature changes.

of this observation is the local conversion of δ to α followed by the growth of α . This possibility was ruled out because (i) the δ polymorph was sufficiently stable (in fact it grew) under the conditions of the study; (ii) the rate of polymorphic conversion should increase with temperature, but the rate of α nuclei appearing on δ decreased with temperature. In addition, we have observed that the α polymorph could nucleate on β (the most stable polymorph of D-mannitol), which proves that cross-nucleation can occur without the transformation of the initial polymorph.

To assess how cross-nucleation affects the kinetics of crystallization, a sample of 10% PVP K15 in D-mannitol was analyzed in a differential scanning calorimeter (TA Instruments DSC Q1000). The sample was melted, allowed to crystallize during cooling at 50, 10, 5, 2, or 0.5 °C/min, and reheated at 10 °C/min. The resulting endotherms of melting (Figure 5) gave the relative amounts of the δ polymorph (lower melting) and the α polymorph (higher melting) that crystallized in the cooling step.¹⁵ Figure 5 shows that the faster the cooling rate, the greater the amount of α in the crystallization product. This effect arose because at faster cooling rate, crystallization occurred at a lower temperature (“x” in Figure 5) and at lower temperature, the rate of cross-nucleation was higher.

In summary, we have measured for the first time the kinetics of cross-nucleation between polymorphs in D-mannitol and D-mannitol containing 10% w/w PVP. We found that $J_{\alpha/\delta}$ increased with decreasing temperature and the addition of PVP. Such data are essential for developing theories of crystallization in polymorphic systems and for understanding the effect of additives on crystallization.

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References and Notes

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- (12) Let the origin of the δ spherulite be A and the site of α nucleation be B. After time t , the α/δ boundary, point C, is defined by $AB = R_\delta$, $AC = R_\delta + v_\delta t$, and $BC = v_\alpha t$, from which $\theta = 2(180^\circ - \angle ABC)$ can be solved.
- (13) The standard deviation of $J_{\alpha/\delta}$ is given by $\Delta J/J = \sqrt{(\Delta k/k)^2 + (\Delta v_\delta/v_\delta)^2 + (\Delta h/h)^2}$, where Δk , Δv_δ , and Δh are the standard deviations of the slope k of the $n - R_\delta^2$ plot, δ growth rate, and sample thickness. Δv_δ at 105 °C was taken to be 5% of v_δ , which was approximately the same as Δv_δ at other temperatures.
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