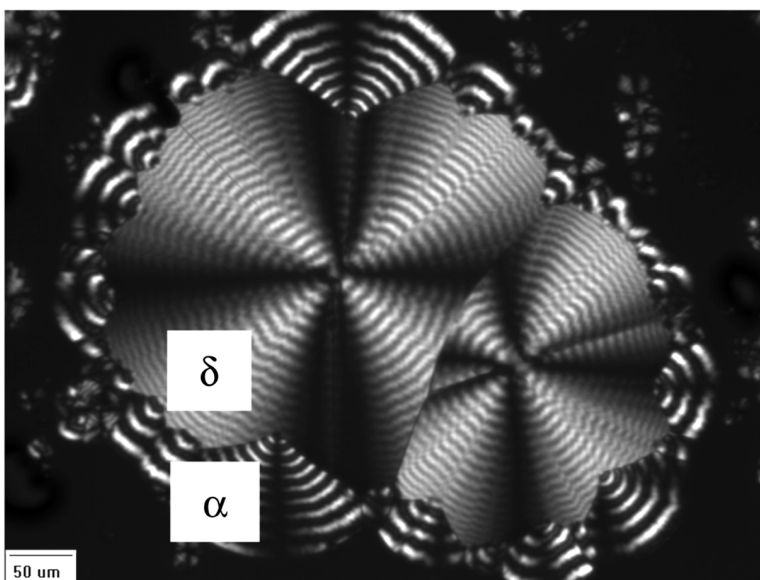


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*J. Am. Chem. Soc.*, **2003**, 125 (21), 6380-6381 • DOI: 10.1021/ja0351544 • Publication Date (Web): 06 May 2003

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## Nucleation of One Polymorph by Another

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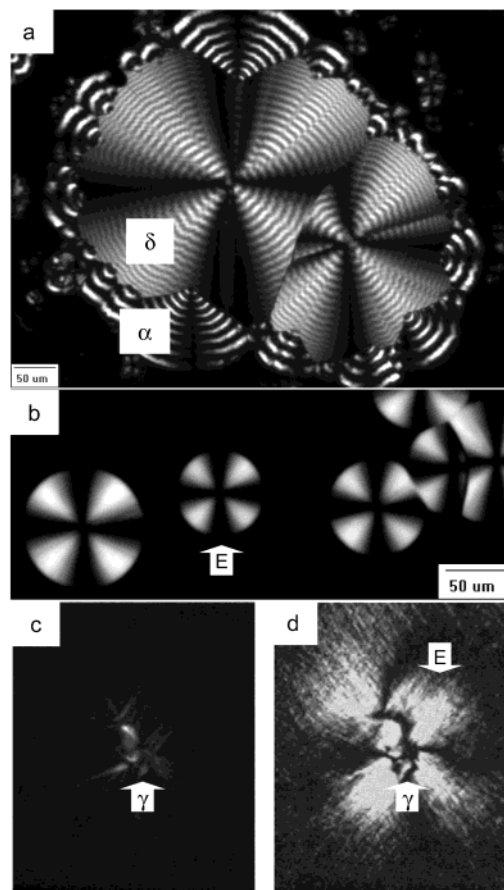
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Controlling polymorphism, the ability of a molecule to crystallize in different lattices or conformations, is essential to the manufacture of specialty chemicals and an unsolved problem in chemical research.<sup>1</sup> Without adequate control, polymorphism can cause inconsistent product quality and even sudden disappearance of known crystal forms.<sup>2</sup> As isomerism is to organic chemistry, polymorphism (“supramolecular isomerism”) is pertinent to supramolecular chemistry and crystal engineering.

Nucleation in polymorphic systems has been treated as competing processes of homogeneous nucleation of alternative polymorphs.<sup>3,4</sup> Concomitant polymorphs<sup>1</sup> have been attributed to simultaneous nucleation or conversion of polymorphs. Surfaces of foreign substances can initiate nucleation,<sup>5</sup> even with polymorphic selectivity;<sup>6</sup> however, it is generally assumed that crystals of one polymorph continue to crystallize in a supersaturated medium without nucleating other polymorphs. Although observed in a solution-mediated polymorphic conversion,<sup>7</sup> nucleation of one polymorph by another has not been demonstrated in the course of crystallization. Reported here is a direct observation of this phenomenon *without polymorphic conversion* during the melt crystallization of D-mannitol and D-sorbitol, two hexitols with polymorphism<sup>8–12</sup> of importance to drug and food industries.

Hot-stage microscopy<sup>13</sup> showed that the melt of D-mannitol (99+%, polymorph  $\beta$ , Aldrich) crystallized on cooling near 120 °C. The crystallization occurred in seconds on 5–20 °C/min cooling and often in two stages: first as the  $\delta$  polymorph ( $P2_1$ ,  $a = 5.095$  Å,  $b = 18.254$  Å,  $c = 4.919$  Å,  $\beta = 118.6^\circ$ )<sup>8</sup> and then as the  $\alpha$  polymorph ( $P2_12_12_1$ ,  $a = 8.939$  Å,  $b = 18.778$  Å,  $c = 4.896$  Å).<sup>8</sup> The two stages were more clearly observed in the presence of an additive that slightly retarded crystallization. Figure 1 shows the result obtained with 10% w/w poly(vinylpyrrolidone) (PVP;  $K = 17$ , Aldrich). The  $\alpha$  polymorph nucleated on the  $\delta$  polymorph and grew to consume the remaining liquid. At 5 °C/min cooling, PVP increased the crystallization time to ca. 1 min, during which time the temperature fell ca. 5 °C. The polymorphs were identified via melting point and Raman microscopy, wherein a HeNe laser was focused on an area of interest (ca. 1  $\mu\text{m}$  in diameter), and backscattered signal was collected.<sup>14</sup> The observed melting points ( $\delta$  155 °C,  $\alpha$  166 °C) agree with ref 15 and were ca. 2 °C lower with PVP present. The banding in Figure 1a arose from concerted twisting of crystal fibrils when growing in the presence of PVP.<sup>16</sup>

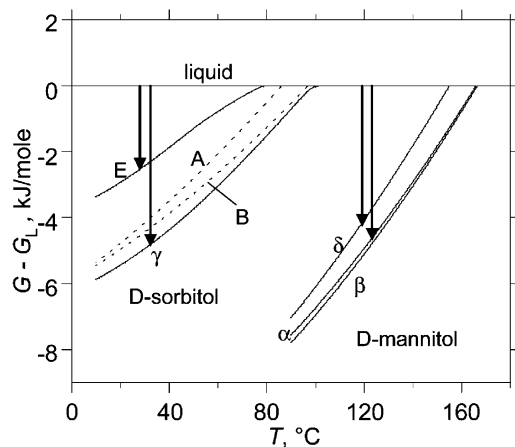
The melt of D-sorbitol (99+%, polymorph  $\gamma$ , Aldrich) crystallized slowly on storage at 22 °C. The spherulites thus formed (Figure 1b) were polymorph E (mp 80 °C),<sup>10</sup> different from the commercial polymorph  $\gamma$  (mp 100 °C). When seeded with  $\gamma$  (Figure 1c) at room temperature, the melt crystallized around the seeds (Figure 1d); however, the new crystals were *not* the  $\gamma$  polymorph (seed), but the E polymorph. Heating the sample in Figure 1d to 87 °C (between the mp's of E and  $\gamma$ ) melted all new crystals, but the  $\gamma$  seeds showed no visible growth. Cooling back to room temperature caused the E phase to grow again, and the process could be repeated.



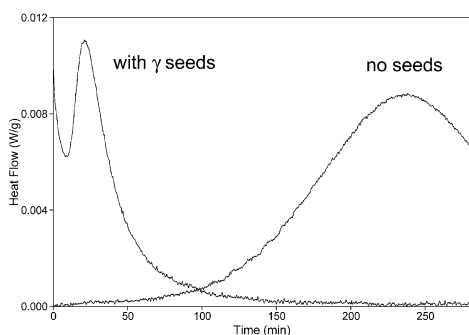
**Figure 1.** (a) Spherulites crystallized from D-mannitol melt containing 10% w/w PVP. The  $\delta$  polymorph (inner spherulites) crystallized first, and the  $\alpha$  polymorph (outer spherulites) nucleated on  $\delta$ . (b) Spherulites of the E polymorph of D-sorbitol crystallized without seeding. (c) D-Sorbitol melt seeded with the  $\gamma$  polymorph at time zero. (d) Same  $\gamma$  seeds in (c) and new crystals grown around them. The new growth was not the  $\gamma$ , but the E polymorph. The scale in (b) also applies to (c) and (d).

The data of differential scanning calorimetry (DSC) were used to calculate<sup>17</sup> the polymorphs' free energies relative to their liquid, Figure 2. Thus, the first polymorph of D-mannitol to crystallize ( $\delta$ ) was the least stable, and the next ( $\alpha$ ) was the second least stable. This behavior conforms to Ostwald's law of stages (OLS);<sup>18</sup> however, contrary to OLS, no polymorphic conversion down the ladder of free energy ( $\delta$  to  $\alpha$  and  $\alpha$  to  $\beta$ )<sup>19</sup> was observed. Consistent with OLS, D-sorbitol crystallized first as the least stable polymorph (E), but contrary to OLS, no subsequent crystallization of or conversion to more stable polymorphs (A, B, and  $\gamma$ ) occurred within the time of experiment. It is noteworthy that seeding with the stable phase  $\gamma$  caused the metastable phase E to crystallize.

The effect of  $\gamma$  seeds on D-sorbitol crystallization was studied with DSC. A physical mixture of the  $\gamma$  and E polymorphs (1:1 w/w) was heated to 87 °C to melt the E but not the  $\gamma$  phase and



**Figure 2.** Free energies of polymorphs relative to their liquid. Data sources: D-mannitol, ref 15; D-sorbitol, ref 11 (broken lines), and this work (solid lines).<sup>20</sup> Arrows indicate crystallization driving forces near temperatures of experiment.



**Figure 3.** Effect of  $\gamma$  seeds on the crystallization of the E polymorph of D-sorbitol at 40 °C.

cooled to 40 °C. Figure 3 shows that the crystals of the  $\gamma$  polymorph eliminated the 2 h nucleation period required in the absence of seeds. A DSC rescan confirmed that the new crystals grown from the  $\gamma$  seeds melted at 80 °C and therefore were the E polymorph.

This study demonstrated that seeds of one polymorph can nucleate another of higher or lower thermodynamic stability without polymorphic conversion. In the cases examined, the late-nucleating polymorph dominated the end product. This effect arises from heterogeneous nucleation between polymorphs and faster growth rate of the new polymorph. This effect needs to be included in theories of polymorphic nucleation, which currently treat only homogeneous processes.<sup>3,4</sup> This effect gives an alternative explanation for concomitant polymorphs: rather than simultaneous homogeneous nucleation or interconversion,<sup>1,3</sup> they may arise from heterogeneous nucleation between polymorphs. The explanation is plausible given the general dominance of heterogeneous over homogeneous nucleation. Finally, this effect may explain failures to obtain target polymorphs via seeding<sup>21</sup> and the dependence of polymorphic outcome on sample size.

The relative growth rates of polymorphs afford a test of the theories of crystal growth. For example, the theory of interface-controlled growth,<sup>22</sup> which applies to melt crystallization (no

compositional change), holds that crystal growth rate depends on  $R_1$  and  $R_2$ , where  $R_1$  is the rate at which molecules arrive at the growth interface, and  $R_2$  is the rate at which molecules at the growth interface enter the crystal lattice. For two polymorphs in the same melt,  $R_1$ , essentially the rate of self-diffusion, should be the same, but  $R_2$  should differ because of different driving forces of crystallization (Figure 2). Thus, the more stable polymorph should grow faster than the less stable polymorph. This prediction agrees with the D-mannitol result (the more stable  $\alpha$  grew faster), but disagrees with the D-sorbitol result (the more stable  $\gamma$  grew more slowly). The discrepancy may arise from kinetic barriers not included in the classical theory (e.g., barriers for conformational change required for crystallization).

Heterogeneous nucleation between polymorphs should not be limited to the polyols examined here or to melt crystallization. It is hoped that further studies will elucidate the thermodynamic and kinetic factors controlling this phenomenon and its treatment in theories of polymorphic nucleation and concomitant polymorphs. Where this effect prevails, same-substance seeding becomes ineffective for polymorph-specific crystallization, and alternative techniques, such as nucleation templates<sup>6</sup> and solution additives,<sup>23</sup> may prove valuable.

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JA0351544