Measuring Free-Energy Difference between Crystal Polymorphs through Eutectic Melting

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We describe a method to measure the free-energy difference, ΔG, between crystal polymorphs from their calorimetric data of eutectic melting with a common additive. The use of different additives yields ΔG as a function of temperature. The method is suitable for crystals that chemically decompose or physically transform before melting. It applies to not only true polymorphs but also pairs of racemate and conglomerate of resolvable enantiomers. We illustrate the method with the polymorphs of glycine, D-mannitol, and tazofelone and report a new value (123 °C) for the enantiotropic transition temperature of α and γ glycine. We show how different additives (including a liquid additive, water) can be used for different compounds. The ΔG data thus obtained are important for structure-stability studies and controlling crystallization in polymorphic systems.

Introduction

As illustrated by diamond and graphite, crystal polymorphs can coexist at the same temperature despite their different thermodynamic stability. Coexisting polymorphs are important for developing drugs and other specialty chemicals, elucidating structure-property relations, and testing theories of crystallization and crystal structure prediction.[1,2] The free-energy difference, ΔG, between polymorphs is a fundamental property for studying and controlling polymorphism. For coexisting polymorphs, ΔG can be defined and measured over wide ranges of temperature, sometimes from nearly 0 K to melting points. ΔG can be obtained from the polymorphs' heat capacities,[3] solubilities,[4] vapor pressures, and heats and temperatures of melting.[5] Here, we describe a new method to measure ΔG on the basis of eutectic melting and differential scanning calorimetry (DSC).

Teetsov and McCrone used eutectic-melting temperatures, T_e, measured by hot-stage microscopy (HSM), to study the polymorphs of HMX (an explosive).[6] From each polymorph's T_e with a common additive, they obtained the stability order (sign of ΔG) of the polymorphs near the T_e; by varying the additive, they determined how the stability order changes with temperature (Figure 1). We have adapted this idea to DSC.[7−9] We chose DSC over HSM because DSC yields not only temperatures but also heats of melting and, thus, not only the sign but also the magnitude of ΔG. We have used an equation without detailed derivation to calculate ΔG from the calorimetry data of eutectic melting.[7] Herein, that derivation is provided. In addition, we show how this method is useful for crystals that chemically decompose or physically transform before melting, how different additives (including water, a liquid additive) enable studies of different chemical systems, and how the method can be used to study the relation between racemic and chiral crystals of resolvable enantiomers, which is important to chiral resolution by crystallization.[10,11]

We illustrate the eutectic-melting method with three systems that have been studied in our laboratory (Chart 1).[8,12−16] α and

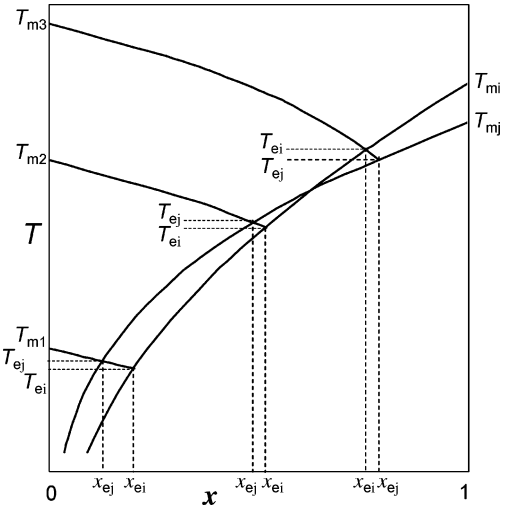
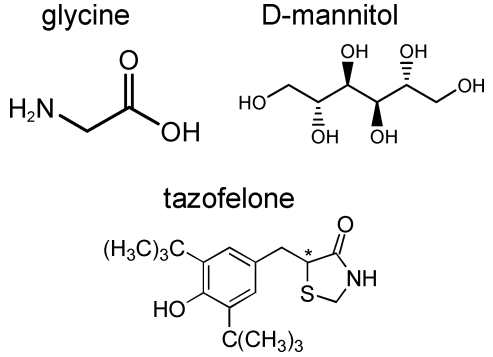


Figure 1. Relative stability of two polymorphs (i and j) can be obtained as a function of temperature from their eutectic melting points with additives (1, 2, and 3). Ideal mixing is assumed in drawing the mp curves of i and j as single curves (colligative properties). With nonideal mixing, the mp curves will be different for each additive.

CHART 1: Compounds Studied



γ Glycine are of interest because of their unusual crystal chemistry and still poorly understood phase relation. An achiral molecule, glycine can form both achiral (α, $P2_1/n$) and chiral

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(γ, $P3_1$ or $P3_2$) polymorphs. α and γ are known to be enantiotropic, with γ being more stable at low temperature,[17−19] but the literature disagrees on their transition temperature T_t. From direct transformations, Iitaka reported $T_t < 165$ °C[17] and Perlovich et al. reported $T_t < 165-200.7$ °C;[19] Park et al. reported $T_t = 177$ °C on the basis of extrapolation of solubility data determined by DSC.[20] Glycine decomposes on melting, which makes the method of pure melting[5] inapplicable. The heat capacities of α and γ glycine have been measured from 5 to 304 K,[21] but without melting data, they could not be combined in the usual way[3] to yield $G_\alpha - G_\gamma$. The bridging of heat-capacity data through heats of solution[19] led to large errors in estimated $G_\alpha - G_\gamma$ and no prediction of T_t. Here, we report a direct determination of $G_\alpha - G_\gamma$ from −4 to 177 °C through eutectic melting and $T_t = 123$ °C.

D-Mannitol crystallizes as three solvent-free polymorphs (α, β, and δ)[22] and a hemihydrate.[13] The stability order of the polymorphs above 25 °C is β (most stable) > α > δ (least stable).[23] On the basis of the fact that δ has the lowest melting point but the highest heat of fusion, Burger et al. suggested that δ is the most stable at 0 K.[24,25] Our aim here was to evaluate this conclusion through eutectic-melting data. We did this for two reasons. First, the melting points of α and β (166.0 and 166.5 °C) are very close, which makes extrapolations from melting data less reliable. Second, the δ polymorph melts incongruently (mp ≈ 155 °C), which makes it difficult to measure its temperature and heat of melting. Through eutectic melting, we could directly determine the free-energy difference between α and β below their melting points and measure the congruent melting of δ.

Tazofelone, a chiral molecule and a 5-lipoxygenase inhibitor for treating inflammatory bowel diseases, is of interest because it can crystallize both as racemates and after chiral separation, as homochiral crystals.[8] Like crystals of other chiral molecules,[10] the racemates of tazofelone are significantly more stable than the conglomerate of the opposite homochiral crystals. This structure-stability relation is important to chiral separation by crystallization and, though widely accepted, remains poorly established as a result of sampling bias.[26] Here, we report relative free energies of the racemate and conglomerate forms of tazofelone determined through eutectic melting to extend our previous results from melting data.[8]

Theoretical Section

Equation 1 is used to calculate the free-energy difference between two polymorphs, i and j, from melting data:[5]

$$(G_j - G_i)_{T_{mi}} = \Delta H_{mj}(T_{mi} - T_{mj})/T_{mj} + \Delta C_{pmj}[T_{mj} - T_{mi} - T_{mi}\ln(T_{mj}/T_{mi})] \quad (1)$$

Here, T_{mi} and T_{mj} are the melting temperatures of i and j, ΔH_{mj} is the heat of melting of j, and ΔC_{pmj} is the C_p change upon melting j. The subscript T_{mi} signifies that $G_j - G_i$ is evaluated at T_{mi}. Exchanging i and j in eq 1 yields an equation for calculating $G_j - G_i$ at T_{mj}. Equation 2 is used to calculate the free-energy difference between a racemate (R) and a conglomerate (C) of resolvable enantiomers from melting data:[10]

$$(G_C - G_R)_{T_{mA}} = \Delta H_{mR}(T_{mR} - T_{mA})/T_{mR} + RT_{mA}\ln 2 + \Delta C_{pmR}[T_{mA} - T_{mR} - T_{mA}\ln(T_{mA}/T_{mR})] \quad (2)$$

We define a racemate (racemic compound; R) as a crystal in which the opposite enantiomers (*d* and *l*) exist in the same unit cell, an enantiomorph (A) as a crystal of either *d* or *l*, and a conglomerate (C) as an equal-molar physical mixture of the enantiomorph of *d* and the enantiomorph of *l*. One mole of R or C is assumed to contain 0.5 mol of each enantiomer. In eq 2, T_{mA} and T_{mR} are the melting temperatures of A and R, ΔH_{mR} is the heat of melting of R, and ΔC_{pmR} is the C_p change upon melting R.

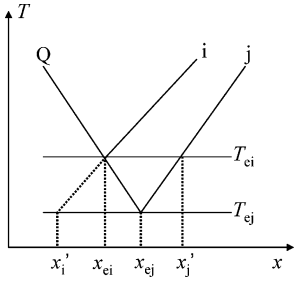

Figure 2. Enlarged view of Figure 1 to show eutectics of polymorphs i and j with one additive (Q).

We now show that if calorimetric data of the *eutectic melting* of i and j (or A and R) with some additive Q are known, $G_j - G_i$ (or $G_C - G_R$) can be calculated at the corresponding eutectic temperatures. With reference to Figure 2 (enlarged view of Figure 1 near the eutectic points with one additive), assume polymorphs i and j of compound P form eutectics with Q. Let x_{ei}, T_{ei}, and ΔH_{mei} be the composition (in mole fraction), melting temperature, and heat of melting of the i−Q eutectic. Let x_{ej}, T_{ej}, and ΔH_{mej} be the corresponding properties of the j−Q eutectic. We give two derivations of the equivalent of eq 1, the first to obtain the principal term and the second to capture minor effects. For the first derivation, note that the liquidus lines in Figure 2 are solubility curves and write the free-energy difference between i and j at T_{ei} as

$$(G_j - G_i)_{T_{ei}} = RT_{ei}\ln(x_j'/x_{ei}) \quad (3)$$

where x_j' is the solubility of j at T_{ei}. Define a function $f = \ln[x_j/(1 - x_Q)]$, where x_Q and x_j are the solubilities of Q and j at temperature *T*. The value of *f* at T_{ei} is $\ln(x_j'/x_{ei})$. Because $f = 0$ at T_{ej} (intersection of the Q and j liquidus lines), for small $|T_{ej} - T_{ei}|$, we can write

$$\ln(x_j'/x_{ei}) \approx [df/d(1/T)]_{T_{ej}}(1/T_{ei} - 1/T_{ej}) \quad (4)$$

because $df/d(1/T) = d\ln x_j/d(1/T) + [d\ln x_Q/d(1/T)]x_Q/(1 - x_Q) = -[\Delta H_j + \Delta H_Q x_Q/(1 - x_Q)]/R$, where ΔH_j is the differential heat of solution of j into a saturated solution of Q and ΔH_Q is the differential heat of solution of Q into a saturated solution of P. At T_{ej}, the value of $df/d(1/T)$ is

$$[df/d(1/T)]_{T_{ej}} = -[(1 - x_{ej})\Delta H_Q + x_{ej}\Delta H_j]/(x_{ej}R) = -\Delta H_{mej}/(x_{ej}R) \quad (5)$$

From eqs 3, 4, and 5, we obtain

$$x_{ej}(G_j - G_i)_{T_{ei}} \approx \Delta H_{mej}(T_{ei} - T_{ej})/T_{ej} \quad (6)$$

For the second derivation, consider process a:

$$[x_{ej}\mathrm{i} + (1 - x_{ej})\mathrm{Q}]_{T_{ei}} \rightarrow [x_{ej}\mathrm{j} + (1 - x_{ej})\mathrm{Q}]_{T_{ei}} \quad (a)$$

which converts a physical mixture of i and Q to a physical mixture of j and Q at T_{ei}. The free-energy change of process a

is $x_{ej}(G_j - G_i)_{T_{ei}}$. Process a is then carried out through the following steps:

$$[x_{ej}\mathrm{i} + (1 - x_{ej})\mathrm{Q}]_{T_{ei}} \xrightarrow{(a1)} [x_{ei}\mathrm{i} + (1 - x_{ei})\mathrm{Q}]_{T_{ei}} \xrightarrow{(a2)}$$
$$\{x_{ei}\mathrm{P} + (1 - x_{ei})\mathrm{Q}\}_{T_{ei}} \xrightarrow{(a3)} \{x_{ej}\mathrm{P} + (1 - x_{ej})\mathrm{Q}\}_{T_{ei}} \xrightarrow{(a4)}$$
$$\{x_{ej}\mathrm{P} + (1 - x_{ej})\mathrm{Q}\}_{T_{ej}} \xrightarrow{(a5)} [x_{ej}\mathrm{j} + (1 - x_{ej})\mathrm{Q}]_{T_{ej}} \xrightarrow{(a6)}$$
$$[x_{ej}\mathrm{j} + (1 - x_{ej})\mathrm{Q}]_{T_{ei}}$$

Here, the bracket [...] represents a solid mixture and {...} a solution. Adding the ΔH and ΔS of a1 to a6, applying $\Delta G = \Delta H - T\Delta S$, and simplifying the result (see Appendix), we obtain

$$x_{ej}(G_j - G_i)_{T_{ei}} = \Delta H_{mej}(T_{ei} - T_{ej})/T_{ej} + \Delta C_{pej}[T_{ej} - T_{ei} - T_{ei}\ln(T_{ej}/T_{ei})] + RT_{ei}\{x_{ej}\ln(x_{ej}/x_{ei}) + (1 - x_{ej})\ln[(1 - x_{ej})/(1 - x_{ei})]\} \quad (7)$$

where ΔC_{pej} is the C_p change upon melting the j−Q eutectic. The first term in eq 7, which is the same as that in eq 6, is usually the largest. The ΔC_p term is positive and usually small compared to the first term for small $|T_{ej} - T_{ei}|$ (several kelvin).[27] ΔC_{pej} can be measured by DSC or estimated from $\Delta C_p/\Delta H_m \approx 0.003$/K.[5] The RT term is positive and small compared to the first term for small $|x_{ej} - x_{ei}|$.[28] Equation 7 holds upon exchanging i and j. Setting $x_{ej} = x_{ei} = 1$ reduces eq 7 to eq 1 (for pure melting).

Racemate and Conglomerate of Resolvable Enantiomers. We now obtain the equivalent of eq 7 for calculating the free-energy difference between the racemate (R) and the conglomerate (C) of two opposite and resolvable enantiomers from the eutectic-melting data of R with Q and A with Q, where A is an enantiomorph and Q is an additive. (Note that eq 7 applies if the melting of the C−Q eutectic, rather than the A−Q eutectic, has been measured.) Let x_{eR}, T_{eR}, and ΔH_{meR} be the composition, melting temperature, and heat of melting of the R−Q eutectic and x_{eA}, T_{eA}, and ΔH_{meA} be the corresponding properties for the A−Q eutectic. Let a represent either d or l (single enantiomer).

We give the second derivation only. Consider process b:

$$[x_{eR}\mathrm{R} + (1 - x_{eR})\mathrm{Q}]_{T_{eA}} \rightarrow [x_{eR}\mathrm{C} + (1 - x_{eR})\mathrm{Q}]_{T_{eA}} \quad (b)$$

which converts a physical mixture of R and Q to a physical mixture of C and Q at T_{eA}. The free-energy change of process b is $x_{eR}(G_C - G_R)_{T_{eA}}$. Process b is then carried out through the following steps:

$$[x_{eR}\mathrm{R} + (1 - x_{eR})\mathrm{Q}]_{T_{eA}} \xrightarrow{(b1)} [x_{eR}\mathrm{R} + (1 - x_{eR})\mathrm{Q}]_{T_{eR}} \xrightarrow{(b2)}$$
$$\{x_{eR}/2\ d + x_{eR}/2\ l + (1 - x_{eR})\mathrm{Q}\}_{T_{eR}} \xrightarrow{(b3)} \{x_{eR}/2\ d +$$
$$x_{eR}/2\ l + (1 - x_{eR})\mathrm{Q}\}_{T_{eA}} \xrightarrow{(b4)} \{x_{eR}a + (1 - x_{eR})\mathrm{Q}\}_{T_{eA}} \xrightarrow{(b5)}$$
$$\{x_{eA}a + (1 - x_{eA})\mathrm{Q}\}_{T_{eA}} \xrightarrow{(b6)} [x_{eA}\mathrm{A} + (1 - x_{eA})\mathrm{Q}]_{T_{eA}} \xrightarrow{(b7)}$$
$$[x_{eR}\mathrm{A} + (1 - x_{eR})\mathrm{Q}]_{T_{eA}} \xrightarrow{(b8)} [x_{eR}\mathrm{C} + (1 - x_{eR})\mathrm{Q}]_{T_{eA}}$$

Adding the ΔH and ΔS of individual steps, applying $\Delta G = \Delta H - T\Delta S$, and simplifying the result (see Appendix), we obtain

$$x_{eR}[(G_C - RT\ln 2) - G_R]_{T_{eA}} = \Delta H_{meR}(T_{eR} - T_{eA})/T_{eR} + \Delta C_{peR}[T_{eA} - T_{eR} - T_{eA}\ln(T_{eA}/T_{eR})] + RT_{eA}\{x_{eR}\ln(x_{eA}/x_{eR}) + (1 - x_{eR})\ln[(1 - x_{eA})/(1 - x_{eR})]\} \quad (8)$$

where ΔC_{peR} is the C_p change upon melting the R−Q eutectic. Setting $x_{eR} = x_{eA} = 1$ reduces eq 8 to eq 2 (for pure melting). By a similar procedure, we obtain eq 9 for calculating $G_C - G_R$ at T_{eR}:

$$x_{eA}[(G_C - RT\ln 2) - G_R]_{T_{eR}} = \Delta H_{meA}(T_{eR} - T_{eA})/T_{eA} + \Delta C_{peA}[T_{eA} - T_{eR} - T_{eR}\ln(T_{eA}/T_{eR})] + RT_{eR}\{x_{eA}\ln(x_{eA}/x_{eR}) + (1 - x_{eA})\ln[(1 - x_{eA})/(1 - x_{eR})]\} \quad (9)$$

where ΔC_{peA} is the C_p change upon melting the A−Q eutectic.

Experimental Section

Materials. Glycine (α polymorph) and D-mannitol (β polymorph) were obtained from Mallinckrodt. Seeds of γ glycine were obtained by crystallizing glycine from an aqueous solution adjusted to pH 3.8 with HCl.[17] A larger supply of γ glycine was prepared by seeding a supersaturated aqueous solution (no pH adjustment) with γ seeds to initiate crystallization and then stirring the resulting slurry for 9 days until there was full conversion. δ and α D-mannitol were made by melt crystallization at slow (0.5 °C/min) and fast (2−10 °C/min) cooling rates, respectively. Tazofelone was synthesized by Lilly Research Laboratories (Indianapolis, IN).[8] Benzil, acetanilide, *p*-acetophenetidide, benzanilide, dulcitol, I-erythritol, and xylitol were obtained from Sigma-Aldrich and used without further purification. Deionized water was used for preparing glycine/ice eutectics.

DSC. DSC was performed with a TA Instruments DSCQ1000 under a 50 mL/min N_2 purge. Glycine, D-mannitol, and eutectic mixtures containing glycine or D-mannitol were scanned at 1 °C/min or 2 °C/min in crimped Al pans. Tazofelone and its eutectic mixtures were scanned at 10 °C/min in crimped Al pans. The temperature and heat flow were calibrated using indium. The melting and eutectic-melting data reported were the average of two to three measurements. The melting temperatures were the onsets of melting endotherms. Estimated standard errors were ±0.05 °C for temperatures and ±0.1 kJ/mol for heats.

Eutectic-Melting Method. DSC provides precise temperatures (T_e) and heats (ΔH_{me}) of eutectic melting. Precise determination of eutectic compositions (x_e) is possible but tedious. We have chosen to obtain x_e by first estimating it from pure melting data, then verifying it experimentally, and finally refining it using observed T_e. Our procedure is as follows:

(1) Choose eutectic additives on the basis of the temperature of interest and solubility. Standard additives are used for characterizing organic crystals by HSM.[29] From these, we chose benzil, acetanilide, *p*-acetophenetidide, and benzanilide for tazofelone. For glycine, we chose four alditols (ducitol, D-mannitol, I-erythritol, and xylitol)[30] because the standard additives are not melt-miscible with glycine.

(2) Estimate eutectic composition x_e. If the temperatures and heats of melting of P are known (as in the cases of D-mannitol and tazofelone), then estimate x_e by solving the crossing point of the mp curves of P and Q: for P, $\ln x = (\Delta H_{mP}/R)(1/T_{mP} -$

$1/T$), where P = i, j, A, or R; for Q, $\ln(1 - x) = (\Delta H_{mQ}/R)(1/T_{mQ} - 1/T)$. If these data are unavailable due to decomposition (glycine), first measure the eutectic melting point using a P/Q mixture (50:50, w/w) and then calculate x_e from the mp curve of Q.

(3) Prepare eutectic mixtures according to the estimated x_e with gentle grinding.

(4) Measure the temperatures (T_e) and heats (ΔH_{me} in J/g) of eutectic melting by DSC.

(5) Refine x_e from the measured T_e. Calculate the eutectic composition from each mp curve:

$$x_e(P) = \exp[(\Delta H_{mP}/R)(1/T_{mP} - 1/T_e)] \quad (10)$$

$$x_e(Q) = 1 - \exp[(\Delta H_{mQ}/R)(1/T_{mQ} - 1/T_e)] \quad (11)$$

If the melting of P cannot be measured (glycine), set $x_e = x_e(Q)$; otherwise, set $x_e = [x_e(P) + x_e(Q)]/2$.[31] If the recalculated x_e is not significantly different from that predicted in step 2 (less than 5%), go to step 6. Otherwise, prepare a new mixture at the recalculated x_e and remeasure ΔH_{me}. In our experience, this is rarely necessary. A small deviation from the true x_e does not affect T_e and affects ΔH_{me} only slightly.

(6) Calculate the heat of melting ΔH_{me} in kJ/mol:

$$\Delta H_{me}\ (\text{in kJ/mol}) = M_{eff}\Delta H_{me}\ (\text{in J/g})/1000 \quad (12)$$

where M_P and M_Q are the molecular weights of P and Q, $M_{eff} = [x_e M_P + (1 - x_e)M_Q]$ is the "effective molecular weight" of the eutectic, and ΔH_{me} (in J/g) is the experimental heat of eutectic melting in J/g.

(7) Calculate $G_j - G_i$ using eq 7 or $G_C - G_R$ using eqs 8 and 9.

Method of Equal-Weight Mixtures. For glycine and other high T_m systems, we found it advantageous to use a 50/50 (w/w) mixture rather than a mixture at x_e. Because of its high T_m, the x_e of glycine with a low-melting additive is relatively small. At the 50/50 (w/w) composition, a wide temperature gap exists between the eutectic temperature T_e and the liquidus curve of glycine. Thus, heating the 50/50 (w/w) mixture just past T_e yields a well-defined endotherm. The energy of this endotherm, $\Delta H_{me50/50}$ (in J/g), is related to the heat of eutectic melting ΔH_{me} (in kJ/mol) by[32]

$$\Delta H_{me} = 2\Delta H_{me50/50}(1 - x_e)M_Q/1000 \quad (13)$$

An equal-weight mixture makes it easier to obtain uniform mixing than a mixture at low x_e. An equal-weight mixture also yields sharper DSC endotherms of eutectic melting. This principle is seen by analyzing the mixing of two components (C1 and C2) required for their eutectic melting. Slow liquid mixing causes broad melting endotherms and low precision of measured melting points. Slow liquid mixing occurs between two viscous liquids, as between glycine and alditols, and in mixtures in which one component (such as C1) has low concentration and must diffuse throughout the sample for thorough mixing. Increasing the concentration of C1 increases the contact area between C1 and C2 and decreases distances of diffusion required for liquid mixing. This in turn sharpens the DSC endotherm of eutectic melting. This effect was verified experimentally with glycine/alditol mixtures.

Results and Discussion

Glycine. Figure 3 and Table 1 show the DSC data of eutectic melting of glycine polymorphs with dulcitol, D-mannitol, I-erythritol, xylitol, and ice. These additives covered the temperature range from −4 to 177 °C. With dulcitol, the highest-melting additive, the eutectic melting point of α is higher than that of γ, $T_{e\alpha} > T_{e\gamma}$, indicating α is more stable near 177 °C. With lower-melting additives, the order of melting changes from $T_{e\alpha} > T_{e\gamma}$ (D-mannitol) to $T_{e\alpha} \approx T_{e\gamma}$ (I-erythritol) and to $T_{e\alpha} < T_{e\gamma}$ (xylitol and ice). Thus, the stability order of α and γ glycine reverses near 115 °C. Ice was used to extend our measurement to below 0 °C. We formed crystalline mixtures of glycine and ice by cooling aqueous solutions of glycine (13.5%, w/w) in hermetically sealed DSC pans. Under this condition, β glycine crystallized when the cooling rate was 5 °C/min and γ glycine crystallized when the cooling rate was 1 °C/min.[33,34] Reheating these mixtures at 0.1 °C/min yielded $T_{e\beta} = -3.8$ °C and $T_{e\gamma} = -2.9$ °C, which agree with ref 33. α Glycine did not crystallize

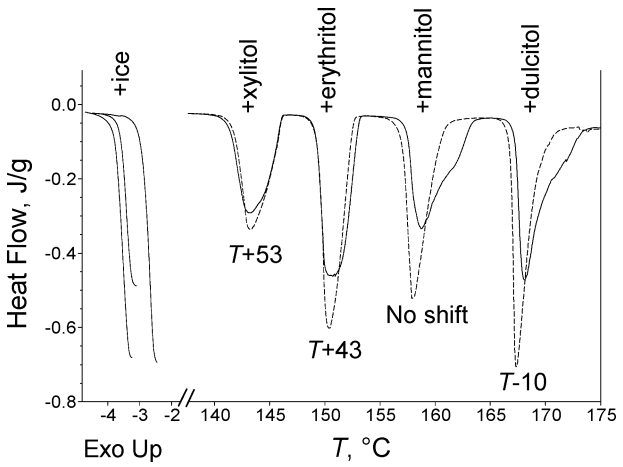

Figure 3. Eutectic-melting endotherms of α and γ glycine. With alditols: α (solid line), γ (dashed line). The label $T \pm x$ indicates the temperature shift (by x °C) applied to the thermograms to improve readability. With ice: eutectic melting of β, α, and γ shown from left to right.

TABLE 1: DSC Data of Eutectic Melting of Glycine and D-Mannitol

	glycine		D-mannitol		
	γ	α	α	β	δ
Additive = Dulcitol[a]					
x_e	0.36	0.33	0.71	0.71	
T_e, °C	176.7	177.2	155.2	155.6	
ΔH_{me}, kJ/mol	41.5	44.8	55.6	52.8	
Additive = D-Mannitol[a]					
x_e	0.28	0.27	n.a.	n.a.	n.a.
T_e, °C	156.8	157.4	n.a.	n.a.	n.a.
ΔH_{me}, kJ/mol	42.6	42.7	n.a.	n.a.	n.a.
Additive = Erythritol[a]					
x_e	0.12	0.12	0.16	0.15	0.20
T_e, °C	115.2	115.2	112.9	113.2	111.4
ΔH_{me}, kJ/mol	35.8	36.6	43.2	41.7	41.5
Additive = Xylitol[a]					
x_e	0.15	0.15	0.07	0.06	0.08
T_e, °C	88.6	88.3	89.7	89.9	89.3
ΔH_{me}, kJ/mol	33.0	32.4	36.1	36.4	34.5
Additive = Ice					
x_e	0.025	0.029			
T_e, °C	−2.9	−3.6			
ΔH_{me}, kJ/mol[b]	6.0	6.0			

[a] T_m (°C) and ΔH_m (kJ/mol) of pure alditols: dulcitol, 187.7, 66.8; D-mannitol, 166.4, 54.9; I-erythritol, 118.9, 41.7; xylitol, 93.2, 37.4. [b] Assumed to be identical with heat of melting of pure ice because of low x_e.

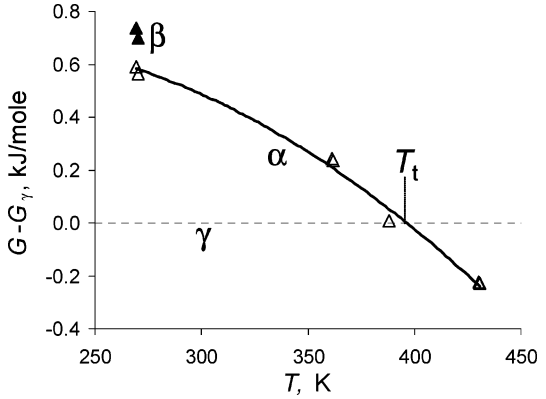

Figure 4. $\Delta G - T$ plot of glycine polymorphs (α, β, and γ). $T_t = 123$ °C is the transition point of α and γ glycine.

directly from the frozen solution and was introduced by adding crystals to a saturated solution at 25 °C. We obtained $T_{e\alpha} = -3.6$ °C.

Figure 4 shows the free-energy difference between α and γ glycine calculated from eutectic-melting data. The free-energy difference between β and γ at the eutectic points with ice was also included. The dulcitol data was excluded because the corresponding T_e exceeded the $\gamma \rightarrow \alpha$ transformation temperature in pure glycine and was regarded as imprecise. The equilibrium transition point (T_t) between α and γ glycine was determined to be 123 °C from the temperature at which $\Delta G = 0$. This result agrees with Iitaka[17] but is significantly below Park et al.'s 177 °C.[20] To confirm our result, we verified by X-ray diffraction that the $\gamma \rightarrow \alpha$ transformation indeed occurred at 165 °C, as Iitaka reported. We also established by DSC that this transformation can happen at a temperature as low as 160 °C and, thus, $T_t < 160$ °C. From the $(G_\alpha - G_\gamma)/T - 1/T$ and the $-(G_\alpha - G_\gamma) - T$ plots, we obtained the enthalpy and entropy differences between α and γ glycine: $H_\alpha - H_\gamma = 1.9$ kJ/mol, $S_\alpha - S_\gamma = 5.0$ J/(K mol) (for $T = -4$ to 177 °C).

D-Mannitol. α and β D-mannitol melt congruently at nearly the same temperatures (166.0 and 166.5 °C).[24] Polymorph δ melts incongruently (mp ≈ 155 °C) because the unstable liquid formed on melting crystallizes to α, which then melts congruently (Figure 5, top). This incongruent melting raises questions about the precision of the δ polymorph's T_m and ΔH_m (measured by integrating across all thermal events). We were interested in observing and measuring the congruent melting of δ D-mannitol in a eutectic mixture. Figure 5 (bottom) shows that, with a eutectic additive (I-erythritol in this case), δ D-mannitol does melt congruently. The eutectic-melting method is, thus, useful for studying unstable polymorphs. Figure 6 shows the $\Delta G - T$ diagram calculated from the eutectic-melting data (Table 1). The new data points are consistent with extrapolations from melting data (thick, short lines near the T_m values).[24] The combined data support the conclusion[24] that the relation between α and β is monotropic and the relations between δ and β and between δ and α are likely enantiotropic. The near convergence of G_α and G_β curves near the G_L curve explains the closeness of their melting points. The enthalpy and entropy differences between the D-mannitol polymorphs from this study are $H_\alpha - H_\delta = 2.3$ kJ/mol, $S_\alpha - S_\delta = 8.3$ J/(K mol); $H_\beta - H_\delta = 0.8$ kJ/mol, and $S_\beta - S_\delta = 4.8$ J/(K mol) (for $T = 90-165$ °C).

Tazofelone. Our eutectic-melting data (Table 2), along with the melting data already reported,[8] yielded the free-energy difference between the racemate RII and the conglomerate over about 70 °C (Figure 7). Figure 7 shows a good correlation between $G_C - G_{RII}$ obtained from the melting data (the thick,

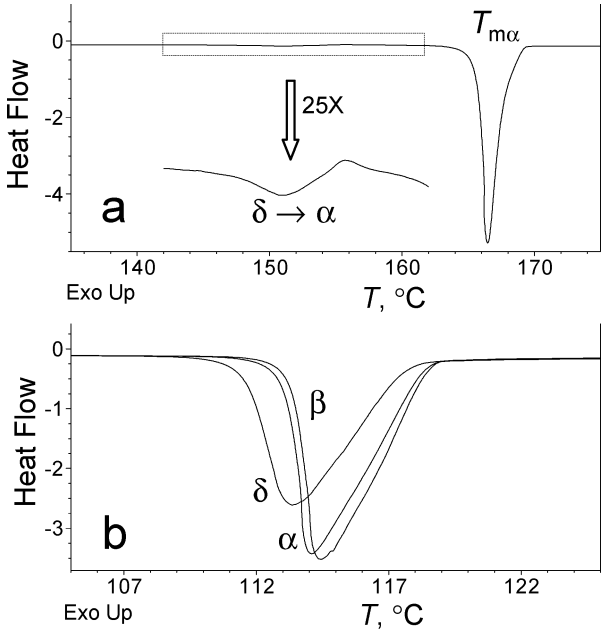

Figure 5. δ D-mannitol melts incongruently in the pure form (a) because the metastable liquid crystallizes to α (see expanded view). It melts congruently in the presence of I-erythritol (b).

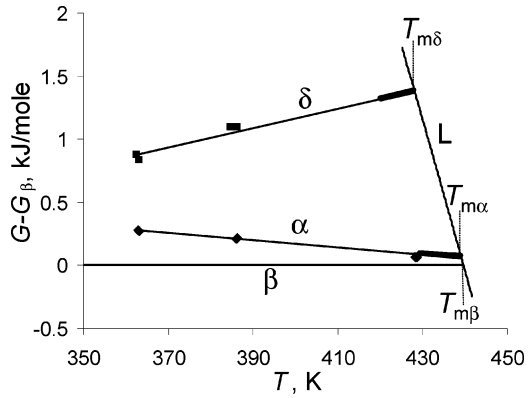

Figure 6. $\Delta G - T$ plot of D-mannitol polymorphs. L, liquid. ΔG from melting data is shown by the thick short lines.

TABLE 2: Melting and Eutectic Melting of Tazolfelone[a]

additive		RII[b]	A
benzanilide	x_e	0.52	0.60
	T_e, °C	133.8	122.6
	ΔH_{me}, kJ/mol	33.3	25.6
phenacetin	x_e	0.33	0.45
	T_e, °C	120.3	114.2
	ΔH_{me}, kJ/mol	32.3	27.0
acetanilide	x_e	0.19	0.31
	T_e, °C	102.2	94.7
	ΔH_{me}, kJ/mol	22.6	20.0
benzil	x_e	0.11	0.22
	T_e, °C	90.6	85.4
	ΔH_{me}, kJ/mol	23.5	22.1

[a] Pure melting data: $T_m = 154.7$ (RII), 150.5 (A) °C; $\Delta H_m = 39.2$ (RII), 24.5 (A) kJ/mol (ref 8). [b] From ref 8.

short line at T_{mA}) and the eutectic-melting data (solid circles). The values of $G_C - G_{RII}$ (3−5 kJ/mol) are significantly larger than those of $G_{RI} - G_{RII}$ (less than 0.2 kJ/mol).[8] The values of $H_C - H_{RII}$ (11 kJ/mol) and $S_C - S_{RII}$ [19 J/(K mol)] are also significantly higher than the corresponding values between RI and RII [2.7 kJ/mol and 6.7 J/(K mol)].[8] The large $G_C - G_{RII}$

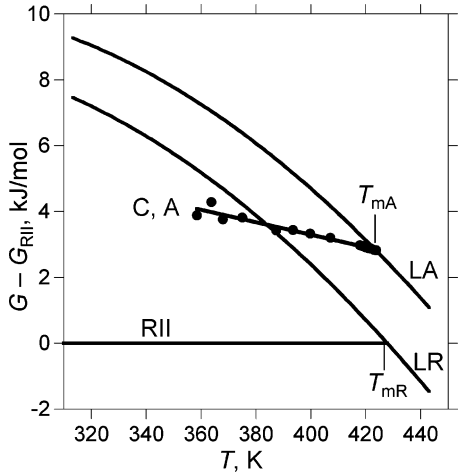

Figure 7. Free energies of the conglomerate (C), enantiomorph (A), racemic liquid (LR), and enantiomerically pure liquid (LA) of tazofelone relative to its racemate RII.

suggests that C cannot spontaneously crystallize from a racemic solution (such crystallization yields RI or RII). However, C was obtained by first resolving the pure enantiomers, then crystallizing them separately, and finally physically mixing the crystals of opposite enantiomers.[8] Thus formed, the conglomerate can exist at room temperature and under mild heating (to 100 °C) despite its high free energy (ca. 5 kJ/mol above RII at 300 K).

Eutectic-Melting Method. To date we have applied the eutectic-melting method to the polymorphic systems of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (ROY),[7,9] tazofelone,[8] D-mannitol, and glycine. Whenever possible, the eutectic-melting method has been combined with the pure melting method[5] to extend the temperature of measurement. It is experimentally and conceptually convenient to treat the two methods as one. The melting/eutectic-melting method complements the two common techniques, heat capacity[3] and solubility,[4] for measuring the free-energy difference between polymorphs. The heat-capacity method remains the most fundamental, offering the free energies, not just free-energy differences, of polymorphs from their heat capacities measured as a function of temperature from nearly 0 K. This method requires a relatively long equilibration time, which may be undesirable for polymorphs of short lifetimes, and 1−10 g of materials, which may be unavailable in early studies of polymorphs. To relate one polymorph to another, the method requires thermodynamic data of the polymorphs' transformation, melting, dissolution, vaporization, or combustion. The solubility method uses the equation $G_j - G_i = RT \ln(x_j/x_i)$ to calculate the free-energy difference between polymorphs from their solubilities x_i and x_j. This method requires no data on polymorphic transformation or melting but is limited to relatively low temperatures (up to the solvent's boiling point) and is sensitive to errors from solution-mediated transformations and formation of cocrystals with the solvent. Precise measurement of solubility requires approximately 0.1−1 g of materials. The chief advantage of the melting/eutectic-melting method is that it can be implemented with modern DSC and can be carried out rapidly with small quantities of material (1−10 mg per analysis). The fast scanning enables studies of highly unstable polymorphs that otherwise transform before melting, during long equilibration, or when they come into contact with solvent.

Structure-Stability Relations in Molecular Crystals. The thermodynamic data of polymorphs are useful for understanding structure-stability relations in molecular crystals. One structure-stability relation widely accepted by chemists and germane to this work is that a racemate is generally more stable than the corresponding conglomerate.[10,26] Whereas the crystals of tazofelone follow this relation, the crystals of glycine do not. Glycine's chiral polymorph γ is more stable than its achiral polymorph α below 123 °C. This raises questions as to why glycine, an achiral molecule, prefers a chiral crystal structure and how the preference for racemic crystal structures is restored in higher amino acids. We will address these questions in a subsequent paper.

Conclusions

We have described the thermodynamic principles and experimental implementation of a eutectic-melting method for determining the free-energy difference between crystal polymorphs. By changing the eutectic additive, the method enables the measurement of ΔG as a function of temperature. The method is applicable to true polymorphs and to pairs of racemate and conglomerate of resolvable enantiomers. It is especially suitable for crystals that chemically decompose (glycine) or physically transform (δ D-mannitol) before melting. This is a general method for studying polymorphs because eutectic formation is common in binary mixtures and different additives (including liquid additives) are available to achieve eutectic melting. It can be carried out by DSC quickly, with minimal materials, and over a wide range of temperatures. This method complements other methods for studying the relative stability of polymorphs. The data obtained from such studies are important to understanding, controlling, and predicting crystal polymorphs.

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Appendix. Derivation of Equations 7 and 8

Equation 7. The enthalpy and entropy changes of steps a1−a6 are

$$\Delta H = (x_{ei} - x_{ej})(H_i - H_Q)_{T_{ei}} \qquad \Delta S = (x_{ei} - x_{ej})(S_i - S_Q)_{T_{ei}} \quad \text{(a1)}$$

$$\Delta H = \Delta H_{mei} \qquad \Delta S = \Delta H_{mei}/T_{ei} \quad \text{(a2)}$$

$$\Delta H = -(x_{ei} - x_{ej})(H_{LP} - H_{LQ})_{T_{ei}}$$
$$\Delta S = -(x_{ei} - x_{ej})(S_{LP} - S_{LQ})_{T_{ei}} - R[x_{ej} \ln x_{ej} + (1 - x_{ej}) \ln(1 - x_{ej}) - x_{ei} \ln x_{ei} + (1 - x_{ei}) \ln(1 - x_{ei})] \quad \text{(a3)}$$

$$\Delta H = C_{pL(x_{ej})}(T_{ej} - T_{ei}) \qquad \Delta S = C_{pL(x_{ej})} \ln(T_{ej}/T_{ei}) \quad \text{(a4)}$$

$$\Delta H = -\Delta H_{mej} \qquad \Delta S = -\Delta H_{mej}/T_{ej} \quad \text{(a5)}$$

$$\Delta H = -C_{pC(x_{ej})}(T_{ej} - T_{ei}) \qquad \Delta S = -C_{pC(x_{ej})} \ln(T_{ej}/T_{ei}) \quad \text{(a6)}$$

In the equations above, H_i, H_{LP}, H_Q, and H_{LQ} are the molar enthalpies of i, the liquid of P (LP), Q, and the liquid of Q (LQ), respectively; S_i, S_{LP}, S_Q, and S_{LQ} are the corresponding molar entropies; $C_{pL(x_{ej})}$ is the molar heat capacity of the solution $\{x_{ej}P + (1 - x_{ej})Q\}$; and $C_{pC(x_{ej})}$ is the molar heat capacity of

the crystalline mixture $[x_{ej}\mathrm{j} + (1 - x_{ej})\mathrm{Q}]$. Adding the ΔH and ΔS of each step (a1−a6), we obtain

$$\Delta H = \Delta H_{mei} - \Delta H_{mej} + \Delta C_{pej}(T_{ej} - T_{ei}) + (x_{ej} - x_{ei})[(H_{LP} - H_i) - (H_{LQ} - H_Q)]_{T_{ei}}$$

$$\Delta S = \Delta H_{mei}/T_{ei} - \Delta H_{mej}/T_{ej} + \Delta C_{pej}\ln(T_{ej}/T_{ei}) + (x_{ej} - x_{ei})[(S_{LP} - S_i) - (S_{LQ} - S_Q)]_{T_{ei}} - R[x_{ej}\ln x_{ej} + (1 - x_{ej})\ln(1 - x_{ej})] + R[x_{ei}\ln x_{ei} + (1 - x_{ei})\ln(1 - x_{ei})]$$

where ΔC_{pej} is the molar heat capacity change upon melting the j−Q eutectic. We have assumed ΔC_{pej} to be constant because $|T_{ej} - T_{ei}|$ is usually small (less than several kelvin).

Applying $\Delta G = \Delta H - T\Delta S$, we obtain

$$x_{ej}(G_j - G_i)_{T_{ei}} = \Delta H_{mej}(T_{ei} - T_{ej})/T_{ej} + \Delta C_{pej}[T_{ej} - T_{ei} - T_{ei}\ln(T_{ej}/T_{ei})] + (x_{ej} - x_{ei})[(G_{LP} - G_i)_{T_{ei}} - (G_{LQ} - G_Q)_{T_{ei}}] + RT_{ei}\{[x_{ej}\ln x_{ej} + (1 - x_{ej})\ln(1 - x_{ej})] - [x_{ei}\ln x_{ei} + (1 - x_{ei})\ln(1 - x_{ei})]\}$$

where $(G_{LP} - G_i)_{T_{ei}}$ is the molar free-energy difference between LP and i at T_{ei} and $(G_{LQ} - G_Q)_{T_{ei}}$ is the molar free-energy difference between LQ and Q at T_{ei}. The third and fourth terms in the above equation vanish if $x_{ej} = x_{ei}$. If $x_{ej} \neq x_{ei}$, we estimate these terms by substituting into eq 1 $(G_{LP} - G_i)_{T_{ei}} = -RT_{ei}\ln x_{ei}$ and $(G_{LQ} - G_Q)_{T_{ei}} = -RT_{ei}\ln(1 - x_{ei})$, which hold if P and Q form ideal solutions. On rearranging the resulting terms, we obtain eq 7.

Equation 8. The enthalpy and entropy changes of steps b1−b8 are

$$\Delta H = C_{pC(x_{eR})}(T_{eR} - T_{eA}) \qquad \Delta S = C_{pC(x_{eR})}\ln(T_{eR}/T_{eA}) \tag{b1}$$

$$\Delta H = \Delta H_{meR} \qquad \Delta S = \Delta H_{meR}/T_{eR} \tag{b2}$$

$$\Delta H = -C_{pL(x_{eR})}(T_{eR} - T_{eA}) \qquad \Delta S = -C_{pL(x_{eR})}\ln(T_{eR}/T_{eA}) \tag{b3}$$

$$\Delta H = 0 \qquad \Delta S = -Rx_{eR}\ln 2 \tag{b4}$$

These results follow the assumption of ideal mixing between the liquid of Q (LQ), the liquid of *d* (LD), and the liquid of *l* (LL). The mixing between LD and LL is assumed to be ideal.[10]

$$\Delta H = (x_{eA} - x_{eR})(H_{LA} - H_{LQ})_{T_{eA}} \qquad \Delta S = (x_{eA} - x_{eR})(S_{LA} - S_{LQ})_{T_{eA}} + R[x_{eR}\ln x_{eR} + (1 - x_{eR})\ln(1 - x_{eR}) - x_{eA}\ln x_{eA} - (1 - x_{eA})\ln(1 - x_{eA})] \tag{b5}$$

$$\Delta H = -\Delta H_{meA} \qquad \Delta S = -\Delta H_{meA}/T_{eA} \tag{b6}$$

$$\Delta H = -(x_{eA} - x_{eR})(H_A - H_Q)_{T_{eA}} \qquad \Delta S = -(x_{eA} - x_{eR})(S_A - S_Q)_{T_{eA}} \tag{b7}$$

$$\Delta H = 0 \qquad \Delta S = 0 \tag{b8}$$

In the equations above, H_A, H_{LA}, H_Q, and H_{LQ} are the molar enthalpies of A, the liquid of A (LA), Q, and the liquid of Q (LQ); S_A, S_{LA}, S_Q, and S_{LQ} are the molar entropies of A, LA, Q, and LQ; $C_{pL(x_{eR})}$ is the molar heat capacity of the solution $\{x_{eR}/2\ d + x_{eR}/2\ l + (1 - x_{eR})\mathrm{Q}\}$; and $C_{pC(x_{eR})}$ is the molar heat capacity of the crystalline mixture $[x_{eR}\mathrm{R} + (1 - x_{eR})\mathrm{Q}]$.

Adding the ΔH and ΔS of individual steps (b1 − b8), we obtain

$$\Delta H = \Delta H_{meR} - \Delta H_{meA} + \Delta C_{peR}(T_{eA} - T_{eR}) + (x_{eA} - x_{eR})[(H_{LA} - H_A) - (H_{LQ} - H_Q)]_{T_{eA}}$$

$$\Delta S = \Delta H_{meR}/T_{eR} - \Delta H_{meA}/T_{eA} + \Delta C_{peR}\ln(T_{eA}/T_{eR}) + (x_{eA} - x_{eR})[(S_{LA} - S_A) - (S_{LQ} - S_Q)]_{T_{eA}} - Rx_{eR}\ln 2 + R[x_{eR}\ln x_{eR} + (1 - x_{eR})\ln(1 - x_{eR})] - R[x_{eA}\ln x_{eA} + (1 - x_{eA})\ln(1 - x_{eA})]$$

where $\Delta C_{peR} = C_{pL(x_{eR})} - C_{pC(x_{eR})}$ is the molar heat capacity change upon melting the R−Q eutectic. We have assumed ΔC_{peR} to be constant because $|T_{eA} - T_{eR}|$ is usually small (less than several kelvin).

Applying $\Delta G = \Delta H - T\Delta S$, we obtain

$$x_{eR}(G_C - G_R)_{T_{eA}} = \Delta H_{meR}(T_{eR} - T_{eA})/T_{eR} + \Delta C_{peR}[T_{eA} - T_{eR} - T_{eA}\ln(T_{eA}/T_{eR})] + RT_{eA}x_{eR}\ln 2 + (x_{eA} - x_{eR})[(G_{LA} - G_A)_{T_{eA}} - (G_{LQ} - G_Q)_{T_{eA}}] + RT_{eA}\{[x_{eA}\ln x_{eA} + (1 - x_{eA})\ln(1 - x_{eA})] - [x_{eR}\ln x_{eR} + (1 - x_{eR})\ln(1 - x_{eR})]\}$$

where $(G_{LA} - G_A)_{T_{eA}}$ is the molar free-energy difference between LA and A at T_{eA} and $(G_{LQ} - G_Q)_{T_{eA}}$ is the molar free-energy difference between LQ and Q at T_{eA}. Moving the ln 2 term to the left-hand side and estimating the last two terms as we did for eq 7, we obtain eq 8.

References and Notes

(1) Byrn, S. R.; Pfeiffer, R. R.; Stowell, J. G. *Solid State Chemistry of Drugs*, 2nd ed.; SSCI, Inc.: West Lafayette, IN, 1999.

(2) Bernstein, J. *Polymorphism in Molecular Crystals*; Oxford University Press: New York, 2002.

(3) Westrum, E. F.; McCullough, J. P. Thermodynamics of Crystals. In *Physical Chemistry of the Organic Solid State*; Fox, D., Labes, M. M., Weissberger, A., Eds.; Interscience Publishers: New York, 1963.

(4) (a) Beckmann, W.; Boistelle, R.; Sato, K. *J. Chem. Eng. Data* **1984**, *29*, 211. (b) Higuchi, W. I.; Lau, P. K.; Higuchi, T.; Shell, J. W. *J. Pharm. Sci.* **1963**, *52*, 150. (c) Milosovich, G. *J. Pharm. Sci.* **1964**, *53*, 484.

(5) Yu, L. *J. Pharm. Sci.* **1995**, *84*, 966.

(6) Teetsov, A. S.; McCrone, W. C. *Microsc. Cryst. Front* **1965**, *5*, 13.

(7) Yu, L.; Stephenson, G. A.; Mitchell, C. A.; Bunnell, C. A.; Snorek, S. V.; Bowyer, J. J.; Borchardt, T. B.; Stowell, J. G.; Byrn, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 585.

(8) Reutzel, S.; Russell, V.; Yu, L. *J. Chem. Soc., Perkin Trans. 2* **2000**, *5*, 913.

(9) Chen, S.; Guzei, I. A.; Yu, L. *J. Am. Chem. Soc.* **2005**, *127*, 9881.

(10) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing Company: Malabar, FL, 1991.

(11) Li, Z. J.; Grant, D. J. W. *J. Pharm. Sci.* **1997**, *10*, 1073.

(12) Yu, L.; Ng, K. *J. Pharm. Sci.* **2002**, *91*, 2367.

(13) Yu, L.; Milton, N.; Groleau, E.; Mishra, D.; Vansickle, R. *J. Pharm. Sci.* **1999**, *88*, 196.

(14) Yu, L.; Mishra, D.; Rigsbee, D. *J. Pharm. Sci.* **1998**, *87*, 774.

(15) Telang, C.; Suryanaryana, R.; Yu, L. *Pharm. Res.* **2003**, *20*, 1939.

(16) Yu, L. *J. Am. Chem. Soc.* **2003**, *125*, 6381.

(17) (a) Iitaka, Y. *Proc. Jpn. Acad.* **1954**, *30*, 109. (b) Iitaka, Y. *Acta Crystallogr.* **1961**, *14*, 1.

(18) Sakai, H.; Hosogai, H.; Kawakita, T.; Onuma, K.; Tsukamoto, K. *J. Cryst. Growth* **1992**, *116*, 421.

(19) Perlovich, G. L.; Hansen, L. K.; Bauer-Brandl, A. *J. Therm. Anal. Calorim.* **2001**, *66*, 699.

(20) Park, K.; Evans, J. M. B.; Myerson, A. S. *Cryst. Growth Des.* **2003**, *3*, 991.

(21) Drebushchak, V. A.; Kovalevskaya, Y. A.; Paukov, I. E.; Boldyreva, E. V. *J. Therm. Anal. Calorim.* **2003**, *74*, 109.

(22) Walter-Levy, L. *C. R. Acad. Sci. Paris* **1968**, *267*, 1779.
(23) Jones, F. T.; Lee, K. S. *Microscope* **1970**, *18*, 279.
(24) Burger, A.; Henck, J.-O.; Hetz, S.; Rollinger, J. M.; Weissnicht, A. A.; Stöttner, H. *J. Pharm. Sci*. **2000**, *89*, 457.
(25) Burger, A.; Ramberger, R. *Mikrochim. Acta* **1979**, 259−271 and 273−316.
(26) Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.
(27) The leading term in the Taylor series expansion of the ΔC_p term in $T_{ej} - T_{ei}$ is $\Delta C_{pej}(T_{ej} - T_{ei})^2/(2T_{ei})$.
(28) The leading term in the Taylor's expansion of the RT term in $x_{ej} - x_{ei}$ is $(x_{ej} - x_{ei})^2/[2x_{ei}(1 - x_{ei})]$.
(29) McCrone, W. C. *Fusion Methods in Chemical Microscopy*; Interscience Publishers: New York, 1957.
(30) Lacourt, A.; Delande, N. *Microchem. J. Symp. Ser.* **1962**, *2*, 259.
(31) It is possible that the simple average can be improved by a weighted average because, if $x_e \rightarrow 0$, x_e(Q) should better approximate x_e than x_e(P) and, if $x_e \rightarrow 1$, x_e(P) should better approximate x_e than x_e(Q). However, for consistency with our previous results (refs 7 and 8), we used the simple average here.
(32) To derive eq 13, first calculate the weight fraction of the 50/50 (w/w) mixture of P and Q that participates in the eutectic melting. $f_w = 0.5 + 0.5x_eM_P/[(1 - x_e)M_Q] = M_{eff}/[2(1 - x_e)M_Q]$. ΔH_{me} in J/g is $\Delta H_{me50/50}/f_w$. ΔH_{me} in kJ/mol is $M_{eff}\Delta H_{me50/50}/f_w/1000 = 2\Delta H_{me50/50}(1 - x_e)M_Q/1000$.
(33) Chongprasert, S.; Knopp, S. A.; Nail, S. L. *J. Pharm. Sci.* **2001**, *90*, 1720.
(34) Pyne, A.; Suryanarayanan, R. *Pharm. Res.* **2001**, *18*, 1448.