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On the Polymorphism of Pharmaceuticals and Other Molecular Crystals. I

Theory of Thermodynamic Rules

By

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With 3 Figures

Micro-methods play an important part in the investigation of polymorphic organic substances, especially pharmaceuticals, forming molecular crystals. The methods include thermomicroscopy, infrared spectroscopy and thermal analysis, especially differential scanning calorimetry (DSC), which is becoming more and more important.

Unfortunately, it seems that the more data become available, the less is attention paid to clear interpretations; sometimes erroneous conclusions have been drawn. To avoid misinterpretations, we have used energy/temperature phase-diagrams in previous publications[1-3].

With these it is easy to demonstrate the rule of thumb, that in the case of enantiotropism the transition of two polymorphic modifications is endothermic, whereas for monotropic forms it is exothermic. Instead of the enthalpy of transition the difference in the heats of fusion may, in most cases, be used. Moreover, the modification which is the more unstable at 0 K should have the lower density. Similar rules were first formulated by Tammann[4] in 1913. However, he only gave some "probability" arguments on a purely thermodynamic basis, without accounting for the nature of polymorphism. Moreover, many new data have since become available (see part II[5]). Hence it appears necessary to look more closely at the general applicability of these rules, in the light of present knowledge.

Solids which form molecular crystals can now be described in terms of approximate models, mainly based on semi-empirical intermolecular potentials[6-8]. Such models have been successfully used to calculate the heat and temperature of transition, and sometimes the accompanying changes in volume, for certain polymorphic substances, such as p-dichlorobenzene[7] or n-alkanes[8]. However, the models have to be applied individually for each substance, with more or less experimental information involved, and no direct generalization to arbitrary systems seems possible[9, 10]. Therefore we are still often restricted to plausibility arguments when deriving thermodynamic relations of polymorphic systems.

In the first part of this work we briefly show the plausibility of the above-mentioned rules, as well as of a rule concerning infrared data, on the basis of statistical mechanics. In part II[5] we apply the rules to the data for more than 200 polymorphic transitions, taken from the literature and our own experiments.

Thus the aims of this contribution are as follows.

(1) To confirm the rules above both theoretically and experimentally.

(2) To present them as a useful tool for clarifying the stability relations between various polymorphic forms, as well as a means of avoiding erroneous interpretations of DSC measurements. In addition, other criteria for determining the stability behaviour are discussed.

(3) To suggest a unified representation of the stability relations in polymorphic systems in the form of energy/temperature diagrams.

We confine our attention to molecular crystals. However, it may be expected that to some extent, the rules also hold for other types of solids.

Thermodynamic Aspects

We consider two modifications (A and B) of a molecular crystal at constant pressure, usually 1 bar. Let A be the phase which is the more stable at 0 K, and $\Delta X = X_B - X_A$ for any thermodynamic variable X. (We assume that it is possible to define all thermodynamic quantities for the metastable state[11].) At a possible first-order *transition point* (T_p) (enantiotropism, Fig. 1a), the equilibrium condition implies that the (molar) free energies* are equal at T_p, so that the (molar) enthalpy difference is

$$\Delta H = \Delta G + T_p \Delta S = 0 - T_p \left(\frac{\partial \Delta G}{\partial T} \right) > 0 \qquad (1)$$

* Often called "free enthalpies".

Since T_p is positive, ΔH must have the same sign as ΔS, and as ΔS is positive at T_p[12] we conclude that *near a first-order transition point, only endothermic transitions from the low-temperature to the high-temperature phase are possible and vice versa*[12].

As the actual *transition temperature* (T_1 or T_2 in Fig. 1) usually does not coincide with T_p, the question arises whether this rule can be extended to all temperatures in the case of enantiotropism,
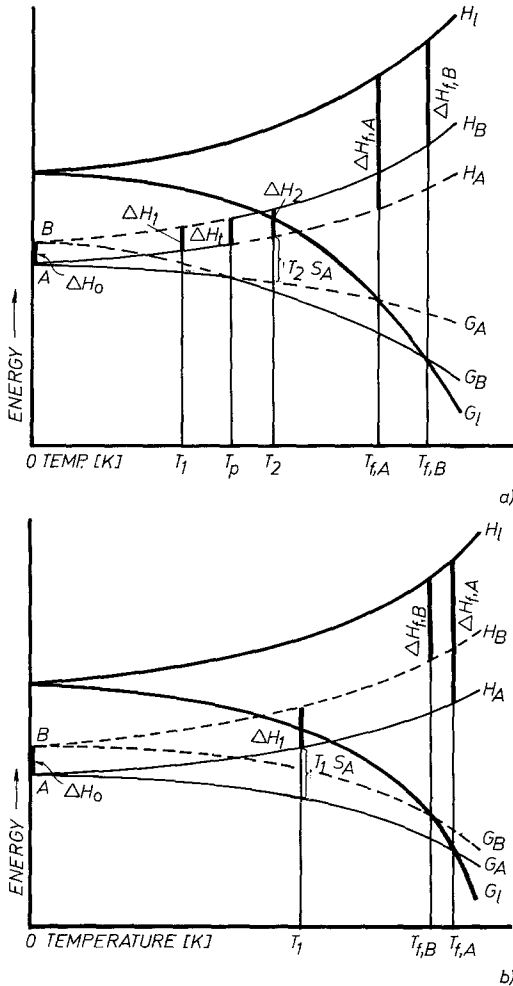

Fig. 1. Energy/temperature diagrams of dimorphic systems
(a) Enantiotropic systems, (b) monotropic systems. (T_p: transition point; T_f: fusion point; H: molar enthalpy; G: molar free energy; S: molar entropy; A, B: crystalline modifications; l: liquid phase)

and how monotropism can be included. To answer this question, we now look at the behaviour of ΔH and ΔS.

Enthalpy and Entropy Relations Between the Polymorphs

At 0 K we may neglect the small differences in the zero-point oscillation energy[13] and in PV (except for very high pressures), so ΔH_0 is determined by the structural potential energy. As seen from the literature, the differences in *conformation* and hence in the corresponding energy and entropy are rather slight in most polymorphic systems, so the difference ΔH_0 is mainly determined by the *lattice* properties.

To a first approximation the thermal motion of a crystal lattice consists of independent harmonic oscillations (normal modes), each of which can be described as the motion in a potential field (Fig. 2).
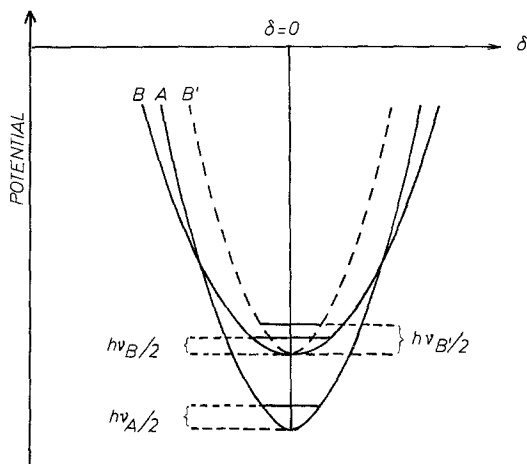
Fig. 2. Harmonic oscillator potentials of a lattice mode for mods. A and B. δ may be an intermolecular distance or a lattice angle or a linear combination of distances and angles, referred to the equilibrium position ($\delta=0$). B' corresponds to the exceptional case, that an eigenfrequency of mod. B is not lower than the respective frequency of mod. A

(Polymorphism in metals has been discussed on a similar basis[14].) In this approximation the thermal expansion is neglected[9], and the molar specific heat is given by[15]

$$c_p = c_v = \frac{k}{n} \sum_v \frac{(h\nu/kT)^2 \exp(h\nu/kT)}{[\exp(h\nu/kT) - 1]^2} \tag{2}$$

(n = number of moles in the crystal, h = Planck's constant, k = Boltzmann constant).

The shape of the potential well determines the frequency (ν), and the sum of the potentials gives the lattice energy. If a specific potential well is deeper for one modification, the frequency will be larger (Fig. 2). Hence for mod. B — having a smaller binding energy — the frequencies of the lattice oscillations (librations and vibrations[16]) are usually shifted to lower values. Thus, if we assume for simplicity that

$$\nu_A \geq \nu_B \tag{3}$$

holds for all frequencies ν, we can conclude immediately that Δc_p is always positive, since each term in (2) is monotonically decreasing if ν increases*. Since modification A also has the lower zero-point enthalpy, with $\Delta c_p > 0$ we have

$$\Delta H = \int_0^T \Delta c_p \, dT + \Delta H_0 > 0 \tag{4}$$

and

$$\Delta S = \int_0^T \frac{\Delta c_p}{T} \, dT + \Delta S_0 > 0, \tag{5}$$

where $\Delta S_0 = 0$ if both forms are ordered crystals; a disordered phase is always less stable than the ordered one at 0 K, leading to $\Delta S_0 > 0$ in this case.

For real crystals, the harmonic approximation is not valid and relation (3) does not always holds. Anharmonic effects lead to mode coupling and to thermal expansion, so that additional terms in the specific heat have to be considered[17]. However, these terms are small compared with the right-hand side of (2), as has also been shown experimentally[18-20]. Thus, the corresponding part of Δc_p is also expected to be small. Anharmonic effects may also give rise to the appearance of an additional "soft" mode at T_p[21], thus further increasing the heat capacity of the high-temperature phase and so Δc_p.

A more severe problem is the fact that relation (3) holds only on the average; moreover, the frequency depends on the width as well as the depth of the potential well, so a smaller potential depth may not necessarily imply a lower frequency (cf. B' in Fig. 2). Of course, it is impossible to derive generally similar inequalities for Δc_p, ΔH and ΔS; even in the simple case of metals no general features can be detected in comparing the phonon spectra of two modifications[14]. The results $\Delta H > 0$ and $\Delta S > 0$ are nevertheless supposed to hold, because the deviations may cancel after summation and integration and be compensated by ΔH_0 and ΔS_0, respectively. However, we must take exceptions into account. At least for Δc_p, exceptions have been found experimentally[19, 22, 23].

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* This can be proved by differentiating with respect to ν.

In some rare cases the interaction between the conformation of the molecules and the lattice structure is not negligible (conformational polymorphism[6]). In this case ΔH_0 does not necessarily correlate with the lattice energy difference, and Eqs. (4) and (5) are not necessarily fulfilled, thus also giving rise to possible exceptions.

Order-Disorder Transitions

Some kinds of disordered phases can also be regarded as polymorphous. Moreover, it may require considerable experimental effort to decide whether a given solid phase shows elements of disorder. Thus we briefly discuss special features of such transitions. The disordered phase always corresponds to form B since the bonds between the randomly arranged molecules must be weaker, leading to a smaller binding energy. The entropy difference resulting from disorder is roughly $\Delta S_0 \approx R \ln N$ per mole, where N is the number of equivalent positions or orientations occupied at random by the molecules[22, 24, 25].

In the pretransition region, where disorder effects gradually increase, Δc_p becomes negative if the transition is of purely second order (Fig. 3). However, we may define a hypothetical phase A
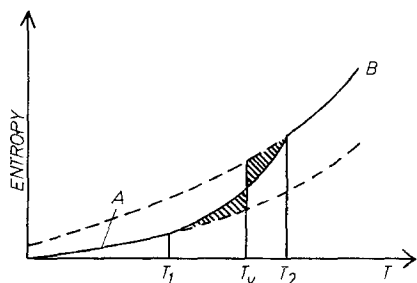

Fig. 3. Replacement of a second-order transition at T_2 by a virtual first-order transition at T_v

without the occurrence of disorder effects (dashed line in Fig. 3), and replace the pretransition region by a virtual first-order transition[22], such that the hatched areas are equal (Fig. 3).

In rotational transitions the orientation of a specific group (e. g. $-CH_3$) or of the whole molecule begins to "jump" at random, which on a time-average looks like a rotation[22, 24, 26, 27].

The thermodynamic effect of this "rotation" is often negligible, since the corresponding observed heat capacities are about $6\,R$ instead of $4.5\,R$ for free rotation[26]. Thus rotational disorder can usually be treated thermo-

dynamically like static orientational disorder. However, it may explain sometimes a slightly negative Δc_p, as in 2-methylpropane-2-thiol (modifications I and II)[22], assuming that the number of degrees of freedom is slightly reduced by the change to hindered rotation.

The Heat-of-Transition Rule (HTR)

Knowing that ΔH and ΔS are usually positive, we suppose that the H curves do not intersect and the G curves may intersect at most once (Fig. 1). Concerning the last statement, only one exception has been claimed, namely iron; but its significance was doubted[12].

Thus, since only transitions to a lower free energy are possible, the plausibility of the rule mentioned in the introduction has now been confirmed by statistical-mechanical arguments. We want to formulate it as follows:

HTR: (a) *If an* endothermal transition *is observed at some temperature it may be assumed that there is a transition point below it, i. e. the two forms are related* enantiotropically *(Fig. 1a).*

   (b) *If an* exothermal transition *is observed at some temperature it may be assumed that there is no transition point below it, i. e. the two forms are either related* monotropically *(Fig. 1b) or the transition temperature is higher (Fig. 1a).*

In the last case a second, endothermic transition has to be observed above the transition temperature, as for 2,4,6-tribromophenol, for example[5].

This rule has often been used without being explicitly mentioned, and rather uncritically[12, 27−31], but exceptions cannot be excluded *a priori*, particularly in the case of conformational polymorphism. We have found only a few possible exceptions in the literature, and further investigations may lead to a revision of the corresponding data, as in the case of o-nitrotoluene[5]. Thus, the rule may be applied with confidence.

The Heat-of-Fusion Rule (HFR)

Frequently the rate of transformation is so small that the heat of transition cannot be measured easily by *DSC*. Instead, the difference between the heats of fusion of the lower melting form (II) and the higher melting form (I) may often be used in applying the *HTR* (cf. Fig. 1). In other words:

HFR: *If the higher melting form has the lower heat of fusion the two forms are usually* enantiotropic, *otherwise they are* monotropic.

Of course, the difference between the heats of fusion, $\Delta H_{f, II} - \Delta H_{f, I}$, is not exactly equal to the heat of transition. To estimate the error we can use the relation

$$\Delta H_{II \to I} (T = T_{f, I}) = \Delta H_{f, II} + \int_{T_{f, II}}^{T_{f, I}} (c_{p, l} - c_{p, II}) \, dT - \Delta H_{f, I} \qquad (6)$$

(l refers to the supercooled liquid; note that $I = B$ in Fig. 1a and $I = A$ in Fig. 1b).

Assuming the integrand to be bounded by M

$$|c_{p, l} - c_{p, II}| \leqq M \qquad (7)$$

the error can be bounded by

$$\left| \int_{T_{f, II}}^{T_{f, I}} (c_{p, l} - c_{p, II}) \, dT \right| \leq |T_{f, I} - T_{f, II}| \cdot M \qquad (8)$$

A reasonable choice for M is $0.005 \, \Delta H_f$ per degree.

If the error estimated by Eq. (8) is greater than the difference of the heats of fusion, the result can be improved by measuring the heat of crystallization, $H_{c, II}$, below $T_{f, II}$ and estimating

$$c_{p, I} - c_{p, II} \cong \frac{\Delta H_{f, II} - \Delta H_{c, II}}{T_{f, II} - T_{c, II}} \qquad (9)$$

Thus (6) gives

$$\Delta H_{II \to I} (T = T_{f, I}) \cong \Delta H_{f, II} - \Delta H_{f, I} + \frac{\Delta H_{f, II} - \Delta H_{c, II}}{T_{f, II} - T_{c, II}} \cdot (T_{f, I} - T_{f, II})$$

$$(10)$$

With this value for the heat of transition, the HTR can be applied now, as is demonstrated in part II[5] for acetaminophen. It should be emphasized however, that in most cases we investigate in part II the HFR is found to be valid.

Density Rule (DR)

In comparing different structures of molecular crystals it is found in most cases that the only important contribution to the zero-point enthalpy results from the lattice energy, as stated above.

In the absence of orientated interactions such as hydrogen bonds, this energy merely depends on the distance between the molecular

"surfaces" or, more exactly, between the outer atoms of neigh-bouring molecules. Since the atom-atom potentials have a very steep repulsive section it is clear that the molecular "surfaces", deter-mined by the condition that these potentials assume their minima, can hardly overlap[13, 32]. On the other hand, for geometrical reasons the molecules cannot "touch" each other everywhere, i. e. most of the atom-atom distances will be somewhat greater than corresponds to the respective minima.

Thus the minimum potential energy, giving the stable form at 0 K, will be achieved to a good approximation by minimizing the distances between adjacent molecules, i. e. by close packing (except in those rare cases where the influence of the molecular conformation cancels the advantage of close packing[13]). Assuming simple un-directed interactions with the same strength on the whole surface, this requirement is essentially equivalent to maximizing the density or packing coefficient.

If directed forces such as hydrogen bonds are present, the cor-responding short contacts predominantly determine the intermo-lecular potential energy, and the atom-atom potential method fails[9]. In this case, it is not possible to conclude a correlation between density and potential energy — especially if two structures, each of which, of course, corresponds to a *local* minimum of this energy, differ in the arrangement of these contacts. Sometimes it may be more efficient to have an optimal arrangement of the hydrogen-bond interactions but rather large distances between the rest of the molecular surfaces, rather than having shorter distances every-where. In this case the density of an unstable phase may be higher (e. g. resorcinol[33]).

In the case of a disordered crystal, the potential energy and the macroscopic structure are obtained by averaging over the different positions or orientations[26]. It is clear that such "average molecules" have a smaller binding energy and are more extended than individual ones, leading to a more open structure.

Resuming the discussion, we conclude that the form which is stable at 0 K usually has the highest possible density, or more generally:

DR: *If one modification of a molecular crystal has a lower density than the other, it may be assumed to be less stable at absolute zero.*

The experimental data we have collected in part II[5] show only a few exceptions to this rule.

Infrared Rule (IRR)

If hydrogen bonds predominate in the crystal structure, their strength mainly determines the oscillatory motion of the lattice. As before, we may assume that the frequencies of the corresponding modes are higher if the binding energy of the intermolecular hydrogen bonds is higher, thus reducing the entropy according to Eqs. (2) and (5). On the other hand, a hydrogen bond loosens the corresponding N-H or O-H bond, more or less strongly. Hence the infrared frequencies of the respective stretching vibrations are lowered, depending the strength of the hydrogen bonds[34-36]. These vibrations are scarcely excited at ambient temperature, so their entropy effect is negligible.

The whole effect is most pronounced if the vibrations are only weakly coupled to the rest of the molecule, which is usually the case for O-H, N-H or symmetric NH_2 stretching vibrations. Thus, to be specific, we take only the highest absorption frequency into consideration and formulate a readily applicable rule as follows.

IRR: *If the first absorption band in the infrared spectrum of a hydrogen-bonded molecular crystal is higher for one modification than for the other, that form may be assumed to have the larger entropy.*

This statement is related to the convergence properties of the free-energy curves, since the entropy at constant pressure is given by $S = -\partial G/\partial T$ (Fig. 1). The combination of this rule with $\Delta S > 0$ (see above) suggests that the modification which absorbs at higher frequencies is also less stable at $0\,K$.

As only the "first peak" is considered here, without accounting for other effects on the entropy, more exceptions may be expected than for the other rules. Indeed, exceptions have been found in several cases, as will be seen in part II[5].

More Than Two Modifications

In this case the previous rules have to be applied to each combination of any modifications.

Acknowledgement

Summary

On the Polymorphism of Pharmaceuticals and Other Molecular Crystals. I

On the basis of statistical mechanics, it is shown that the following rules concerning the relative stability of different polymorphic modifications are usually obeyed. (1) The enthalpy of transition of two enantiotropic forms is always positive at temperatures above their transition point, and negative at temperatures below the transition point or between monotropic forms (heat-of-transition rule). (2) Instead of the heat of transition, the difference in the heats of fusion may generally be used (heat-of-fusion rule). (3) If a modification is less dense, it is less stable at absolute zero. (4) For hydrogen-bonded crystals, the modification for which the first absorption band in the infrared spectrum is at higher frequencies has the larger entropy. The possibility of exceptions is discussed.

Zusammenfassung

Über die Polymorphie von Arzneistoffen und anderen Molekülkristallen. I

Mit Argumenten der statistischen Mechanik wird gezeigt, daß im Hinblick auf die relative Stabilität polymorpher Modifikationen von Molekülkristallen im allgemeinen folgende Regeln gelten. 1. Die Umwandlungsenthalpie zweier enantiotroper Formen ist über ihrem Umwandlungspunkt immer positiv, unter dem Umwandlungspunkt oder zwischen monotropen Formen negativ (Umwandlungswärme-Regel). 2. Statt der Umwandlungswärme kann meist auch die Differenz der Schmelzwärmen verwendet werden (Schmelzwärme-Regel). 3. Eine Modifikation von geringerer Dichte weist am absoluten Nullpunkt die geringere Stabilität auf. 4. Bilden zwei Modifikationen Kristalle mit Wasserstoffbrücken, so hat diejenige die größere Entropie, deren erste Bande im IR-Spektrum bei höheren Frequenzen liegt. Auf mögliche Ausnahmen von diesen Regeln wird hingewiesen.

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