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An up-to-date approach to drug polymorphism

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Abstract

Topological rules for constructing (p,T) diagrams of drug polymorphs are discussed following a classical approach founded upon the Ostwald's principle of least vapor pressure. This method allows the definition of hierarchy stabilities among the crystal varieties of a polymorph as a function of temperature and pressure. It has been applied to two trimorphic drugs: sulfanilamide and piracetam. The overall monotropy of the metastable orthorhombic α-variety of sulfanilamide was demonstrated. In fact, it cannot possess any stability region, even at high pressures. The method for piracetam showed a sensitivity to the set of experimental data to which it is applied. Depending on the values of the transition temperatures of forms II (triclinic) and III (monoclinic) to form I (monoclinic), three kinds of (p,T) representations were derived. Preliminary applications of a high-pressure piezothermal method did not discern the three different kinds of (p,T) diagrams. © 1998 Elsevier Science B.V.

Keywords: Monotropy; Ostwald's principle; Polymorphism; Solid transitions; Stability

1. Introduction

One of the goals of studies on polymorphism is to define, if it exists, the thermodynamically stable domain of each crystalline phase of a substance.

From the experimental viewpoint of thermal analysis, transitions between two crystal varieties can be described by means of the Clapeyron equation:

$$\mathrm{d}p/\mathrm{d}T = \Delta H/(T\Delta V),$$

which incorporates entropy and volume variations at the transformation. Complementary applications of calorimetric and dilatometric (or crystallographic) methods to a solid–solid transition allow the slope of the equilibrium curve to be calculated. However, in the case of a trimorphic substance, the set of experimental data is only rarely complete, because some expected solid transitions are hardly ever observed. In this case, enthalpy changes may be computed by applying the first principle of thermodynamics.

As for drugs and excipients, metastable forms often possess the highest dissolution rates and, consequently, the highest bioavailability. Thus, it is of great interest to define a stability hierarchy among different varieties at least as a function of temperature. For this to be achieved, topological rules can be defined to describe the polymorphism of a given substance by means of a (p,T) phase diagram [1,2]. Further on, a classical approach for describing polymorphism founded upon the fundamental Ostwald's rule [3], according to which the stable variety exhibits the lowest vapor pressure, is given. For the sake of applying this approach to as large a number of polymorphs as possible, for which at least three solid forms are known, the phenomenology of trimorphism is developed and applied to the cases of sulfanilamide and of 2-oxo-1-pyrrolidineacetamide (piracetam).

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2. General rules

Riecke [4] pointed out that the number of triple points in the (p,T) diagram of a substance existing under n crystal varieties is equal to that, C, of the distributions of the ensemble of the $n+2$ phases into groups of $p=3$ phases:

$$C = (n+2)!/[p!(n+2-p)!],$$

p being the number of phases at each triple point and $n+2$ the ensemble of the phases. In the case of trimorphism ($n=3$), this formula leads to the prediction of 10 triple points. By naming S_1, S_2, S_3, l and v the three solid modifications, the liquid and the vapor phases of the body, respectively, the 10 triple points are: S_1-S_2-v, S_1-S_3-v, S_2-S_3-v, S_1-S_2-l, S_1-S_3-l, S_2-S_3-l, S_1-l-v, S_2-l-v, S_3-l-v and S_1-S_2-S_3. They cannot be all stable and must be located in the phase diagram according to the following rules:

(a) The fusion triple points S_i-l-v are situated on the vapor–liquid equilibrium curve l-v (Fig. 1(a)). By applying the Ostwald's principle, it is argued that the stable triple point is the one located at the highest temperature.
(b) At each stable triple point, the extensions of the stable two-phase equilibrium curves are metastable (Fig. 1(b)), those of the metastable curves at each metastable triple point are supermetastable (Fig. 1(c)), and those of the supermetastable curves at each supermetastable triple point are hypermetastable (Fig. 1(d)), as previously pointed out by Oonk [5]. This rule is referred to as the alternation one.

S_i-l-v triple points can be considered as fusion ones because, during DSC measurements performed on samples in sealed pans, the fusions occurred in the presence of a vapor phase filling the inner free volume of the pan. Since melting and solid transition curves, according to Oonk's and our current approaches, may be represented by straight lines up to high pressures (200 MPa), the Clapeyron equation allows the slopes of these equilibria to be calculated from a set of data obtained at room pressure. This leads to the isolation of the S_i-S_j-l triple points and, consequently, in the case of trimorphism, the S_i-S_j-S_k one, where all solid transition lines converge. So, the S_i-S_j-v triple points, whose corresponding solid transitions are not experimentally observed, may be localized by building the phase diagram as discussed. In particular, the application of the alternation rules permits the determination of the degree of stability of each triple point. For the sake of simplicity in calculations, the pressures of the S_i-S_j-v triple points are taken to be equal to zero.

3. Applications

3.1. Sulfanilamide

Data used for the sulfanilamide (p,T) diagram construction [6] are reported in Table 1. The temperature and enthalpy changes at the $\alpha\rightarrow\gamma$ and $\beta\rightarrow\gamma$ transitions and the γ-fusion temperature have been measured [7]. The $\alpha\rightarrow\beta$ enthalpy changes had to be estimated from the ones at the transitions $\beta\rightarrow\gamma$ and $\alpha\rightarrow\gamma$, respectively, as follows:

$$\Delta H_{\alpha\rightarrow\beta} = \Delta H_{\alpha\rightarrow\gamma} - \Delta H_{\beta\rightarrow\gamma}$$

The α- and β-fusion temperatures have been reported [8]. Significant results are those related to the solid transitions, i.e.:

$$\Delta H_{\alpha\rightarrow\gamma} < \Delta H_{\beta\rightarrow\gamma} \text{ and } T_{\alpha\rightarrow\gamma} < T_{\beta\rightarrow\gamma},$$

as well as crystallographic data [9–11] from which volume changes were calculated. It ensues that the

Table 1
Data used for construction of the sulfanilamide (p,T) diagram in Fig. 2

Form (M=172.2)	α	β	γ
T_{fus}^{a}/K	423	429	438
Triple point	α-l-v	β-l-v	γ-l-v
V/(cm^3 g^{-1})	0.6764	0.6604	0.6719
Transition	**α→β [e]**	**β→γ [e]**	**α→γ [e]**
T_{trs} [b]/K	533	391	381
Triple point	α-β-v	β-γ-v	α-γ-v
ΔH_{trs} [c]/(J g^{-1})	−0.7	+10.9	+10.2
ΔV [d]/(cm^3 g^{-1})	−0.016	+0.0115	−0.0045
(dp/dT)/(MPa K^{-1})	+0.175	+2.42	−5.95

[a] Fusion temperature.
[b] Transition temperature.
[c] Enthalpy change at the transition.
[d] Specific volume change at the transition.
[e] Estimated values.

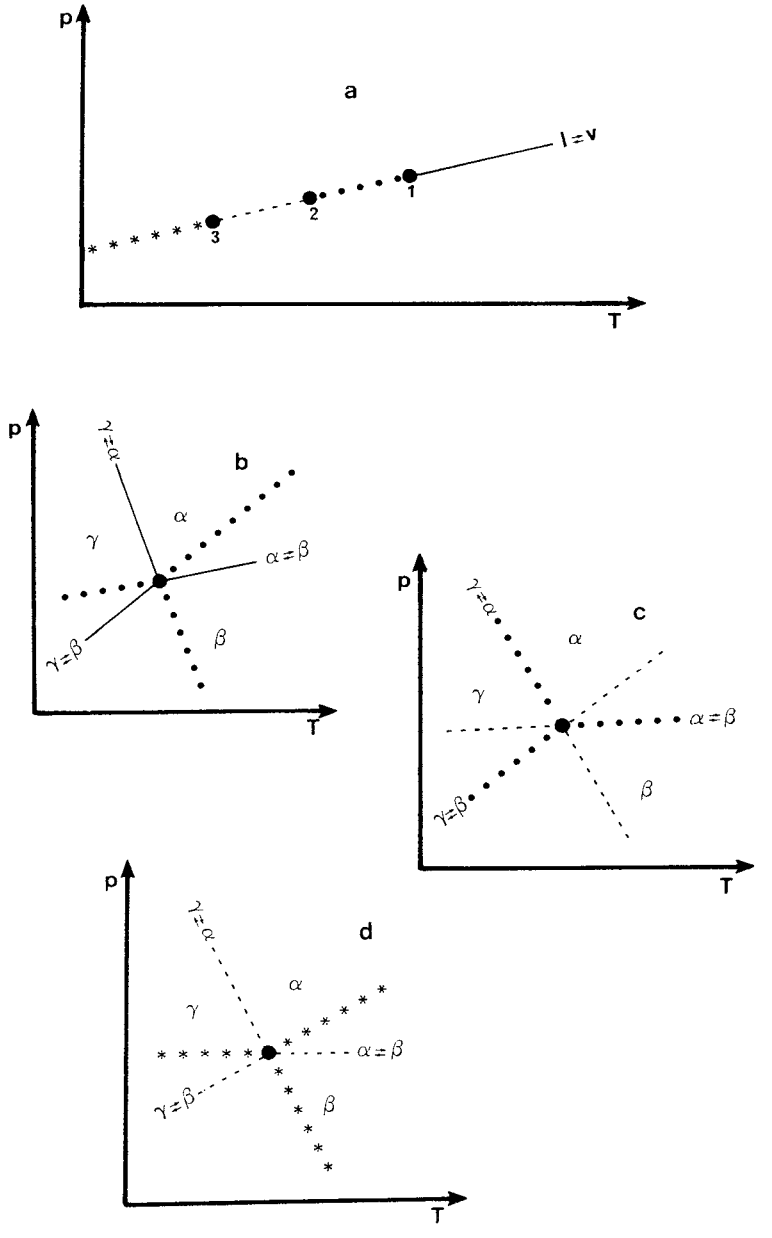

Fig. 1. (a) Hierarchy of stability of the melting triple points of three polymorphs in the (p,T) diagram of a trimorphic substance. (1) S_1-l-v, stable; (2) S_2-l-v, metastable; and (3) S_3-l-v, supermetastable. Equilibria; (———) stable equilibrium; (• • •) metastable equilibrium; (- - -) supermetastable equilibrium; and (* * *) hypermetastable equilibrium. b,c and d: Extensions of two-phase equilibrium curves built around a (b) stable, (c) metastable, or (d) supermetastable triple point concerning the α, β and γ forms of a pure solid substance: (———) stable equilibrium; (• • •) metastable equilibrium; (- - -) supermetastable equilibrium; and (* * *), hypermetastable equilibrium.

metastable $\alpha \rightarrow \gamma$ equilibrium line has a negative slope, while the one of the stable $\beta \rightarrow \gamma$ equilibrium is positive. Hence, these lines have to converge at very low pressures and, consequently, the α-variety cannot possess any stability domain. This is an example of overall monotropy. In a previous paper [2], the importance to discern between overall or 'true' monotropy and high-pressure enantiotropy was emphasized. In

fact, a crystal variety, as the β-form of As_2Te_3 [12] which possesses a high-pressure stable domain, can exhibit a monotropic behavior at room pressure [12,13]. In the case of sulfanilamide, only the β- and γ-varieties own a stability domain. The former is stable at room temperature, the latter is the high-temperature stable form. Because the γ-form converts into the β-one, even at high temperatures, when non-hydrostatic pressure is applied [14], it is a probable low-pressure enantiotropic form. The (p,T) diagram of sulfanilamide (Fig. 2) should be similar to that of the sulfur dimorphism. Computed data for α→β transition corroborate our finding about the overall monotropy of phase α. As a matter of fact, the α-β-v triple point is situated at a temperature higher than that of melting of the γ-variety.

Crystal energy calculations for each variety were performed [6] using the atom–atom potential method [15], according to which energy is expressed as the sum of the interatomic energies of a molecule and its surroundings. Since the molecules are linked through hydrogen bonding, a comparative study of three kinds of intermolecular potentials, MCMS [16], HHL [17] and HHL/CNDO-2 was performed. The results are reported in Table 2. Also from these calculations, form β is found to be the most stable one at ordinary conditions. The disagreement in metastability between forms α and γ (from the phase diagram, it turns out that the γ-form would be the less stable form at room temperature) may be ascribed to the parameter values of the sulfur–sulfur potential, which are less accurately known than those of the other atoms.

3.2. Piracetam

Piracetam crystallizes into at least three crystal forms, I (monoclinic), II (triclinic) and III (monoclinic). The crystal structures of the last two varieties are already known [18,19]. More recently, the structure of phase I has been solved from X-ray powder diffraction using the AAP method [20]. Density and thermodynamic data in Table 3 are the same as reported previously [21]. For this compound, II–I and III–I equilibrium lines converged at high pressures toward the stable triple point I-II-III. By using data reported in Table 3, the III-I and the II-I lines can be described by the equations: p/MPa=2.10((T/K)−392) and p/MPa=2.16((T/K)−399), respectively.

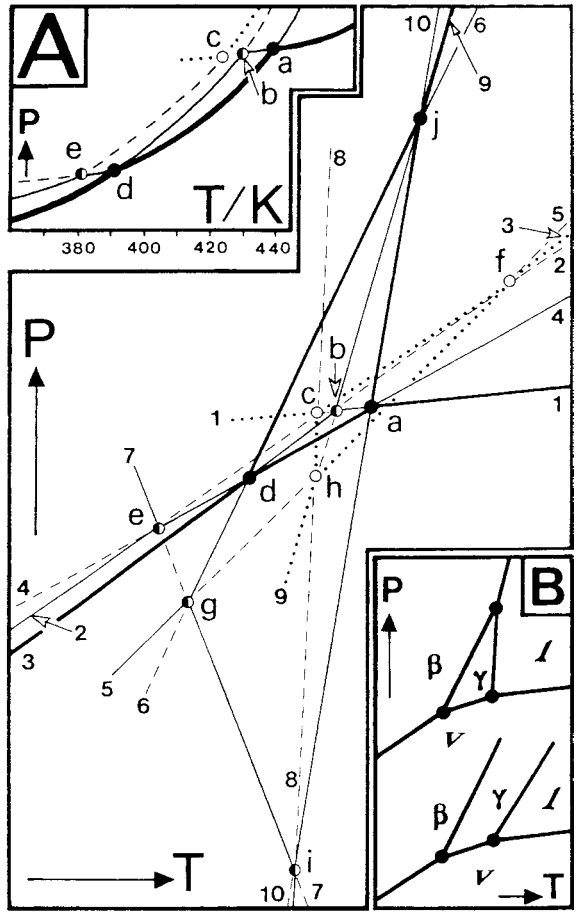

Fig. 2. Sulfanilamide p,T phase diagram. Triple points: (a) γ-l-v; (b) β-l-v; (c) α-l-v; (d) β-γ-v; (e) α-γ-v; (f) α-β-v; (g) α-β-γ; (h) α-β-l; (i) α-γ-l; and (j) β-γ-l. Two-phase equilibrium curves: (1) l-v; (2) α-v; (3) β-v; (4) γ-v; (5) α-β; (6) β-γ; (7) α-γ; (8) α-l; (9) β-l; and (10)) γ-l. Inset A: Location of the experimentally observed triple points. Inset B: Representation of the stable phase regions. Upper part: Low-pressure enantiotropy of form γ. Lower part: overall enantiotropy of form γ. Triple points: black: stable, black and white: metastable, white: supermetastable.

The coordinates of the I-II-III triple point, which is situated on the stable portion of the I-II line, are then T=662 K and p=568 MPa. Since $T_{II\rightarrow I}>T_{III\rightarrow I}$, it ensues that each phase should possess a stability domain: the variety I at low pressures, as will be demonstrated, and at high temperatures, the variety II at low pressure and low temperatures, and the variety III at high pressures, whatever the temperature. The derived (p,T) diagram is drawn in Fig. 3. In order

Table 2
Sulfanilamide: E_T (kJ mol^{-1}): reticular energy, E_C (kJ mol^{-1}): electrostatic contribution, d (g cm^{-3}): density, S(Å): overall shift of the molecular center in the calculated structure with respect to the X-ray one [a]

	X-rays	MCMS	HHL	HHL/CNDO/2
α-Form orthorhombic Pbca, Z=8				
E_T		−90.04	−105.06	−80.12
E_C		−7.36	−50.50	−7.53
d	1.478	1.53	1.29	1.42
S		0.60	1.50	0.64
β-Form monoclinic P2$_1$/c, Z=4				
E_T		−100.71	−113.18	−85.35
E_C		−15.82	−46.86	−9.96
d	1.514	1.59	1.42	1.46
S		0.07	0.43	0.32
γ-Form monoclinic P2$_1$/c, Z=4				
E_T		−94.31	−105.31	−81.13
E_C		−11.34	−49.62	−8.24
d	1.488	1.57	1.30	1.44
S		0.80	0.69	1.03

Densities have been obtained by X-ray measurements ([9–11]). Energies have been calculated by applying the MCMS ([16]), the HHL ([17]), and the HHL/CNDO/2 intermolecular potentials, respectively.

Table 3
Data used for the drawing the piracetam (p,T) diagram in Fig. 3 [a]

Form (M=142.2)	I	II	III
T_f [b]/K	426	415	412
Triple point	I-l-v	II-l-v	III-l-v
V/(cm^3 g^{-1})	0.7657	0.7380	0.7321
Transition	II→I	III→II	III→I
T_{tr} [c]/K	399	>622	392
Triple point	II-I-v	III-II-v	III-I-v
ΔH_{tr} [d]/(J g^{-1})	+24	+4	+28
ΔV [e]/(cm^3 g^{-1})	+0.028	+0.006	+0.034
(dp/dT)/(MPa K^{-1})	+2.16	+1.66	2.10

[a] In Ref. [21] the lowest estimated temperature for the III-II-v triple point was 428 K. However, by taking into account the topological location of the I-II-III triple point, the first one has to be situated on the same equilibrium line, II-III, at $T>T_{(I\text{-}II\text{-}III)}$, i.e. at $T>662$ K.
[b] Fusion temperature.
[c] Transition temperature.
[d] Enthalpy change at the transition.
[e] Specific volume change at the transition.

to give a prominent representation of the (p,T) domain demarcated by the three fusion triple points and by the I-II-v and I-III-v ones, the representation of the high-pressure and of the high-temperature ranges has been contracted. Consequently, the p and T values of the I-II-III, II-III-l and II-III-v triple points appear as unrealistically low on Fig. 3.

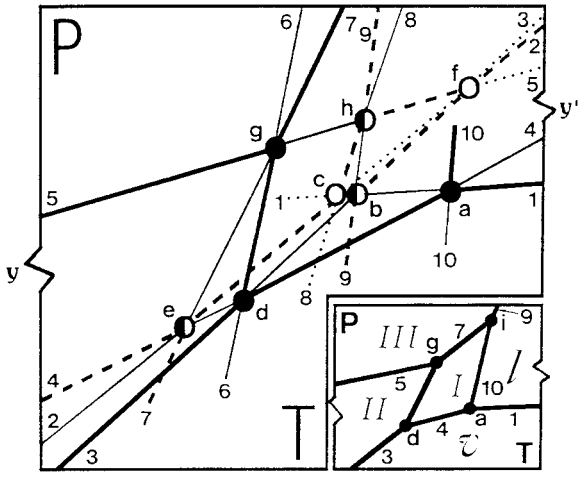

Fig. 3. Piracetam p,T phase diagram. Triple points: (a) I-l-v; (b) II-l-v; (c) III-l-v; (d) I-II-v; (e) I-III-v; (f) II-III-v; (g) I-II-III; (h) II-III-l; (i) I-III-l; and (j) I-II-l. ((+) experimental, and (*) not represented). Two-phase equilibrium curves: (1) l-v; (2) III-v; (3) II-v; (4) I-v; (5) II-III; (6) I-II; (7) I-III; (8) III-l; (9) II-l; and (10) I-l. Stability hierarchy. Triple points: black: stable, black and white: metastable, white: supermetastable. Two-phase equilibrium curves: thick: stable, thin: metastable, dashed: supermetastable, dotted: hypermetastable. Insert: stable phase domains whether curves 7 and 10 meet point i at high pressures. The portion of the diagram above the pressure axis foldings y and y' is actually situated at very high pressures and to be shifted toward higher temperatures.

Hierarchy stability, it can be argued, for the three solid phases is the same as obtained by AAP lattice-energy calculations [20]. The temperature of the II-l-v melting triple point (415 K) is that of the weak endotherm recorded on some curves of form II: it is a consequence of its incomplete transition into phase I on heating. By applying the first rule for constructing phase diagrams, we argue that the I-l-v triple point is stable, while II-l-v and III-l-v are metastable and supermetastable, respectively.

According to the transition temperatures into phase I ($T_{III\to I}<T_{II\to I}$), triple points II-l-v and III-I-v are stable and metastable, respectively. Some experimental findings agree with this (p,T) representation. Firstly, form I, which may be easily obtained by heating forms II and III, is not stable at room tem-

perature and rapidly transforms into form II. Secondly, form III, which is the densest phase at ordinary conditions, should own a stability domain at high pressures, according to Le Chatelier's principle and routine experience of polymorphs.

Ter Minassian [22] has recently found that phase I is a low-pressure enantiotropic one by applying a piezothermal method [23] to the study of the piracetam transitions under pressure. This method, whose suitability to pressure linear scans was improved [24], is based upon the principle that heat is liberated when a hydrostatic constraint is applied on matter; the determination of the expansivity of matter is possible by measuring its heat of compression. The method is based on the Maxwell thermodynamic equation, which gives the isothermal variation of the entropy S resulting from a variation of the pressure p:

$$(\delta S/\delta p)_T = -(\delta V/\delta T)_p$$

Thus, the entropy change at a first-order transition may be determined by varying pressure at a fixed temperature. Entropy changes correspond to the peak areas on traces, where the $(\delta V/\delta T)_p$ derivative is expressed as a function of pressure. By decreasing pressure at the constant temperature T=443 K, after compression up to ca. 200 MPa of a sample of the variety III, the III→I transition and the I-fusion were recorded at 156 and at 113 MPa, respectively. Taking into account the temperatures of these transitions at room pressure, it can be shown that III-I and I-l equilibrium lines converge at high pressures toward the III-I-l triple point.

Nevertheless, the (p,T) phase diagram deduced from our thermodynamic data disagrees with the stability hierarchy argued from the energy vs. temperature diagram reported by Kühnert-Brandstätter et al. [25]. The reason of this disagreement is that they measured $T_{III\rightarrow I} > T_{II\rightarrow I}$. By applying our approach to their results, we derive two kinds of diagrams drawn in Fig. 4. In the first one, the high-pressure stable form would be form II, which is in disagreement with the density hierarchy between phases II and III. In the second one, phase II would be monotropic. Such an outcome disagrees with the apparent enantiotropic behavior of phase II which has already been referred to by Kühnert-Brandstätter et al. [25]. On the other hand, preliminary high-pressure results do not allow the discrimination between these various eventualities. Further work, in particular at high pressures, is still required in order to remove ambiguities about the kind of (p,T) diagram for piracetam.

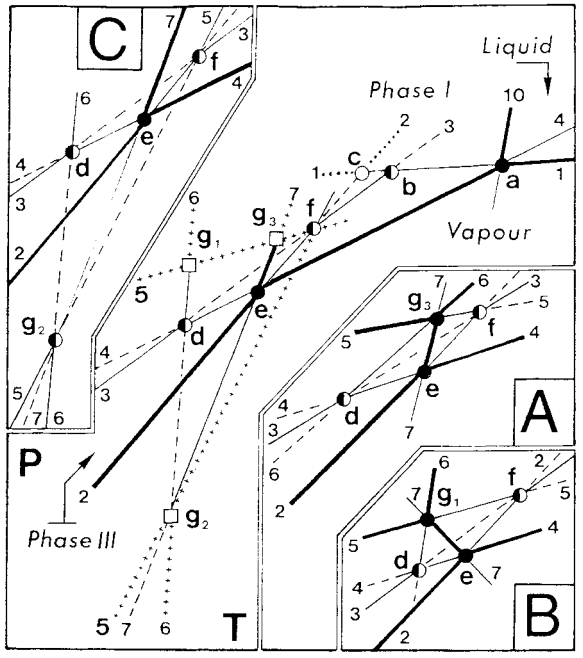

Fig. 4. Piracetam p,T diagram constructed from data in Ref. [25]. Stabilities, triple points and two-phase equilibrium curves have the same labeling as in Fig. 4. $g1$, $g2$ and $g3$ are possible locations of triple point g(I-II-III). $(+\,+\,+)$ denotes extensions of the two-phase equilibrium curves for which stability hierarchies are not taken into account.

4. Conclusions

In this report, a classical approach used to construct (p,T) phase diagrams has been presented and applied to experimental works. Its application allows to restore the intrinsic thermodynamic meaning of concepts such as 'stability' and 'metastability'. Moreover, macroscopic knowledge of polymorphism phenomenology can be broadened by complementary applications of thermodynamics (calorimetry and dilatometry) and crystallography. This approach permits the establishment of a stability hierarchy among crystal varieties of a polymorph, although it shows the strong dependence of the kind of diagram on the accuracy of the experimental data. Another important

feature is its suitability for being used to validate lattice-energy calculations.

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