J Therm Anal Calorim (2010) 102:357–360
DOI 10.1007/s10973-010-0856-z

Phenomenology of polymorphism and topological pressure–temperature diagrams

Description of the phase relationship involving Atovaquone polymorphs I and III

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Received: 12 March 2010 / Accepted: 27 April 2010 / Published online: 19 May 2010

Abstract Although polymorphism of drug molecules is often studied with extensive and excellent experimental data, pressure appears to be a forgotten variable. In this article, an analysis is provided of the phase behavior of Atovaquone using available literature data. A pressure–temperature diagram is constructed topologically by way of the Clapeyron equation. The method leads to the conclusion that Atovaquone phase I and III behave enantiotropically, like α- and β-sulfur do in their paradigmatic P–T diagram, and that phase I is stable at room temperature and under “ordinary” pressure.

Keywords Polymorphism · Enantiotropy · Pressure–temperature phase diagram · Drug · Atovaquone

Introduction

In an early “Online First” article [1], two polymorphs of the drug Atovaquone (ATO) are characterized structurally and calorimetrically with an excellent set of experimental data. It is reported that phase I transforms into phase III endothermically at 462 K ($\Delta_{\mathrm{I-III}}H = 6.815$ J g^{-1}) and that phase III melts at 493 K ($\Delta_{\mathrm{fus(III)}}H = 95.415$ J g^{-1}). The density of ATO I (1.353 g cm^{-3}) is higher than that of ATO III (1.328 g cm^{-3}), determined from crystal structures obtained at room temperature. In addition, it is reported that, upon cooling of the melt, ATO crystallizes into phase III with no detectable trace of phase I. It is concluded that the transition I–III is irreversible, and that ATO III is the thermodynamically stable polymorph at room temperature. Moreover, the case is considered by the authors as an exception to the “density rule” according to which the more stable phase should exhibit the higher density.

This article offers an alternative view on the phase behavior of ATO using the above-mentioned data in combination with well-established thermodynamic principles.

Data analysis

Atovaquone phase I (ATO I) endothermically transforms into ATO III on heating. According to Le Chatelier’s principle, this indicates that ATO III becomes the more stable phase at temperatures higher than the transition temperature. The density of ATO I is higher than that of ATO III. According to Le Chatelier’s principle, this indicates that ATO I should become the more stable phase at higher pressure (which is also a thermodynamic variable, despite the fact that it is seldom taken into account).

Transition I → III has all characteristics of a first-order phase transition (discontinuities in enthalpy and presumably in volume at 462 K) or in other words of a shifting monovariant two-phase equilibrium, conform to the Gibbs phase rule. Thus, the transition in question, which is accompanied with positive entropy and volume changes, can be represented by a monotonous convex curve, approximated by a straight line over reasonably short intervals in a P–T diagram. Only if the curve has a positive slope dP/dT, can it comply with Le Chatelier’s principle, as shown in Fig. 1a. Moreover, the value of this slope can be calculated, assuming that the difference in the specific

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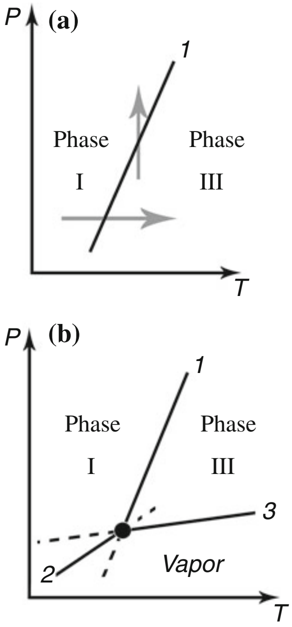

Fig. 1 **a** Relative position of the stable phase regions for phases I and III of Atovaquone in accordance with Le Chatelier's principle. The *vertical arrow* represents the transformation of phase III into phase I with increasing pressure, and the *horizontal arrow* represents the transformation of phase I into phase III upon heating. **b** Relative position of the stable phase regions for phases I, III, and vapor around the triple point I–III–*Vap* (*filled circle*), and positions of the corresponding equilibrium curves I–III (*1*), I–*Vap* (*2*), and III–*Vap* (*3*) together with their metastable extensions (*dashed*). *Vap* vapor

volumes Δv, remains constant with temperature, using the well-known Clapeyron equation:

$$\frac{dP}{dT} = \frac{\Delta S}{\Delta v} \qquad (1)$$

in which, $\Delta S = \Delta H/T$ (ΔH = enthalpy change at temperature T). It leads to $dP/dT = +1.06$ MPa K^{-1}, i.e., a positively sloped curve, as qualitatively inferred from Le Chatelier's principle.

As far as DSC experiments are concerned, the inner volume of sealed DSC pans will always contain some dead volume, which will be saturated with the specimen's vapor in accordance with thermodynamic equilibrium. The effect of vaporization-induced weight loss on the enthalpy may be neglected in the case of low vapor pressures. However, it ensues that transition-related DSC peaks represent triple points involving two condensed phases and the vapor phase (i.e., invariant conditions of constant temperature and constant pressure), rather than equilibria involving only two condensed phases. The only required approximation is to consider air molecules in the pans as a negligible impurity. Thus, Fig. 1a can be improved by topologically locating the triple point I–III–*Vap* at the lower end of the I–III equilibrium curve, and by adding the sublimation curves I–*Vap* and III–*Vap* to the graph (see Fig. 1b), so that the metastable counterparts of the two-phase equilibrium curves alternate with their stable parts. This follows the so-called "alternation rule" [2], a consequence of the projection onto the P–T plane of three monotonous $G(P,T)$ surfaces (one surface represents a single phase, G is Gibbs energy) intersecting as described by Gaskell [3].

Thus, phase I enantiotropically transforms into phase III, i.e. transition I–III is reversible in the thermodynamic sense, independent of whether it reverts experimentally. (Thermodynamics does not preclude a system from being in a metastable state.) This is in contrast with the conclusion in Ref. [1], that the transition does not revert after the melt recrystallized into phase III. It is worth reminding that such an observation agrees with the rule of stages by Ostwald [4] that metastable phases crystallize first from the melt. It seems that the thermodynamic behavior of Atovaquone is but another example of this "rule".

Discussion

Since the authors determined the melting enthalpy of phase III at Tfus(I) = 493 K, a more complete picture of the phase relationships involving phases I and III can be constructed qualitatively in the form of one of four topological P–T diagrams formerly drawn by Bakhuis Roozeboom for dimorphism [5]. Of these four possibilities, the two cases representing enantiotropy may be applicable to Atovaquone, depending on whether equilibrium curves I–III and III–L (L = liquid) diverge or converge as the pressure increases (Fig. 2).

The slope of the equilibrium III–L can be calculated with the Clapeyron equation (1), if the liquid density is known. This value is lacking, as unfortunately is often the case in thermodynamic assessments of phase behavior. Nevertheless, melting of molecular compounds is usually accompanied with a volume increase. In a note on the relationship between organic solid and liquid density at the triple point, Goodman et al. found that a simple ratio, $\rho_S(Tt)/\rho_L(Tt) = 1.17$, is adequate and reliable for most organic compounds ($\rho_S(Tt)$ and $\rho_L(Tt)$ are solid and liquid densities at triple point Tt, respectively) [6]. Recently determined specific volume changes upon melting agree rather well with Goodman et al.'s ratio (see Table 1). Moreover, it can be seen that the lattice expansion for organic crystals from room temperature to their respective temperature of fusion is in the order of 2% only (Table 1).

From the foregoing, it can be assumed that the specific volume of the liquid is larger by 5–15% in comparison with the specific volume of the polymorphs at room temperature. Neglecting lattice expansion (cf. Table 1) the volume change at the melting temperature of phase III can be estimated within 0.0377 and 0.1130 $cm^3\ g^{-1}$. With these values, the slope dP/dT for the III–L equilibrium curve is found to be within 5.1 and 1.7 MPa K^{-1}, a value similar to those reported in Table 1, and in any case larger than 1.06 MPa K^{-1}, the dP/dT slope for the I–III equilibrium curve. Moreover, even with a difference $\Delta_{III-L}v$ as high as 20% with respect to the specific volume of phase III at 298 K, dP/dT (III–L) is found to be 1.285 MPa K^{-1}. This

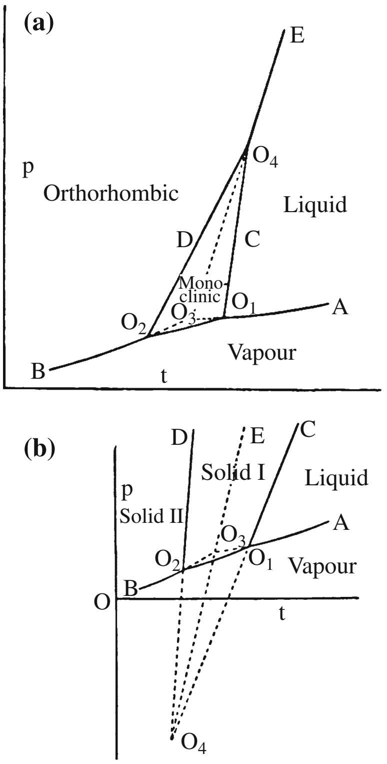

Fig. 2 Original drawings by Bakhuis Roozeboom who described in 1901 two possible cases of enantiotropic behavior [5]. **a** P–T diagram of sulfur which shows that the orthorhombic polymorph becomes the sole stable phase at higher pressure, where the behavior of the monoclinic polymorph is monotropic. **b** Overall enantiotropic behavior. Solid I and solid II exhibit its own stable phase regions independent of pressure

entails that equilibrium curves I–III and III–*L* should cross in the higher-pressure phase region of the P–T diagram. The crossing point is the I–III–*L* triple point, as shown in Fig. 3a.

Similar to curve I–III intersecting the triple point I–III–*Vap* (cf. Figs. 1, 3), the stable part of the melting curve III–*L* should intersect triple point III–*L*–*Vap*, which is connected to triple point I–III–*Vap* by the sublimation curve III–*Vap*. The latter is the equilibrium curve involving the two phases shared by these two triple points. Now, the P–T region, where phase III is stable, is enclosed by a triangle defined by three stable triple points (cf. Fig. 3a). A triple point involving I–*L*–*Vap* still needs to be found.

At triple point I–III–*L*, equilibrium I–*L* should become stable with increasing pressure in accordance with the alternation rule. It ensues that the d*P*/d*T* slope for equilibrium curve I–*L* should be smaller than that for the III–*L* equilibrium curve. Furthermore, equilibrium curve I–*L* should pass through all triple points with which it shares two common phases. Next to I–III–*L*, this should be triple point I–*L*–*Vap*, which is metastable since it is located at the intersection of the metastable extensions of the I–*L*, *L*–*Vap*, and I–*Vap* curves inside the triangle of stable phase III (cf. Fig. 3b).

As $\Sigma(\Delta H) = 0$ and $\Sigma(\Delta v) = 0$ at triple point I–III–*L*, $\Delta_{\text{I}-L}H$ can be estimated to be about 102 J g^{-1} (i.e., $\Delta_{\text{I}-\text{III}}H + \Delta_{\text{III}-L}H$). It is inferred from Fig. 3 that $T_{\text{I}-L}$ should be found between $T_{\text{I}-\text{III}} = 462$ K and $T_{\text{III}-L} = 493$ K and that the slope d*P*/d*T* for equilibrium I–*L* should be smaller than that for equilibrium III–*L*.

Concluding remarks

A realistic description of the phase relationships between polymorphs can be obtained, if pressure is not neglected as a variable. With calorimetric and crystallographic data together with basic classical thermodynamics, it is even shown that it is not necessary to measure pressure directly.

On the other hand, structural information is crucial for the topological determination of relative stabilities of polymorphs by means of the Clapeyron equation. However, the specific volumes provided by structural information

Table 1 Experimental specific volumes for a number of molecular compounds in the solid (v_S) and molten (v_L) state, relative volume increase in the solid state 298 K—T_{fus}, related specific volume changes (Δv) upon melting, density ratios (ρ_S/ρ_L) taking ρ_S at 298 K and T_{fus} over ρ_L at T_{fus}, and values of the d*P*/d*T* slope of the melting curve

Compound	v_S(298 K)/ cm^3 g^{-1}	$v_S(T_{\text{fus}})$/ cm^3 g^{-1}	$(v_S(T_{\text{fus}}) - v_S(298))/v_S(298)$	$v_L(T_{\text{fus}})$/ cm^3 g^{-1}	$\Delta v(T_{\text{fus}})$/ cm^3 g^{-1}	$\rho_S(T_{\text{fus}})/\rho_L(T_{\text{fus}})$	$\rho_S(298\ \text{K})/\rho_L(T_{\text{fus}})$	$(\text{d}P/\text{d}T)_{S-L}$/ MPa K^{-1}	Ref.
Paracetamol phase I	0.7758	0.7935	0.0228	0.9090	0.1155	1.15	1.17	3.75	[7]
								4.96	[8]
Paracetamol phase II	0.7522	0.7682	0.0213	0.9025	0.1343	1.17	1.20	3.14	[7]
								4.14	[8]
Biclotymol phase I	0.7853	0.8000	0.0187	0.9033	0.1033	1.13	1.15	2.54	[9]
Progesterone phase I	0.8631	0.8801	0.0197	0.9590	0.0789	1.09	1.11	2.68	[10]
Progesterone phase II	0.8506	0.8652	0.0172	0.9524	0.0872	1.11	1.12	2.29	[10]
Lidocaine	0.9617	0.9762	0.0151	1.0338	0.0576	1.06	1.08	3.56	[11]

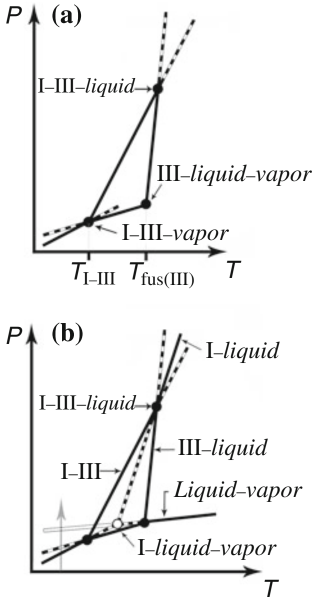

Fig. 3 **a** Crossing at triple point I–III–*L* of curves I–III and III–*L* originating from I–III–*Vap* and III–*L*–*Vap*, respectively. **b** Stable (*solid line*) and metastable (*dashed line*) parts of equilibrium curve I–*L* crossing stable triple point I–III–*L* and metastable triple point I–*L*–*Vap*. The *vertical gray arrow* at $T < T_{\text{I–III}}$ intersects equilibrium curves involving the vapor phase in the direction of decreasing stability: curve I–*Vap*, curve III–*Vap*, and curve L–*Vap*. The Ostwald rule states that the lower the vapor pressure the more stable the phase

should be accurate enough to infer work-related inequalities ($\Delta v = |w|/p$), as should information on the specific volume of the molten state. An analysis of polymorph densities based on a survey of the Cambridge Crystallographic Database has led to the conclusion that the "majority of polymorph pairs exhibit significantly different thermal expansion behavior and their density-temperature lines can cross" [12]. This indicates that a lack of precision in the determination of densities might lead to a wrong sign of the dP/dT slope for the I–III equilibrium curve. Nonetheless, this would not lead to a different conclusion as to the enantiotropic character of the I → III transition. The P–T diagram would contain a I–III equilibrium with a negative slope and a triple point I–III–*L* positioned at negative pressure, as depicted in Fig. 2 (right side, i.e., condition involving expanded metastable condensed phases).

In any case, using the available literature data for Atovaquone polymorph I and III, transition I → III must be an enantiotropic transition. Furthermore, the P–T diagram involving phases I and III most likely resembles the paradigmatic diagram formerly found by Tammann for α- and β-sulfur polymorphs; a diagram that is still found on the hard cover of the first edition of the book in [13].

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