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Tetramorphism of fananserine: p, T diagram and stability hierarchy from crystal structure determinations and thermodynamic studies

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Abstract. The structures of four crystalline phases of fananserine have been solved and their melting properties determined. The p-T diagram for this tetramorphism has been constructed by combining these data. Three out of the four solids are associated with stable p-Tdomains. Two of them have a low-pressure enantiotropic character in narrow p-T domains. The fourth one is intrinsically metastable. The stability ranking agrees with that inferred from solubility measurements at room temperature.

1. INTRODUCTION

Fananserine is a pharmaceutical compound (Fig. 1) for which four crystal forms (I, II, III and IV) have been isolated and the corresponding crystal structures solved (Table 1) [1].

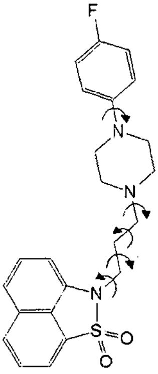

Figure 1. Molecular structure of fananserine.

Form	I	II	III	IV
System	triclinic	monoclinic	monoclinic	monoclinic
a (Å)	8.359(3)	17.887(2)	14.625(4)	8.633(2)
b (Å)	17.228(6)	6.597(1)	14.370(3)	9.714(2)
c (Å)	8.089(4)	9.076(2)	20.356(7)	12.270(2)
α (°)	101.32(3)	90	90	90
β (°)	110.85(4)	94,73(2)	92.84(3)	96.70(1)
γ (°)	86.85(3)	90	90	90
V (Å^3)	1068.2(5)	1067.4(3)	4273(2)	1021.9(3)
Space group	*P*-1	*P*2$_1$	*P*2$_1$/*n*	*P*2$_1$
Z	2	2	8	2
D_{calc}	1.323	1.325	1.323	1.383
R_{wp}	0.128	0.153	—	—
R$_1$	—	—	0.063	0.064

Table 1. Crystallographic data for the four forms of fananserine.

As none of these phases show (at 5 K/min) interconversion before melting, their melting temperatures and enthalpies were measured. No condensation was observed after maintaining form IV in a vacuum for three months at the hot source [T ≈ T_{fus}(IV)] of a temperature gradient. The pressure at which melting occurs at a given temperature and the melting entropy of form IV were obtained by pressure-temperature analysis at several temperatures, whose suitability for studying the polymorphism of organic compounds has previously been demonstrated [2-4].

The present report describes the different steps in the construction of the phase diagram (p-T) of this tetramorphism (20 triple points). The method is based on crystallographic and thermodynamic data, on the Ostwald criterion of lowest vapour pressure and on the rule of alternating stability (or metastability) of the two-phase equilibria forming a triple point [5,6].

Fananserine is a rare, if not original, example of tetramorphism, which is complete in structural and thermodynamic terms. As only the melting of each form is observed, the procedure used to construct the p-T diagram consisted in determining the Si-*l* melting curves, and then to define their intersections (triple points Si-Sj-*l*) from which the Si-Sj equilibria were determined. The temperatures of these equilibria, calculated at 'zero' pressure, were attributed to triple points Si-Sj-*v* (i and j define the solid forms I, II, III and IV of fananserine).

2. EXPERIMENTAL RESULTS AND CONSTRUCTION OF THE PHASE DIAGRAM (p-T)

The specific volumes of the four solids were deduced from crystallographic data obtained at room temperature [V(I) = 0.756, V(II) = 0.755, V(III) = 0.757 and V(IV) = 0.724 cm^3/g]. Form IV is the most dense. The DSC curves (0.5 K/min) of phases II, III and IV show only one melting peak, whereas that of phase I indicates that melting is followed by crystallisation of phase III. The melting temperatures and enthalpies are given in Table 2.

Phase	T_{fus} K	$\Delta_{fus}H$ (J/g)
I	366.3	60.2
II	375.1	65.3
III	374.8	69.0
IV	372.8	82.1

Table 2.

(Phase IV)			
T_{fus} (K)	p_{fus} (MPa)	ΔS_{fus} (e.u.)	$\Delta_{fus}H$ (J/g)
388.5	43.2	11.6	88.0
403.5	88.5	12.1	95.1
413.5	118.2	11.8	95.3

Table 3.

The inequality T_{fus} (II) > T_{fus}(III) was confirmed in several DSC analyses carried out by heating a given mass of form III and an equal mass of form II as reference. The first thermal event, onsetting at 374.8 K, was thus attributed to the melting of form III.

The melting pressure and entropy of phase IV were determined at three temperatures by pressure-temperature analysis (Table 3). Assuming that the melting point at atmospheric pressure (0.1 MPa) differs little from that of the triple point IV-*l*-*v*, the melting curve is thus represented by the line $p_{fus} = 2.914 \times T - 1087.5$ (where p_{fus} and T are expressed in MPa and K, respectively).

Volume variations during melting [$\Delta v(IV \rightarrow l)$ was 0.076 cm^3/g at normal pressure and changed very little with p] were determined using the Clausius-Clapeyron equation. Using the volume at room temperature and the expansion coefficient of IV obtained from crystallographic data, the volume $V(l)$ of the liquid at T_{fus}(IV) was calculated. It was considered to be constant over the rather limited temperature range in which the four phases melt and its value was used to calculate volume variations during the melting of the other phases. The slopes dp/dT and the linear equations for equilibria I-*l*, II-*l* and III-*l* were then determined. The four melting curves intercept at the six triple points Si-Sj-*l* thereby located. The lines for the Si-Sj equilibria were then calculated by forcing the equations to incorporate the triple points Si-Sj-*l*. The slopes were obtained using the Clausius-Clapeyron equation at the temperatures of the triple points Si-Sj-*l* using the enthalpy variations at the Si-Sj transitions, which were deduced, according first law of thermodynamics, from the melting enthalpies at atmospheric pressure and the volume variations calculated from the crystallographic data. The temperatures of the triple points Si-Sj-*v*, whose pressures are very close to 0 MPa, were extrapolated from this pressure and the coordinates of the triple points S_i-S_j-S_k were determined at the intersections of the Si-Sj curves.

The p-T diagram of fananserine (Fig. 2) shows five stable triple points, three of which involve the vapour phase (IV-III-*v* at 364.7 K, III-II-*v* at 369.4 K and II-*l*-*v* at 375.1 K). The other points are triple points IV-III-II (4.5 MPa at 368.8 K) and IV-II-*l* (20.8 MPa at 380.3 K).

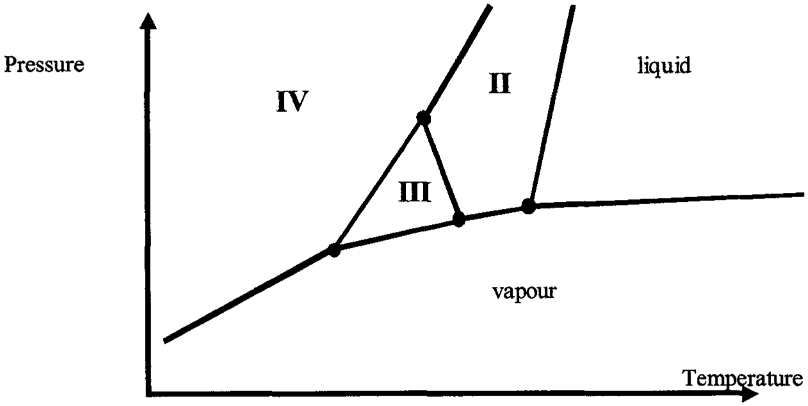

Figure 2. p-T diagram of fananserine (only four out of the five stable triple points appear)

It follows that phases II, III and IV each have their own stability domain, whereas phase I is an intrinsically metastable phase for which the thermodynamic data indicate a monotropic behaviour regardless of the phase (stable or metastable) into which it is passing. However, the stability domains of phases II and III are limited in pressure by that of phase IV, which is already more dense at atmospheric pressure. The stability domain of phase III appears to be limited to the triangle whose vertices are triple points IV-III-*v*, III-II-*v* and IV-III-II. The existence of a limited stability domain was corroborated by the experiment showing that the crystallisation of phase III from the metastable liquid arising from the melting of phase I occurs at a temperature within the calculated stability domain. The domain of phase II is a trapezoid whose vertices are triple points III-II-*v*, II-*l*-*v*, IV-III-II and IV-II-*l*. The stability domain of phase III is limited to the pressure range of 0 to

4.5 MPa by the stable IV-III equilibrium, and that of phase II is limited by the IV-II equilibrium, which is stable from 4.5 to 20.8 MPa.

It should be stressed that the stability ranking resulting from the Ostwald criterion at room temperature is consistent with that deduced from the solubility measurements, i.e. phases IV, III, II then I in order of increasing solubility and vapour pressure. The latter, which is intrinsically metastable, should be defined as 'hypermetastable' according to the nomenclature previously proposed [5,6], and phases III and II as 'metastable' and 'supermetastable', respectively.

3. CONCLUSION

The p-T diagram of fananserine tetramorphism shows that each of the three solid phases (II, III and IV) each have a stability domain whereas the fourth one (I) is an intrinsically metastable phase for which a general monotropic behaviour is indicated. However, the stability domains of phases II and III are limited in pressure by that of phase IV, which is the stable form at room temperature.

The criteria for constructing p-T diagrams, applied to an original case of tetramorphism, again show how crystallographic and thermodynamic data can be combined to determine the stability ranking of solid phases according to temperature and pressure, in the absence of experimental observation of certain transitions. In the present case, the stability domain for phase III appears to be very limited (temperature range of 5 K and pressure range of 5 MPa). Its existence must be confirmed by refining the experimental data from which the diagram is constructed.

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