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On the Dimorphism and the Pressure-Temperature State Diagram of Racemic *m*-Nisoldipine, a Dihydropyridine Calcium Ion Antagonist

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Abstract

The pressure-temperature phase diagram of the dimorphism of racemic *m*-nisoldipine is constructed using temperatures and enthalpies of fusion of forms A and B. At ordinary pressure, the transition from form B to form A is found to occur around 192 K, which indicates that these polymorphs are enantiotropically related and that form A is stable at room temperature. Nevertheless, the phase relationship turns to be monotropic when pressures become greater than about 100 MPa, which indicates that form B becomes the sole stable phase.

Résumé

Le diagramme pression-température du composé racémique m-nisoldipine est construit en utilisant les températures et les enthalpies de fusion des formes A et B. À pression ordinaire, la température de la transition de la forme B en forme A est déterminée à environ 192 K, ce qui indique que ces polymorphes sont en relation énantiotropique, la forme A étant la forme stable à température ambiante. Néanmoins, la relation entre ces phases devient monotropique quand les pressions deviennent supérieures à environ 100 MPa, indiquant ainsi que la forme B devient la seule forme stable.

Keywords

Racemic *m*-nisoldipine; crystalline polymorphism; topological P-T diagram; thermodynamic stability

Mots-clés

m-nisoldipine racémique; polymorphisme cristallin; diagramme P-T topologique; stabilité thermodynamique

1 Introduction

Racemic *m*-nisoldipine, of which the chemical structure is given in Figure 1, is a Ca^{2+} channel antagonist by blocking the current through these potential dependent channels [1-2]. In the solid state, it exhibits crystalline dimorphism and the calorimetric and crystallographic aspects have recently been investigated by Yang et al. [3-4]. It was concluded that "Forms A and B have an enantiotropic relationship with a conversion temperature of 47 °C and form A is the thermodynamically stable form below this temperature"[4]. This conclusion was obtained through solubility data at saturation and the intersection of the respective Van't Hoff plots [4], because no direct experimental transition was observed by differential scanning calorimetry or by X-ray diffraction as a function of temperature.

In the present paper, it will be shown that on thermodynamic grounds this conclusion should be modified. Moreover, through the approach presented here it can be deduced how the relative stabilities of the polymorphs depend on the pressure.

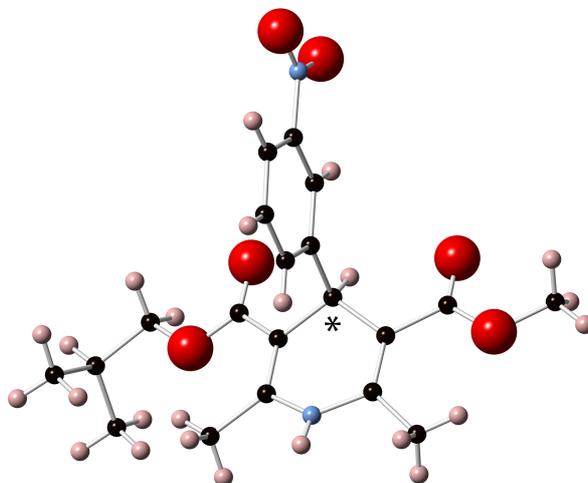


Figure 1. Racemic *m*-nisoldipine: 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid methyl 2-methylpropyl ester, $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_6$, $M = 388.41 \text{ g mol}^{-1}$. An asterisk indicates the stereogenic center. Atom identification: black = C, pink = H, blue = N, red = O.
Molécule de m-nisoldipine racémique. 1,4-dihydro-2,6-diméthyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylique acide méthyl 2-méthylpropyl ester, $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_6$, $M = 388.41 \text{ g mol}^{-1}$. L'atome de carbone asymétrique est identifié par une étoile (). Identification des atomes : noir = C, rose = H, bleu = N, rouge = O.*

2 Available data from the literature

The first crystal structure of *m*-nisoldipine was resolved by Fossheim et al. (compound III in ref [5]), who obtained crystal data at 123 K (Cambridge Structural Database (CSD) code: FULPAD). They reported that the compound had a monoclinic unit cell, setting $\text{P2}_1/\text{n}$, and a melting point of 127-129°C. A similar monoclinic cell was reported by Kapor et al. obtained at 293 K (CSD code: FULPAD01)[6] and later also by Yang et al. (at 298 K, no CSD entries)[3], although the latter group used the setting $\text{P2}_1/\text{c}$. The structure was ascribed to polymorph A, however, form A was reported to melt at 135.8 °C (T_{max}) by Yang et al. with a melting enthalpy $\Delta_{\text{A}\rightarrow\text{L}}H$ of 82.3 J g^{-1} [3]. The second polymorph, form B, was found to be triclinic with a melting point of $T_{\text{B}\rightarrow\text{L}} = 129.2 \text{ °C}$ (T_{max}) and the associated enthalpy $\Delta_{\text{B}\rightarrow\text{L}}H = 88.3 \text{ J g}^{-1}$ [3]. New slightly modified calorimetric data were published one year later by the same group even if the

inequalities (i.e. $T_{B \rightarrow L} < T_{A \rightarrow L}$ and $\Delta_{A \rightarrow L}H < \Delta_{B \rightarrow L}H$) remained the same [4]. In addition to the adjustments in the melting data, solubility experiments had been reported in the second article [4]. These experiments on the two polymorphs in water at temperatures ranging from 25 to 49 °C led to the enthalpies of solution using $\ln(S)$ versus $1/T$ plots in which S stands for saturation concentration (solubility). The data from the four above-mentioned references have been compiled in Table 1.

3 Data analysis

In the approach presented in this paper, the most important aspect is the inequality between the properties of the two polymorphs, such as Δv , ΔH , and ΔT , and in particular their sign, because it defines the global phase behavior of the system and thus which type of pressure-temperature phase diagram the system exhibits. Once these inequalities have been determined correctly, accurate data will simply allow constructing a more accurate phase diagram in relation to the coordinates of the phase equilibria. Thus the inequalities had best be determined from data obtained on the same equipment, as any constant calibration error will be minimal. This would not be the case for different equipment with different calibrations. Therefore for the inequality of the specific volume between the two polymorphs, only the data obtained by Yang et al. will be taken into account [3].

Table 1. Crystallographic and calorimetric data from the literature for forms A and B of racemic m-nisoldipine

Données cristallographiques et calorimétriques pour le composé racémique m-nisoldipine trouvées dans la littérature

| | Form A | Form B | Reference |
|---|---------------------------|------------|-----------|
| Crystal system, | Monoclinic, | Triclinic, | |
| Space group, formula | P2 ₁ /n, Z = 4 | | [5],[6] |
| units per unit cell | P2 ₁ /c, Z = 4 | P-1, Z = 2 | [3] |
| $V_{\text{cell}}/\text{Å}^3$ | 1967.32* | - | [5] |
| | 2005.68** | - | [6] |
| | 2007.36*** | 975.89*** | [3] |
| Specific volume/ cm³ g⁻¹ | 0.76254* | - | [5] |
| | 0.77741** | - | [6] |
| | 0.77821*** | 0.75643*** | [3] |
| T_{fus}/K | 400-402 | - | [5] |
| | 408.95**** | 402.4**** | [3] |
| | 410.94**** | 403.31**** | [4] |
| Heat of fusion $\Delta_{\text{fus}}H/\text{J g}^{-1}$ | 82.3 | 88.3 | [3] |
| | 88.88±1.55 | 90.28±1.09 | [4] |
| Heat of solution /J g⁻¹ | 139.94 | 48.39 | [4] |

* obtained at/obtenu à 123 K

** obtained at/obtenu à 293 K

*** obtained at/obtenu à 298 K

**** values of $T_{\text{peak}} = T_{\text{max}}$ given by the authors (see text), valeurs de $T_{\text{peak}} = T_{\text{max}}$ données par les auteurs (voir texte)

As far as the calorimetric data are concerned, the inequality between the temperatures of fusion had best be determined using DSC curves obtained with the

same equipment. Yang et al. reported DSC curves in the supplementary materials of the CrystEngComm paper [3]. However, instead of the T_{\max} temperatures reported by those authors, in the present paper, the onset temperatures have been determined from the previously reported graphs (see Figure 2) [3]. It is the onset temperature, which will in principle be closer to the thermodynamic temperature of transition, in particular for fusion. Analysis of the aforementioned melting peaks (Figure 2) has led to the temperatures of fusion of $T_{A \rightarrow L} = 133.1^\circ\text{C}$ (or 406.2 K) for form A and $T_{B \rightarrow L} = 126.2^\circ\text{C}$ (399.3 K) for form B.

The melting enthalpies for the two polymorphs as reported by Yang et al. and here reproduced in Table 1 differ significantly between the two papers [3-4]. However, in both cases $\Delta_{A \rightarrow L}H$ is smaller than $\Delta_{B \rightarrow L}H$. The difference between the two papers is due to the integration over the melting peak of form A in the first paper [3], which led to an underestimated value. It can be seen in Figure 2 that point **b** of segment **a-b** is located on the DSC curve before the melting peak of form A reaches the baseline, which is not the case for point **b'** of segment **a'-b'** under the melting peak of form B. If the heat of fusion of form A is determined by integrating the peak above the alternative and more correctly placed baseline a-c, a value very close to the heat of fusion of form B is obtained complicating the interpretation of the ΔH inequality.

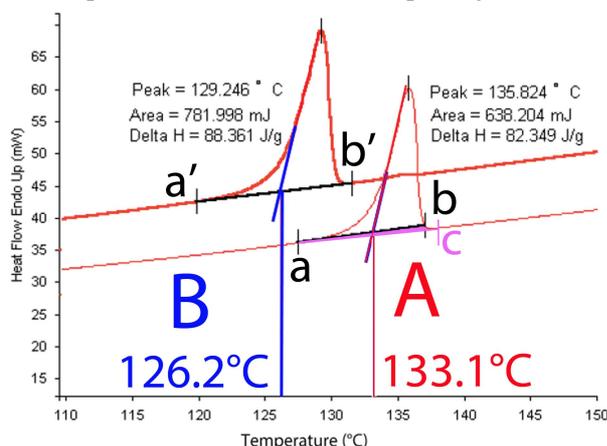


Figure 2. Determination of the onset temperatures of fusion for racemic *m*-nisoldipine forms A and B using the DSC curves in Figure S3 of the electronic supplementary information associated to reference [3]. Underestimation of the melting enthalpy of form A: Baseline a-c is to be used instead of baseline a-b. The underestimation is shown by the area in violet: by weighing the area of peak A and comparing those for baselines a-b and a-c, a value for the melting enthalpy of A close to that of peak B is obtained. Moreover, the large difference between the start of the peak (the start of the upward curvature) and the extrapolated onset temperature may be indicative for the presence of impurities in the *m*-nisoldipine samples.

Détermination des températures de fusion commençante des formes A et B du composé racémique m-nisoldipine, d'après les courbes DSC de la Figure S3 de l'information électronique supplémentaire associée à la référence [3]. Sous-estimation de l'enthalpie de fusion de la forme A : la ligne de base a-c doit être utilisée au lieu de la ligne a-b. La sous-estimation est visualisée par la surface violette : en pesant la surface du pic A au-dessus des lignes de bases a-b et a-c, on obtient une valeur très proche de celle du pic B. De plus, la grande différence entre le début du pic (le début de la courbure vers le haut) et la température de début extrapolée peut indiquer la présence d'impuretés dans les échantillons de m-nisoldipine.

The calorimetric data provided in the second paper [4] seems to be an average over four DSC runs at various heating rates. Thus, the enthalpy of fusion values reported in [4], which seem overall more reliable, will be used in the approach that follows below. However, the melting temperatures obtained through the onset of the peaks from reference [3] will be used by lack of anything better (It is not clear, whether in reference

[4] the melting temperatures are given as T_{\max} or T_{onset}). It can be concluded that forms A and B have melting enthalpies that are very close to each other with form A a slightly lower one than form B leading to a transition enthalpy between the two solids of $\Delta_{B \rightarrow A}H = 1.4 \text{ J g}^{-1}$.

Considering the foregoing, the heats of solution from the Van't Hoff plots of the saturated solutions [4] for forms A and B are very surprising. First of all, the heat of solution of form A is larger than that of form B contrary to the melting data and secondly the difference is extremely large. Fusion and dissolution are similar processes, and although in the case of fusion the system is unary, whereas in the case of dissolution, the system is binary, which may affect phase equilibria, the large change observed here is rather improbable and thus the dissolution data must be unreliable. This is illustrated in figure 3, where the fusion and dissolution processes have been drawn in the form of a cycle (Hess law). These cycles should lead to similar values for the heat of transition from form B to form A, whereas in this case for the heats of solution, they lead to the relatively large value of -91.55 J g^{-1} similar to its heat of fusion, instead of the $+1.4 \text{ J g}^{-1}$ obtained from the fusion data and much more common for heat differences between polymorphs ($1 \text{ to } 20 \text{ J g}^{-1}$). It can be seen that the sign of the transition changes too classifying the same transition simultaneously endothermic (cycle I, DSC data) or exothermic (cycle II, solubility data).

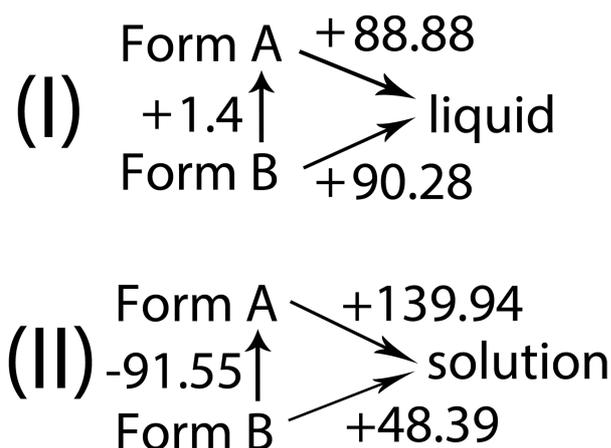


Figure 3. Heat of transition from racemic *m*-nisoldipine form B to form A, determined using either the heats of fusion (cycle I) or the heats of solution (cycle II).

Chaleur de la transition de la forme B du composé racémique m-nisoldipine en forme A, déterminée soit à partir des chaleurs de fusion (cycle I), soit à partir des chaleurs de dissolution (cycle II).

As the solubility data appear to be unreliable, it is likely that the transition temperature between forms A and B of 47°C obtained through these data may not be correct either. A different way to estimate the transition temperature is by using a thermodynamic equation, which has been thoroughly tested in a paper by Yu [7]. It uses the heats and temperatures of fusion of the two polymorphs, although in the present form it neglects the variation of the heat capacities with temperature between the solids and between the liquid and the solid:

$$T_{B \rightarrow A} = \frac{\frac{\Delta_{A \rightarrow L}H - \Delta_{B \rightarrow L}H}{\Delta_{A \rightarrow L}H - \Delta_{B \rightarrow L}H}}{\frac{T_{A \rightarrow L}}{T_{B \rightarrow L}}} = \frac{\Delta_{A \rightarrow L}H - \Delta_{B \rightarrow L}H}{\Delta_{A \rightarrow L}S - \Delta_{B \rightarrow L}S} \approx \frac{\Delta_{B \rightarrow A}H}{\Delta_{B \rightarrow A}S} \quad (1)$$

In this equation $T_{B \rightarrow A}$ is the temperature of transition of form B to form A, and $T_{i \rightarrow L}$ and $\Delta_{i \rightarrow L}H$, the temperature and enthalpy of fusion of form i ($i = A$ or B) respectively. Using $\Delta_{A \rightarrow L}H = +88.88 \text{ J g}^{-1}$, $\Delta_{B \rightarrow L}H = +90.28 \text{ J g}^{-1}$, $T_{A \rightarrow L} = 406.2 \text{ K}$ and $T_{B \rightarrow L} = 399.3 \text{ K}$, $T_{A \rightarrow B}$ is found to be 192.12 K ($-81 \text{ }^\circ\text{C}$), i.e. far below the value of $47 \text{ }^\circ\text{C}$ reported by Yang et al. [4]. It implies that forms A and B are enantiotropically related as was already concluded by Yang et al., however form B, stable below 192 K , endothermically transforms into form A at 192 K as $\Delta_{B \rightarrow A}H$ is positive ($+1.4 \text{ J g}^{-1}$).

To investigate whether the inequality in the heat of transition was determined correctly, because the melting enthalpies were rather close to each other, those melting enthalpies can be interchanged in the calculation using eq. (1). Keeping the melting temperatures as obtained, as they can generally be measured with a relatively high precision, a negative transition temperature is found for the solid phase B into the solid phase A. This result is simply impossible, because firstly negative temperatures do not physically exist and secondly this result is thermodynamically impossible, because B would have the lowest melting enthalpy and form B would therefore necessarily be the "high-temperature" form. As form A has the highest melting point and is thus the most stable phase just below its melting point, the only option for a "virtual" A-B transition temperature would be above the melting point of form A as a metastable solid-solid transition. Obviously, the requirement of a solid-solid transition temperature above the melting point of form A together with the calculated result of a negative transition temperature cannot be true simultaneously.

Finally, it can be argued that the melting enthalpies as determined by DSC possess experimental uncertainties. As in both papers by Yang et al. [3-4], the melting enthalpy of form A is smaller than that of form B, the enthalpy difference between the two forms and obtained through the melting enthalpies, 1.4 J g^{-1} can be varied from 0.4 to 2.4 J g^{-1} , thus implying an experimental error of $\pm 1 \text{ J g}^{-1}$. Maintaining the melting temperatures for which the relative error is much smaller, one finds with eq. (1) for an enthalpy of 0.4 J g^{-1} a transition temperature between A and B of 83 K and for an enthalpy of 2.4 J g^{-1} , one finds 246 K . It can be seen that the range of transition temperatures is rather large, but with a reasonable estimate of the transition enthalpy between forms A and B obtained through the DSC data, the transition temperature appears to be far below 47°C (320 K).

Building on the conclusions that the system is enantiotropic and that form A is the stable form at room temperature and up to its melting point, the influence of pressure on the equilibria can be examined by means of the Clapeyron equation, leading to a topological pressure-temperature (P-T) phase diagram for *m*-nisoldipine, as shown below.

4 Topological P-T phase diagram involving forms A and B

The general procedure for the construction of topological P-T phase diagrams, which has been described in a recent paper [8], has been frequently applied to other cases and validated against experimental results (see references in [8] and [9]). The method can be divided up in three steps:

- 1) Specific volume-temperature (v-T) phase diagrams, in particular of the solids and if possible of the liquids are measured or estimated to calculate (or estimate) the volume changes at the phase transition temperatures.

2) The two-phase equilibrium curves in the P-T diagram are assumed to be straight lines whose dP/dT slopes are determined by the Clapeyron equation using volumetric and calorimetric data. Because the chance that these lines are parallel is basically zero, the two-phase equilibrium curves must intersect at their respective triple points providing the boundary for the different stable-phase regions.

3) The resulting P-T phase diagram can be compared with the four possible cases of dimorphism described by Bakhuis-Roozeboom [10-11].

Following the data in Table 1 and the reasoning in the text above, the difference between the specific volumes of forms A and B at 298 K is equal to $v_A - v_B = 0.77821 - 0.75643 = 0.02178 \text{ cm}^3 \text{ g}^{-1}$. Using the data in Table 1, the linear expansivity of form A can be estimated, because the crystal structure has been determined at 123 K by Fossheim et al. [5] and at 298 K by Yang et al. [3]. In addition, the unit-cell volume obtained by Kapor et al. at 293 K [6] can be used to determine an average unit-cell volume valid at 295.5 K of 2006.52 \AA^3 . This leads to a specific volume for form A of $0.7625 \text{ cm}^3 \text{ g}^{-1}$ at 231 K and of $0.7777 \text{ cm}^3 \text{ g}^{-1}$ at 295.5 K. Using a linear approach, the expansivity α can be calculated as follows: $v_A = v_{0,A} + \alpha T = v_{0,A}(1 + \alpha T)$, leading to a value of $1.17 \times 10^{-4} \text{ K}^{-1}$, near the average expansivity of $2.21 \times 10^{-4} \text{ K}^{-1}$ for solids consisting of small pharmaceutical molecules [8, 12-13]. The expansivity of $1.17 \times 10^{-4} \text{ K}^{-1}$ can be used for form A and in approximation for form B to calculate the specific volumes of both forms at their respective melting points. Now, considering that the mean volume change on melting of the highest melting form, form A, is such that $v_L/v_A = 1.11$ [8, 12-13], the specific volume of the melt at $T_{A \rightarrow L}$ can be estimated to equal $0.87440 \text{ cm}^3 \text{ g}^{-1}$. Thus the volume change on melting of form A equals $v_L - v_A = 0.08665 \text{ cm}^3 \text{ g}^{-1}$. Inserting the latter value with $T_{A \rightarrow L} = 406.2 \text{ K}$ and $\Delta_{A \rightarrow L}H = +88.88 \text{ J g}^{-1}$ into the Clapeyron equation:

$$\frac{dP}{dT} = \frac{\Delta_{A \rightarrow L}H}{T_{A \rightarrow L} \Delta_{A \rightarrow L}V} \quad (2),$$

the value of the slope of the melting equilibrium of form A is found to be 2.53 MPa K^{-1} .

Taking the expansivity of the liquid as $1.19 \times 10^{-3} \text{ K}^{-1}$, which is the average liquid expansivity found for molecular pharmaceutical compounds [8, 12-13], the specific volume of the melt at the melting point of form B, $T_{B \rightarrow L} = 399.3 \text{ K}$ is $0.86956 \text{ cm}^3 \text{ g}^{-1}$. It results in a volume change on melting for form B of $v_L - v_B = 0.10445 \text{ cm}^3 \text{ g}^{-1}$. Using the latter value in the Clapeyron equation for the equilibrium curve between form B and the liquid gives $dP/dT_{B-L} = 90.28/(399.3 \times 0.10445) = 2.16 \text{ MPa K}^{-1}$.

The two melting equilibria can be approximated by straight lines determined through the respective melting temperatures and their slopes. The vapor pressure of nisoldipine is neglected in this approach, but considering the steepness of the slope, this is in most cases fully acceptable. Thus with the melting temperatures 406.2 K for form A and 399.3 K for form B and the vapor pressure taken as 0 MPa (these two melting points represent therefore two triple points: A-L-Vap and B-L-Vap), the expressions for the two phase equilibria become:

$$\text{A-L: } P/\text{MPa} = 2.53 T/\text{K} - 1026 \quad (3)$$

$$\text{B-L: } P/\text{MPa} = 2.16 T/\text{K} - 864 \quad (4)$$

The intersection between the two equilibria is a triple point, where form A, form B, and the liquid are stable. Its coordinates can be calculated by equating eqs. 2 and 3 leading to $T_{A-B-L} = 448$ K and $P_{A-B-L} = 105$ MPa.

Equilibria between two different crystalline polymorphs are in most cases straight lines in P-T diagrams ([9] and references therein). The equilibrium line A-B will intersect triple point A-B-L, which was just obtained above and triple point A-B-Vap. The latter triple point has been obtained through eq. 1 resulting in an equilibrium temperature of 192 K, while taking the vapor pressure as 0 MPa, which at such temperatures is hardly an approximation. Fitting a line through the two triple points results in the expression:

$$\text{A-B: } P/\text{MPa} = 0.41 T/\text{K} - 79 \quad (5)$$

The enthalpy change of the solid-solid equilibrium can be obtained by multiplying the slope of eq. 5 by the equilibrium temperature of 192 K and by the volume change between the two solid phases at 192 K of $\Delta_{B \rightarrow A} V = v_A - v_B = 0.02105 \text{ cm}^3 \text{ g}^{-1}$. This leads to the enthalpy of transition $\Delta_{B \rightarrow A} H = +1.7 \text{ J g}^{-1}$, close to the value of $+1.4 \text{ J g}^{-1}$ obtained by subtracting the heat of fusion of form A from that of form B (see cycle (I) in Figure 3).

With these results, it can be inferred that the topological P-T diagram accounting for the phase relationships involving the two polymorphs of racemic *m*-nisoldipine is of the same type as the state diagram of sulfur, i.e. triple point A-B-L is found at positive pressure as shown in Figure 4 [11].

Table 2. Two-phase equilibrium equations for alternative volume change on melting form A, and P-T coordinates for triple point A-B-L.

Equations décrivant les équilibres à deux phases pour différentes valeurs du changement de volume lors de la fusion de la forme A et valeurs correspondantes des coordonnées P et T du point triple A-B-L.

| v_{liq}/v_A | A-L | B-L | A-B | Triple point A-B-L | |
|----------------------|--------------------|--------------------|------------------|--------------------|---------|
| | | | | T (K) | P (MPa) |
| 1.07 | $P = 3.97T - 1612$ | $P = 3.09T - 1235$ | $P = 0.41T - 78$ | 431 | 97 |
| 1.11 | $P = 2.53T - 1026$ | $P = 2.16T - 864$ | $P = 0.41T - 79$ | 448 | 105 |
| 1.15 | $P = 1.85T - 752$ | $P = 1.67T - 665$ | $P = 0.41T - 79$ | 468 | 114 |

As is shown in the Figure 4, the intersection of line A-L and line B-L (triple point A-B-L) is above the temperature axis. That means that the pressure at the intersection is positive and that the triple point is stable. Below the intersection, the system is enantiotropic and form A is more stable than form B at room temperature and under atmospheric conditions. Above triple point A-B-L, the system becomes monotropic and form B is the only stable form. This trend is consistent with the Le Chatelier principle. According to the data in Table 1, the specific volume of form A is larger than that of form B at 298 K. In other words, form B is denser than form A and thus form B will become more stable on increasing the pressure.

The linear expression for the A-B equilibrium has been calculated based on the triple point A-B-Vap and the triple point A-B-L. Triple point A-B-L has been determined through the equilibria A-L and B-L. Thus, the slopes of these two equilibria affect the position of triple point A-B-L and thus of equilibrium A-B. The two slopes of the melting

equilibria have been obtained through the Clapeyron equation (eq. 2). The largest uncertainty in this slope is the volume change on melting, which was obtained from statistical information. The spread in the statistical data for the volume change on melting is $v_{liq}/v_A = 1.11 \pm 0.04$ [8, 12-13] and therefore volume change on melting can be considered by comparing $v_{liq}/v_A = 1.07, 1.11, \text{ and } 1.15$. For all three values, the slope of the A-B equilibrium line has been calculated and the result has been compiled in Table 2. It can be concluded that the temperature and pressure of triple point A-B-L increases with an increase in v_{liq}/v_A , but the expression for the solid-solid equilibrium A - B remains virtually the same.

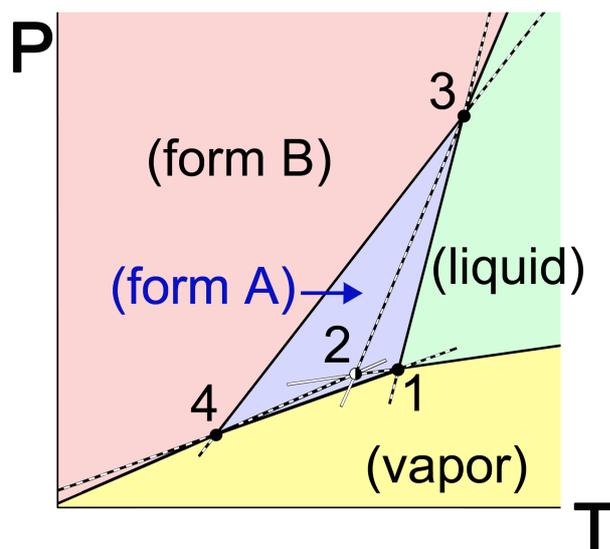


Figure 4. Topological pressure-temperature phase diagram for the dimorphism of racemic *m*-nisoldipine. The diagram corresponds to Bakhuis Roozeboom's type I [10-11], with a relatively limited P-T domain for the stability of form A, which becomes metastable at higher pressures. Triple points: 1 = A-liq-vap, 2 = B-liq-vap, 3 = A-B-liq, 4 = A-B-vap. Two-phase equilibrium lines: 1-2 = liq-vap, 1-3 = A-liq, 2-3 = B-liq, 3-4 = A-B, 1-4 = A-vap, 2-4 = B-vap (liq = liquid, vap = vapor).

Diagramme topologique pression-température du dimorphisme du composé racémique m-nisoldipine. Le diagramme correspond au type I de Bakhuis Roozeboom [10-11], avec un domaine limité en pression et température pour la stabilité de la forme A, qui devient métastable aux pressions élevées. Points triples : 1 = A-liq-vap, 2 = B-liq-vap, 3 = A-B-liq, 4 = A-B-vap. Lignes d'équilibres à deux phases : 1-2 = liq-vap, 1-3 = A-liq, 2-3 = B-liq, 3-4 = A-B, 1-4 = A-vap, 2-4 = B-vap (liq = liquid, vap = vapor).

5 Concluding remarks

Contradictory information in the literature can sometimes be solved by investigating the consistency between the data and by making use of the thermodynamic requirements of the system. Previously, this has been shown in the case of the polymorphism of piracetam [9].

In the present case, the data provided by two papers of the same authors has allowed to validate some of the data (in particular the melting enthalpies mentioned in ref [4]) and to eliminate other data, because they are inconsistent with thermodynamic and calorimetric notions for small organic molecules such as the heat of a solid-solid transition, which must be considerably smaller than a melting enthalpy.

For the phase behavior of racemic *m*-nisoldipine, the present work confirms that forms A and B are enantiotropically related at ordinary pressure, turning to a monotropic relation as pressure reaches about 100 MPa. It also demonstrates that form A, the "high-temperature" form, is most likely the stable form at room temperature since

the temperature of the transition from form B to form A should occur around 192 K, i.e. far below room temperature. Moreover, the use of statistical data for the change in density on melting barely affects the A-B equilibrium line, which depends in this analysis on the position of the A-B-L triple point.

Disclosure of Interest

The authors declare that they have no competing interests.

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