

Enantiomer Resolution by Pressure Increase: Inferences from Experimental and Topological Results for the Binary Enantiomer System (*R*)- and (*S*)-Mandelic Acid

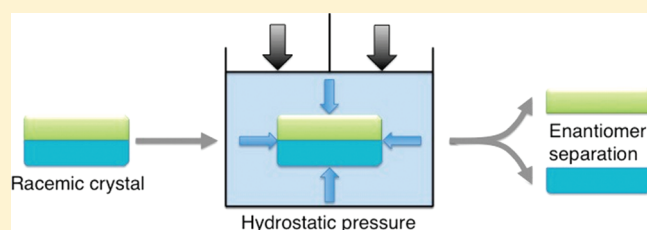
Ivo B. Rietveld,^{*,†} Maria Barrio,[‡] Josep-Lluís Tamarit,[‡] Bernard Do,[§] and René Céolin^{†,‡}

[†]EAD Physico-chimie Industrielle du Médicament, Faculté de Pharmacie, Université Paris Descartes, 4, Avenue de l'Observatoire, 75006 Paris, France

[‡]Grup de Caracterització de Materials (GCM), Departament de Física i Enginyeria Nuclear, Universitat Politècnica de Catalunya, ETSEIB, Diagonal 647, 08028 Barcelona, Spain

[§]Etablissement Pharmaceutique de l'Assistance Publique-Hôpitaux de Paris, Agence Générale des Equipements et Produits de Santé, 7, rue du Fer à Moulin, 75005 Paris, France

ABSTRACT: In pharmacy, racemic compounds are often problematic, because generally only one of the enantiomers possesses therapeutic activity and it is often difficult to separate them. Even though this problem is likely as old as the pharmaceutical industry, one thermodynamically obvious way of separating racemic crystals has never been studied experimentally, which is by using pressure. Data have been obtained on the equilibria of the (*R*)- and (*S*)-mandelic acid system as a function of pressure and temperature. With the use of thermodynamic arguments including the Clapeyron, Schröder, and Prigogine–Defay equations, it has been demonstrated that the conglomerate (crystals of separated enantiomers) becomes more stable than the racemic compound at approximately 0.64 GPa and 460 K. Even though this pressure is still higher than at the bottom of the Mariana Trench, there are no technical obstacles to produce such conditions, making pressure a viable option for separating enantiomers.



INTRODUCTION

The influence of pressure on phase equilibria in binary enantiomer systems and especially on the relative stabilities of racemic compounds and conglomerates has never been studied experimentally, as can be inferred from the book by Jacques, Collet, and Wilen.¹ In the major part of the book, the authors discuss the question of relative stabilities between pure enantiomer mixtures and racemic compounds in terms of calorimetric arguments only, which obviously reduces thermodynamics to a one-dimensional approach. As a result, it is often forgotten that thermodynamics also involves work even if volume changes are small and in certain cases can be neglected. That does not mean, however, that work as a means of exchanging energy with the environment should be ignored, because where subtle processes such as phase changes occur, subtle energy changes may just make the difference.

Jacques et al. did devote a short paragraph to enantiomer resolution by pressure.¹ The authors stated that the inequality of the specific volume between the racemic compound and the pure enantiomers might well increase the possibilities for enantiomer resolution by using pressure. By taking into account the average free energy differences and specific volume differences, they estimated that the necessary pressure for enantiomer resolution could be expected to lie between 100 and 1000 MPa. In a reissue of the book, 13 years later, not a single word had been changed in

the paragraph on pressure.² In 1995, however, Collet and Vigné-Maeder³ used the Clapeyron equation together with modified Schröder and Prigogine–Defay equations to calculate at which temperature and pressure fusion of the racemate coincides with fusion of the conglomerate. They estimated that racemic mandelic acid would transform into a conglomerate at a pressure of about 12 kbar (1.2 GPa) and a temperature of about 770 K. No experiments have ever been carried out to substantiate the calculation.

Even though 17 years have passed since reissuing the above-mentioned book,² knowledge about enantiomer resolution is still wanting, as is clear from the reports on enantiomer resolution in the literature.^{4–7} Furthermore, although direct crystallization of a pure enantiomer from a racemic mixture would generally be the cheaper option, often compounds need to be derivatized, before enantiomer resolution becomes feasible.⁸ Because simple resolution methods, such as direct crystallization, are only available to conglomerates and only 5–10% of the enantiomer systems occur as conglomerates,^{2,9} incorporating pressure as an enantiomerization tool can be an invaluable asset. This approach may have an impact not only on enantiomer resolution but also on the understanding of biological systems under pressure, such as in

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Table 1. Crystal Structure Data of S- and RS-Mandelic Acid

compound	form	symmetry	lattice parameters				density/g · cm ⁻³	T _{fusion} /K	ref
			a/Å	b/Å	c/Å	β/°			
RS	I	orthorhombic	9.66(5)	16.20(8)	9.94(5)		1.299	RT	10
			<i>Pbca</i>	16.060(20)	9.955(6)	9.600(10)	1.317	295	11
			<i>Pbca</i>	9.669(2)	16.183(3)	9.953(2)	1.298	295	12
			<i>Pbca</i>	9.407(1)	15.912(3)	10.195(2)	1.324	150	13
S(+)	II	<i>P2₁/c</i>	5.847	29.241	8.723	92.17	1.356	299	9
		<i>P2₁</i>	8.629(1)	5.861(1)	15.185(2)	102.76(1)	1.349	295	14

deep-sea environments, where pressures reach levels that may cause equilibrium shifts in biological enantiomer systems.

In the present paper, a study of phase equilibria as a function of pressure and temperature of the binary system (R)- and (S)-mandelic acid is reported. It is likely the first in its field.

Literature Data at “Ordinary” Pressure. The binary system (R)- and (S)-mandelic acid (from here on in the text only indicated with R or S, respectively) has been widely studied: Lorenz and Seidel-Morgenstern reported, reviewed, and discussed data from their own experiments and from the literature.^{15,16} The racemic compound (RS from here on) melts at $T = 391–394$ K, and the pure enantiomers melt at $T = 405$ K. Racemic mandelic acid exhibits a second metastable form (RS II), which melts around $T = 381$ K. The eutectic equilibrium ϵ_1 involving R (or S) and (stable) RS was found at 387 K. In addition, the metastable eutectic equilibrium ϵ_2 involving enantiomers S and R was calculated to occur at around 370–374 K, assuming ideality of the enantiomer-based liquidus curves.¹⁶ Fujita et al. experimentally determined that ϵ_2 occurs around 377 K. This value has been corrected, because in their paper T_{\max} values of the peaks are reported instead of the onset temperatures.¹⁷

The crystal structures of S, RS, and RS II under ambient conditions have been solved (Table 1). From these data, the crystallographic densities are important, as they provide the volume changes associated with the phase transitions leading to the work received or performed by the system. Because the racemic form I (RS) is less dense than the equimolar mixture of enantiomers, it can be inferred by the Le Chatelier principle that it should transform into the conglomerate, if the pressure is increased sufficiently. However, RS II may eventually be the most stable form at high pressure, because its density appears to be the highest.

EXPERIMENTAL SECTION

R-, S-, and RS-mandelic acids, C₈H₈O₃, $M = 152.15$ g mol⁻¹, were purchased from Fluka (R and RS) and Aldrich (S) with purities $\geq 99\%$, and they were used as such after an X-ray powder diffraction control.

A mixture of S and RS, 156.49 and 141.15 mg, respectively, was dissolved in water. After complete evaporation, it was carefully homogenized through grinding using pestle and mortar. The final enantiomer mole fractions were $x_R = 0.2394$ and $x_S = 0.7606$.

Differential scanning calorimetry (DSC) experiments were run with a Q100 analyzer from TA-Instruments operated at 10 K min⁻¹. Indium was used as a standard for the calibration of temperature and enthalpy change. Specimens were weighed with a microbalance sensitive to 0.01 mg and sealed in aluminum pans with 30 μ L inner volume.

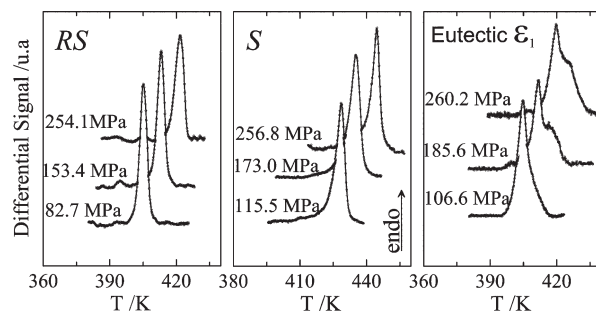


Figure 1. Examples of melting peaks and eutectic peaks at various pressures. Left-hand side, (RS)-mandelic acid; center, (R)-mandelic acid; right-hand side, R–RS eutectic (ϵ_1).

High-pressure differential thermal analysis (HP-DTA) experiments have been performed with an in-house constructed apparatus based on the one by Würflinger.¹⁸

To ensure hydrostatic pressure, specimens were put in in-house-produced cylindrical tin pans filled by a chemically inert perfluorinated fluid (Galden from Bioblock, Illkirch, France).

High-pressure thermal analysis runs were conducted at a rate of 2 K min⁻¹.

RESULTS

The temperature of fusion and the associated change of enthalpy for (R)-mandelic acid were found to be $T_{R(s) \rightarrow \text{liq}} = 405.6(5)$ K and $\Delta H_{R(s) \rightarrow \text{liq}} = 180.2(3.0)$ J g⁻¹ (27.41(46) kJ mol⁻¹), respectively, at ordinary pressure; for (S)-mandelic acid the values were $T_{S(s) \rightarrow \text{liq}} = 405.3(5)$ and $\Delta H_{S(s) \rightarrow \text{liq}} = 176.7(3.0)$ J g⁻¹ (26.88(46) kJ mol⁻¹), respectively. With the assumption that impurities will decrease the melting temperature, the melting point of (R)-mandelic acid was used for the calculations discussed below. The melting point of the racemic compound was found to be $T_{RS(s) \rightarrow \text{liq}} = 392.6(5)$ K together with an enthalpy change of $\Delta H_{RS(s) \rightarrow \text{liq}} = 173.9(3.0)$ J g⁻¹ (26.46(46) kJ mol⁻¹). In addition to the data for the “pure” compounds, the same series of measurements have been performed with a mixture of $x = 0.76$ mol-fraction of S (0.24 of R). This resulted in a temperature for ϵ_1 of 386.4(2.0) K and a temperature for the liquidus of 392.7(2.0) K at ordinary pressure. This value is in close agreement with the temperature found by Lorenz and Seidel-Morgenstern^{15,16} on the liquidus curve for the pure S enantiomer.

For the high-pressure-DTA measurements, the temperatures of fusion of pure R and RS, as well as the temperature of ϵ_1 , were determined by taking the onset of the respective peaks (cf. Figure 1). The uncertainty over these measurements is ± 1 K and ± 0.5 MPa. The P – T lines for the fusion of the pure

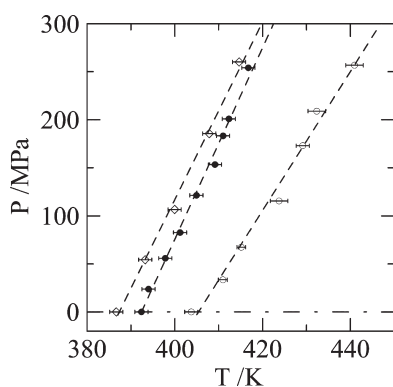


Figure 2. Pressure–temperature melting curves of (R)- and (RS)-mandelic acid, open circles and solid circles, respectively, and the P – T curve of the eutectic equilibrium between either of the enantiomers and (RS)-mandelic acid, ε_1 , open diamonds.

enantiomer and the racemate as well as the stable eutectic ε_1 can be found in Figure 2. Classic thermodynamics dictates that they are monotonously increasing;¹⁹ hence, P (MPa) has been fitted as a function of T (K) using linear functions:

$$R_s \rightarrow \text{liq} : P = -2929(156) + 7.23(37) \times T_{R(s) \rightarrow \text{liq}} \quad (r^2 = 0.987) \quad (1)$$

$$RS_s \rightarrow \text{liq} : P = -3911(130) + 9.97(32) \times T_{RS(s) \rightarrow \text{liq}} \quad (r^2 = 0.993) \quad (2)$$

$$\varepsilon_1 : P = -3579(153) + 9.24(38) \times T_{\varepsilon_1} \quad (r^2 = 0.995) \quad (3)$$

DISCUSSION

Invariant Equilibrium in the P – T – x Diagram of the Mandelic Acid System. Figure 2 is the projection of three P – T diagrams, those of the fusion of R , the fusion of RS , and the eutectic ε_1 , on the plane P – T . Equilibrium ε_1 is monovariant,²⁰ and the related line is the projection of a ruled surface normal to the P – T plane involving three phases: solids R and RS and the eutectic liquid.

Bridgman concluded on the basis of classic thermodynamics that equilibrium curves in the P – T plane are monotonously increasing;^{19,21,22} therefore, these curves can only cross once. Extrapolation of expressions 1, 2, and 3 allows determination as to whether the equilibrium lines cross above or beneath the studied temperature and pressure range, even if the (P , T) location of the intersection will be imprecise (as a result of the extrapolation). Equations 1 ($R_{\text{solid}} \rightarrow \text{liq}$) and 2 ($RS_{\text{solid}} \rightarrow \text{liq}$) cross at negative pressures in the region for metastable, expanded, condensed phases ($T = 358$ K, $P = -341$ MPa), while eqs 2 ($RS_{\text{solid}} \rightarrow \text{liq}$) and 3 (ε_1) cross at higher temperature and pressure ($T = 456.8$ K, $P = 642$ MPa). The two intersections have been indicated in Figure 3 by A and B, respectively, and their corresponding schematized isobaric T – x sections can be found in Figure 3 too.

In section P_A , the melting temperature and pressure of the two enantiomers are equal to those of the racemate RS . The intersection of the two equilibria is a coincidental result of the

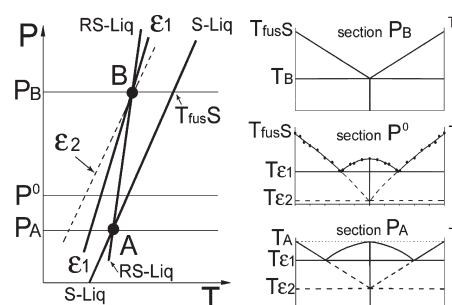


Figure 3. Schematic projection on the P – T plane of the phase equilibria: R –liquid, RS –liquid, R – RS –liquid, and R – S –liquid. At P_A (<0 MPa) the melting points of the pure enantiomers and the racemic compound coincide; a schematic isobaric section is shown on the right (bottom). At ordinary pressure, $P = P^0$, the melting point of the pure enantiomer is higher than that of the racemic compound, but the latter is still more stable than the conglomerate. The section schematically reproduces the experimental T – x diagram at ordinary pressure published by Lorenz and Seidel-Morgenstern.¹⁶ At P_B , the melting point of RS coincides with the eutectic equilibrium R – RS –liquid and the eutectic equilibrium R – S –liquid; a schematic isobaric section is shown on the right (top). At P_B , with increasing pressure, the racemic compound ceases to be stable.

projections on the P – T plane, because the equilibria have neither the solid state, $R(s)$ (or $S(s)$) or $RS(s)$, nor the liquid state, pure $R(l)$ (or $S(l)$) or an equal mixture (l) of R and S , in common. Nonetheless, it implies that the temperature of the eutectic involving the two enantiomers (ε_2) occurs at a temperature lower than ε_1 , the stable eutectic equilibrium. It follows that the composition of the eutectic liquid x_{ε_1} changes with increasing pressure until it converges with the composition of the racemic compound at T_B , P_B .

The real magic occurs at P_B , where in section P_B , equilibria ε_1 and $RS(s) \rightarrow \text{liquid}$ are equal in temperature and pressure. This means that four phases must be in equilibrium on the horizontal line T_B : the two enantiomers, racemate RS , and a liquid phase. This is a real invariant equilibrium with a single temperature and pressure (T_B and P_B), in accordance with the Gibbs phase rule with two independent components (the two enantiomers): $\nu = c + 2 - \phi = 0$ with $c = 2$ and $\phi = 4$.

Above P_B , the eutectic equilibrium ε_2 possesses a higher temperature than ε_1 for a given pressure, and it has become the stable equilibrium. Because ε_2 is part of the invariant equilibrium in point B, a third curve should pass through this point. This curve is the section of the ruled surface (perpendicular to plane P – T) that describes the eutectic equilibrium involving the pure enantiomers, metastable at “ordinary” pressure.

Calculation of the P – T Curve for the Metastable Eutectic $S + R \leftrightarrow \text{Liquid}$. The foregoing inferences will allow the construction of the topological P – T diagram for the composition $x = 0.5$; however, to complete the information about the involved phase equilibria, the P – T curve for the ε_2 equilibrium is calculated and also the evolution of the eutectic composition of ε_1 , which must become 0.5, when both eutectic equilibria intersect. Because the system consists of two optical antipodes, the liquidus curves are calculated under the assumption of an ideal liquid phase.² This means that the Schröder equation can be used:

$$T_{\text{liquidus}} = \frac{T_{R(s) \rightarrow \text{liq}} \Delta S_{R(s) \rightarrow \text{liq}}}{\Delta S_{R(s) \rightarrow \text{liq}} - R \ln(1 - x)} \quad (4)$$

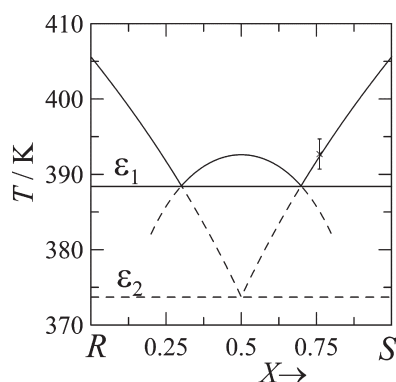


Figure 4. Liquidus lines of (R)- and (S)-mandelic acid and the liquidus of the racemic compound at ordinary pressure $P = P^0$. The intersections give rise to the temperatures and compositions of the eutectic equilibria (stable, ϵ_1 , and metastable, ϵ_2). Broken lines correspond to the metastable equilibria.

Here the equation is written in such a way that the temperature of the liquidus is obtained and $T_{R(s) \rightarrow \text{liq}}$ is the melting temperature of pure R (or S), $\Delta S_{R(s) \rightarrow \text{liq}}$ the associated entropy change of melting of the pure enantiomer R (or S), x is the mole fraction of the enantiomer in the binary mixture, and R is the gas constant. Furthermore, using the Prigogine–Defay equation, the liquidus of the molecular compound (1:1) can be obtained

$$T_{\text{liquidus}} = \frac{T_{R(s) \rightarrow \text{liq}} \Delta S_{R(s) \rightarrow \text{liq}}}{\Delta S_{RS(s) \rightarrow \text{liq}} - R \ln(4x - 4x^2)} \quad (5)$$

where $T_{R(s) \rightarrow \text{liq}}$ stands for the melting temperature of the racemic 1:1-compound and $\Delta S_{R(s) \rightarrow \text{liq}}$ corresponds to the melting entropy of 1 mol of 1:1-compound containing 1 mol of each enantiomer.²³ The equation is again rewritten to obtain the temperature as a function of composition.

Equation 4 with the data on the pure enantiomer, $T_{R(s) \rightarrow \text{liq}} = 405.6$ K and $\Delta S_{R(s) \rightarrow \text{liq}} = 67.6$ J K^{−1} mol^{−1}, results in liquidus lines for the pure compounds R and S, which can be found in Figure 4. Because the phase diagram is symmetrical, the eutectic composition must lie at $x = 0.5$. This leads to the value of 373.7 K for the metastable eutectic between the two pure enantiomers. The stable equilibrium at $P = P^0$ is the racemic compound, for which the liquidus can be found in Figure 4, calculated using eq 5 and the experimental values $T_{RS(s) \rightarrow \text{liq}} = 392.6$ K and $\Delta S_{RS(s) \rightarrow \text{liq}} = 134.8$ J K^{−1} mol^{−1}. The intersection of both liquidus lines is the stable eutectic between the racemic compound and the pure enantiomer at 388.4 K, which is 2 deg higher than the temperature obtained by measurement. This is a reasonable result considering that there is an error of approximately 2 deg over the measured temperature. Moreover, the measurement for the liquidus temperature, the cross on top of the liquidus of the pure enantiomer, lies on the calculated line. This is a strong indication that the assumption of ideality for the liquid phase is correct.

To calculate isobaric sections at higher pressures, the entropy changes for the equilibria must be known. Although there is no experimental data on the evolution of ϵ_2 with pressure, the eutectic must pass through the same point where ϵ_1 and the fusion of the racemic compound intersect ($T = 456.8$ K, $P = 642$ MPa, point B in Figure 3). The melting point of the pure enantiomer can be calculated at this pressure by using eq 1

Table 2. Data Obtained by Combining the Schröder Equation (eq 4) and the Prigogine–Defay Equation (eq 5)

P /MPa	$T_{R(s) \rightarrow \text{liq}}^{\text{eq}} / \text{K}$	$T_{RS(s) \rightarrow \text{liq}}^{\text{eq}} / \text{K}$	$T_{\epsilon_1}^{\text{means}} / \text{K}$	$T_{\epsilon_1}^{\text{calc}} / \text{K}$	$x_{\epsilon_1}^{\text{calc}}$	$T_{\epsilon_2}^{\text{calc}} / \text{K}$
P^0	405	392	387	388	0.30	374
50	412	397	393	394	0.32	380
100	419	402	398	399	0.33	386
200	433	412	409	410	0.36	399
300	447	423	420	421	0.39	412
450	468	438	436	437	0.43	431
600	488	453	452	452	0.48	450
642	494	457	457	457	0.49	455
684	500	461	461	461	0.50	461

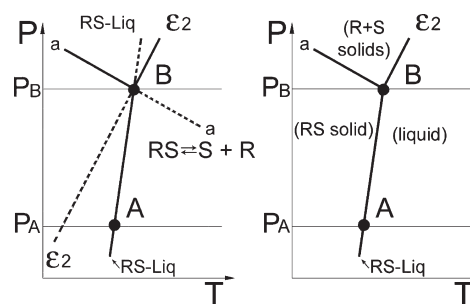


Figure 5. Topological pressure–temperature diagram for section $x = 0.5$ of the P – T – x diagram based on the two enantiomers of mandelic acid. Left-hand side: Line “a–a” is the section of the ruled surface (three-phase equilibrium) that separates the stable phase region of racemic RS at lower pressure from the stable phase region of the $R + S$ equimolar mixture at higher pressure. Right-hand side: phase regions for stable equilibria. Line “a” up to point B marks the P – T conditions above which enantiomer resolution should occur spontaneously, as a stable monovariant equilibrium shifting right on increasing the pressure.

(485.1 K), and the enthalpy of fusion for the pure compound is obtained with the Schröder equation (eq 4), under the assumption that the system still behaves ideally. This leads to an entropy of fusion for the pure enantiomer at 642 MPa of 70.4 J K^{−1} mol^{−1}. Taking into consideration that extrapolations are used to obtain the temperature at the intersection and the temperature of fusion of the pure enantiomer, it can safely be assumed that the entropy changes associated with the phase equilibria are constant for the pressure range under study. In fact, using eq 4 to calculate the temperature of the R – S – Liq eutectic (with the melting temperature 485.1 K and the entropy change obtained experimentally at P^0), one finds 455.4 K, 1.4 deg underneath the temperature obtained from the intersection of eqs 2 and 3.

In Table 2, it can be seen that the calculated temperature for the stable eutectic ϵ_1 only deviates from the measured value within 1 deg (thus, within error). This is a confirmation that the liquid phase remains ideal at higher pressures and that the entropy changes associated with the phase equilibria do not vary much.

The pressure at which the mole fraction of the eutectic liquid of ϵ_1 becomes 0.5 is 42 MPa higher than the value calculated from the intersection of the measured eqs 2 and 3. This is due to extrapolation of experimentally obtained lines, and it indicates that the window for the invariant point is about 456–461 K and 642–684 MPa. The temperature of the metastable ϵ_2 evolves

gradually to the invariant point (last column), in the following equation (P (MPa) and T (K)):

$$\varepsilon_2 : P = -2929.4(2.5) + 7.8418(61) \times T \quad (6)$$

Construction of the Topological P – T Diagram and Enantiomer Resolution of the Racemic Compound. The preceding information allows the construction of the topological P – T diagram for the composition $x = 0.5$ shown in Figure 5, where both the melting line for racemic RS and the line for eutectic ε_2 ($R + S$ mixture) can be found. They intersect at P_B , where their relative stabilities invert. Moreover, point B is the projection of an invariant line along the composition axis normal to the P – T plane, and this line connects four phases in equilibrium: pure enantiomers R and S , the racemic compound RS , and the liquid “Liq” with equimolar quantities of R and S . Therefore, four ruled surfaces in the P – T – x space each involving three phases must converge at the invariant line: 1, $S + RS + \text{Liq}$; 2, $R + RS + \text{Liq}$; 3, $S + R + \text{Liq}$; 4, $R + S + RS$. The intersection of these equilibrium surfaces with the P – T surface at $x = 0.5$ will result in equilibrium lines; however, equilibria 1 and 2 cannot be observed even if they meet at $x = 0.5$, because they do not exist at the exact composition of the racemic compound RS and therefore the intersection does not contain these two eutectic equilibria. The melting of RS necessarily passes through point B , but not as the projection of a ruled surface; this equilibrium between RS and Liq_{RS} exists only at $x = 0.5$. It follows that equilibrium 4 ($R + S + RS$) still needs to be placed in the P – T diagram with the requirement to intersect the other equilibria at point B ; equilibrium 4 is the dissociation of the racemic compound RS into pure enantiomers, which will occur under pressure.

The sign of the slope of the equilibrium between RS and $R + S$ can be found by applying the principle of Le Chatelier. From this principle it can be deduced that the phase with the highest enthalpy is the high-temperature phase and the phase with smallest volume is the high-pressure phase. By extrapolation of the relevant equilibria, it has already been determined that the racemic compound dissociates spontaneously at increased pressure, which is in accordance with the density data in Table 1.

To find the change of enthalpy between the three solid phases ($RS \rightarrow R + S$) is less straightforward. The enthalpy difference has not been measured directly; however, it can be calculated using a thermodynamic cycle through the liquid state. It is assumed that the entropy of fusion of the pure enantiomer and the racemic compound are constant within the pressure and temperature range considered, which as shown above is reasonable. For a mole of unmixed S - and R -molecules, the entropy of fusion, $\Delta S_{R(S) \rightarrow \text{liq}} = \Delta S_{(R+S) \rightarrow \text{liq}}$, is 67.61 J K^{-1} , and for the same number of molecules in the racemic compound the entropy of fusion, $\Delta S_{RS \rightarrow \text{liq}(R+S)}$, is 67.40 J K^{-1} . It has been found by Jacques et al.¹ (Table 2, p 48) that the entropy of mixing in the liquid state, $\Delta S_{\text{liq}(R) + \text{liq}(S) \rightarrow \text{liq}(R+S)}^{\text{mix}}$, for a mole of enantiomers is close to the ideal value of $R \ln 2$. Thermodynamics dictates that the entropy change for the combined processes of melting a mole of unmixed S - and R -mandelic acid molecules at a composition of 0.5 mol fraction, mixing in the liquid state, recrystallization into the racemic compound, and the subsequent dissociation into pure enantiomers must be equal to zero, because the initial and the final state are the same. In equation

$$\Delta S_{(R+S) \rightarrow \text{liq}} + \Delta S_{\text{liq}(R) + \text{liq}(S) \rightarrow \text{liq}(R+S)}^{\text{mix}} + \Delta S_{RS \rightarrow \text{liq}(R+S)} + \Delta S_{RS \rightarrow (R+S)}^{\text{demix}} = 0 \quad (7)$$

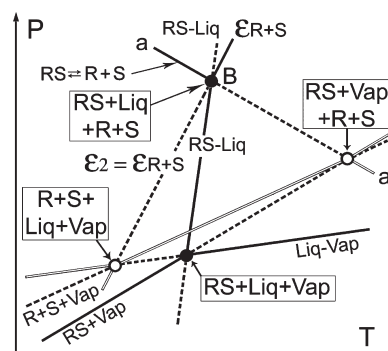


Figure 6. Proposed topological P – T diagram at 0.5 mol-fraction containing the racemic compound I and the equimolar mixture (that behaves as a single phase) of pure enantiomers of mandelic acid. The diagram contains the solid phases, the liquid phase, and the vapor phase. Black lines, stable equilibria; broken lines, metastable equilibria; gray lines, supermetastable equilibria; filled circles, stable invariant equilibria; open circles, metastable invariant equilibria.

where $\Delta S_{RS \rightarrow R+S}^{\text{demix}}$ is the entropy change for demixing in the solid state and its value is found to be equal to $+6.0(2.4) \text{ J K}^{-1}$ for a mole of mandelic acid enantiomers. Because the entropy remains approximately constant, the enthalpy change for the dissociation at P_B and T_B (456 – 461 K and 642 – 684 MPa) should be about $+2.7(1.1) \text{ kJ mol}^{-1}$. This enthalpy change is positive, which implies that the racemic compound is the low-temperature phase and that the slope of the equilibrium line must be negative as drawn in Figure 5. Hence, both increasing pressure and increasing temperature make enantiomer resolution more favorable.

CONCLUDING REMARKS

After a very limited paragraph in the book of Jacques et al. about the possibility of using pressure for enantiomer resolution² and a calculation,³ this is the first experimental study which takes into account the relative stabilities of a racemic compound and its pure enantiomers as a function of both pressure and temperature, i.e., taking into account heat and work. It appears that the racemic compound of mandelic acid may already transform into an equimolar mixture of enantiomers between 0.6 and 0.7 GPa and at 457 K instead of 1.2 GPa and 770 K estimated by Collet.³

As has been mentioned in the introduction, RS -mandelic acid possesses two polymorphs, and the metastable polymorph, RS II, has not been included in the analysis. This does not diminish the results as they are presented here in any way, because they describe the phase relationships between the RS polymorph I and the pure enantiomers. Adding a second polymorph will only complicate the overall P – T – x phase diagram, but not alter the phase relationships between individual phases.

Scott proposed a modified phase rule for equilibria under “ordinary” pressure in binary enantiomeric systems, which contain a mirror plane normal to the composition axis at $x = 0.5$.²⁴ Because the pressure is considered constant, the Gibbs’ phase rule reduces to $\nu = c + 1 - \phi$, and it becomes impossible to allow for coexistence of four phases at invariant conditions. In the present paper it is shown that the original Gibbs’ phase rule does allow for the coexistence of four phases at invariant conditions with no effect of the mirror plane on the phase equilibria. Obviously, it is not advisable to adjust simplified expressions to account for “exceptions” that were never exceptions in the original approach.

With the wish to complete the phase diagram at $x = 0.5$ with the vapor phase, a concise but not exhaustive description of the procedure will be given leading to the P – T diagram shown in Figure 6. As can be found in previous publications,^{25–28} depending on the number of phases in the diagram a specific number of triple points must exist, which can be found by tracing the phase equilibrium lines (in the topological approach, these lines are approximated by straight lines). For two solid phases²⁹ (equimolar mixture of pure enantiomers and racemic compound), one liquid phase and one vapor phase, the number of triple points is 4. The liquid–vapor equilibrium must intersect the RS – Liq equilibrium and the S (or R) equilibrium with the liquid. These intersections are triple points (quadruple points if the pure enantiomers are involved) also involving the equilibria between the solid phases and the vapor phase. The latter equilibria must meet at the equilibrium between the pure enantiomers and the racemic compound resulting in quadruple point $R + S + RS + Vap$ thus completing the diagram. From this diagram, it can be seen that under ambient conditions the vapor pressure of the racemic compound is lower than that of the equimolar mixture of the pure enantiomers, which is fully in agreement with its greater stability.

In relation to a discussion in the literature on the classification of the relationship between a conglomerate and a racemic crystal, whether one could consider them as polymorphs or not,^{30,31} the diagram in Figure 6 presents an interesting perspective. It demonstrates that at the composition of $x = 0.5$ the conglomerate and the racemic crystal from a thermodynamic point of view behave like polymorphs, as the diagram is equivalent to that of two polymorphic crystalline forms.³²

AUTHOR INFORMATION

Corresponding Author

*E-mail: ivo.rietveld@parisdescartes.fr.

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