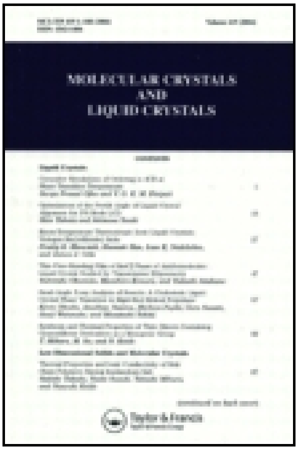

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Solid-Liquid-Vapor Equilibria of Chiral Compounds

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SOLID-LIQUID-VAPOR EQUILIBRIA OF CHIRAL COMPOUNDS

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Abstract We report the thermodynamic equations that control the phase relationships of chiral compounds and discuss the corresponding binary phase diagrams with special concern to the vapor phase. Some unusual features are observed in these diagrams when the vapor-liquid equilibrium intersects the field of existence of the solid phases. Comparison with available data shows a good agreement between theory and experiment.

Knowledge of the phase equilibria of chiral compounds in their pure enantiomeric form and of enantiomer mixtures in the whole range of composition is the starting point for understanding the behavior of these compounds in the solid state and for devising possible methods of resolution. An extensive investigation in this field has been carried out during the last century; a comprehensive review of this subject, containing a general discussion and a great deal of experimental results, has recently been reported by Jacques, Collet and Wilen[1].

The greater part of this research concerns condensed phase equilibria in the absence or in the presence of a solvent. Instead, very little is known about the equilibria involving the vapor phase. In fact, in the already cited book[1], only 6 pages out of more than 400 concern the vapor-solid diagrams and sublimation of enantiomer mixtures. Such studies require the determination of the vapor pressure of solid substances using rather specialized techniques. To the best of our knowledge, the only example of a pressure-temperature (p-T) diagram covering a sufficiently wide temperature range is that of _d_- and _dl_-dimethyl tartrate[2]. Other examples are strictly limited to the vapor-solid equilibrium and do not take into account the phenomena related to the solid-liquid phase transitions[3].

Studies in this field are not only of academic interest, but possess a strong potential for practical applications. In favorable cases, compounds with a higher optical purity can be obtained from partially resolved mixtures by sublimation. This phenomenon was discovered by Kwart and Hoster[4] and examined in greater detail by Garin[5,6]. Recently, Paquette observed an interesting example of spontaneous resolution of a racemate by sublimation[7].

The subject we are discussing falls at the meeting point of solid state chemistry and organic stereochemistry, two fields of research in which we are deeply involved. In particular, we have acquired a great awareness of this kind of problem as a consequence of our studies on the phase diagrams of volatile inclusion compounds[8-11].

In this paper, we describe the complete phase diagrams of pure enantiomers and of their mixtures, both in the case of the existence of a conglomerate and of the formation of a racemic compound. A preliminary report, concerning the p-T diagrams only, has recently been published[12]. Here we discuss the entire matter in more detail and focus our attention on the interconnection between the p-T and the temperature-composition (T-x) or the pressure-composition (p-x) diagrams.

EQUATIONS FOR MONOVARIANT EQUILIBRIA

The equations which govern the phase equilibria of enantiomer mixtures are based on a classic thermodynamic approach and are derived from the well known Clausius-Clapeyron, van Laar-Schröder and Prigogine-Defay equations under some simplifying hypotheses. We assumed that both the liquid and vapor phases behave ideally and that the solid phases are immiscibile. For the sake of simplicity, let us assume that all the enthalpies of transition are constant with temperature; by doing this, we ignore the influence of the difference in specific heat between the various phases. Although this condition is generally thought to be valid[1a], the ΔC_p contribution can be accounted for through standard procedures if a closer agreement between theory and experiment is required.

It should be pointed out that when discussing the phase diagrams, we refer to systems consisting exclusively of the two enantiomers. Any extraneous substance should be considered absent, e.g. chemical impurities, solvents, and, especially, air or other gases. We can visualize a hypothetical experiment in the following way: the solid or liquid components are introduced in a deformable plastic bag which is evacuated and air-tight; the bag is placed in a thermostatted flask inside which pressure can be varied (the same experiment could be carried out with a classic ideal piston). If, at a given temperature, the applied pressure (p_{ext}) is higher than the vapor pressure of the system (p), the bag remains flat (no vapor phase exists for these conditions). When $p_{ext} = p$, it begins to inflate and its volume varies depending on the amount of heat exchanged with the environment or, equivalently, on the ratio between the condensed and the vapor phases. When p_{ext} is lower than p, the content of the bag is completely volatilized and the system exists in the form of superheated vapor.

When p_{ext} exceeds p throughout the whole range of temperatures, only the condensed phases should be taken into account and the phase diagram coincides, for most practical purposes, with that obtained in open air with the usual DSC instruments.

The condensed phase equilibrium of a pure crystalline enantiomer in the presence of a liquid enantiomer mixture is given by the van Laar-Schröder equation[1a]:

$$\ln x = -(L/T) + A \qquad 1)$$

where x is the mole fraction of the excess enantiomer ($x > 0.5$), L (expressed in degrees Kelvin) is an enthalpic factor equal to $\Delta H_f/R$ (ΔH_f = enthalpy of melting, R = gas constant) and A ($= L/T_A$, where T_A is the melting point of the pure enantiomer) is a non-dimensional constant, entropic in nature.

If the racemate forms a crystalline racemic compound, the solid-liquid equilibrium involving this adduct is given by the Prigogine-Defay equation[13]:

$$\ln(x(1-x)/0.25) = -(\Delta H_C/R)((1/T) - (1/T_C)) \qquad 2)$$

ΔH_C being the decomposition (or "melting") enthalpy of the binary compound referred to one mole of the 1:1 AB adduct and T_C the decomposition (or "melting") temperature of the adduct. In an abbreviated form, we write:

$$\ln(x(1-x)) = 2(-(K/T) + C) \qquad 3)$$

where $K = \Delta H_C/2R$ and $C = (K/T_C) - \ln 2$. The factor 2 was introduced, in agreement with Jacques, Collet and Wilen[1b], because K and C refer here to one mole of chiral compound (irrespective of its sign) and not to one mole of the A_RA_S adduct (letter A is used for enantiomers of unspecified configuration; indices R and S are used only when the two species should be identified). Equations 1) and 3) were extensively used for describing the melting behavior of enantiomer mixtures which do not form solid solutions and are used throughout this paper.

The vapor pressure of the pure liquid enantiomers can be expressed in its simplest form by the integrated Clausius-Clapeyron equation:

$$\ln p_L = -(V/T) + B \qquad 4)$$

where $V = \Delta H_v/R$ and ΔH_v is the vaporization enthalpy.

If we assume an ideal behavior in the liquid phase, the same equation, with the same parameters, should be used for any liquid enantiomer mixture. The vapor pressure does not depend on the liquid composition and the binary phase diagram, for distillation reduces to a horizontal line[1c] (see Figure 2a).

As for any volatile crystalline substance, the vapor pressure of a pure enantiomer below its melting point may be written as:

$$\ln p_A = -(W/T) + D = -((L + V)/T) + A + B \qquad 5)$$

The sublimation enthalpy is assumed to be equal to the sum of the melting enthalpy of the crystal and of the vaporization enthalpy of the liquid. From equations 4) and 5), it follows that at T_A, $p_A = p_L$.

If the racemate crystallizes as a conglomerate, the vapor pressure of any enantiomer mixture, both saturated and unsaturated, conforms to equation 4), until the eutectic temperature is reached and the liquid disappears. Solving equations 1) and 5) for the eutectic point ($T = T_Q$, $x = 0.5$), we observe that at T_Q, p equals 2 p_A. Below T_Q, two immiscible solid phases exist, A_R and A_S, each obeying equation 5). The pressure of a eutectic mixture of both enantiomers is therefore given by equation 6):

$$\ln p_E = \ln (2\ p_A) = -\ ((L + V)/T) + A + B + \ln 2 \qquad 6)$$

The assertion that the vapor pressure of a racemic conglomerate is twice as large as that of the pure crystalline enantiomer at the same temperature was first made by Meyerhoffer at the beginning of this century[14]. Equation 6) holds true for mixtures of any composition of the two solid enantiomers.

The sublimation of a racemic compound deserves some additional comment. We can imagine this process divided into two steps: first the decomposition (or the "melting") of the crystalline adduct, and then the vaporization of the liquid phase. As a consequence, the vapor pressure of the racemic compound is obtained by adding equations 3) and 4), both referred to two moles of chiral compound:

$$\ln (x\ (1 - x)) + 2 \ln p_L = \ln (p_{AR}\ p_{AS}) =$$
$$2\ (-\ ((K + V)/T) + B + C) \qquad 7)$$

and considering that for the pure compound $p_{AR} = p_{AS} = \frac{1}{2} p_C$. It follows that for $T < T_C$:

$$\ln p_C = -((K + V)/T) + B + C + \ln 2 \qquad 8)$$

At T_C, $p_C = p_L$.

All the mixtures of the racemic compound and an excess of an enantiomer (say, A_R), at a temperature between T_C and T_Q follow equation 4). At T_Q, $p = p_L$. Below T_Q, $p = p_{AR} + p_{AS}$. p_{AR} is the vapor pressure of the pure enantiomer in excess ($= p_A$), p_{AS} (the vapor pressure of the opposite enantiomer in the racemic compound) is obtained, according to the above discussion as $p_{AS} = p_C^2/(4\ p_A)$. We conclude that the pressure of any mixture of an enantiomer with the racemic compound in the solid state is given by:

$$p = p_A + (p_C^2/(4\ p_A)) \qquad 9)$$

This formula cannot be expressed in a simple logarithmic form. In other words, the usual ln p vs 1/T plot is not linear even though L, K and V are constant with temperature. Deviation from linearity is probably within the experimental error, but, strictly speaking, the slope of the diagram is not a measure of the heat of sublimation.

The composition of the eutectic point depends on temperature and can be obtained using the following equation:

$$x = p_A/p = p_A^2/(p_A^2 + (p_C/2)^2) \qquad 10)$$

Finally, the vapor composition in equilibrium with a pure crystalline enantiomer at a prefixed pressure is given by:

$$\ln x = -((L + V)/T) + A + B - \ln p \qquad 11)$$

and that in equilibrium with the crystalline racemic compound by:

$$\ln(x(1 - x)) = 2(-((K + V)/T) + B + C - \ln p \qquad 12)$$

DISCUSSION

The theoretical phase diagrams of chiral compounds calculated from the preceding equations are reported in Figures 1-6. Some of them have the usual appearance, others show special features and are discussed in more detail. Two distinct cases are described.

a) Systems forming a racemic conglomerate

The p-T projection diagram (Figure 1)[12] is obtained from equations 4), 5) and 6). Points A and Q correspond to the triple point of the pure enantiomer and to the quadruple (eutectic) point of the $A_R + A_S$ mixture respectively. The QAL curve (equation 4) represents the vapor pressure of the

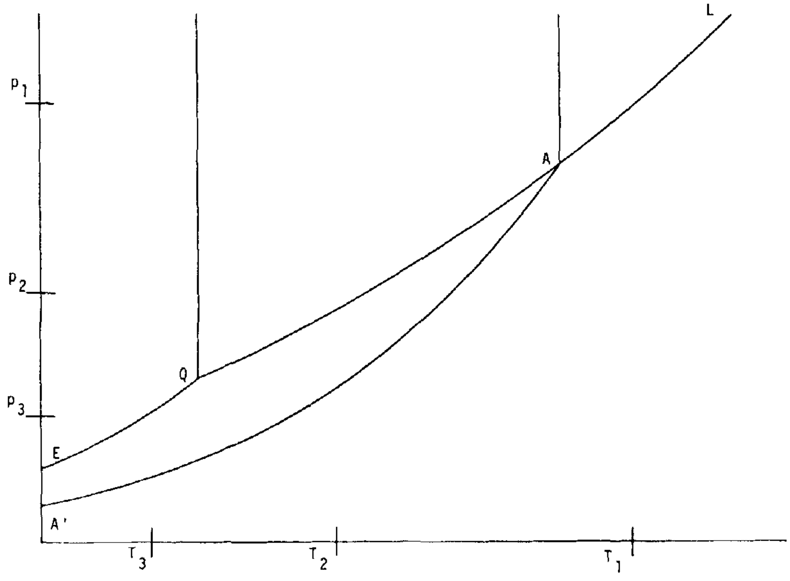

Figure 1. p-T projection diagram of an enantiomer system forming a conglomerate.

liquid, curve A'A (equation 5) that of the pure crystalline enantiomer and EQ (equation 6) that of the racemic conglomerate. As already stated, below T_Q, $p = 2\ p_A$. The two almost vertical lines starting from A and Q represent the solid-liquid equilibrium for the enantiomer and the conglomerate in the absence of the vapor phase (we assume that up to moderately high pressures, T_A and T_Q do not change).

Only the vapor phase exists in the region below the A'A and AL curves for a pure enantiomer: the liquid phase is confined to the region placed above the AL line and the solid phase to the region above A'A. For the racemic conglomerate, the vapor region extends up to the EQ and QL lines, the liquid to the region above QL and the solid is restricted to the region above EQ. Intermediate situations take place for partially resolved compounds: they are better visualized using the T-x and the p-x section diagrams obtained at constant pressure and at constant temperature respectively.

At sufficiently high pressure (p_1, see Figure 1) the phase diagram reported in Figure 2a corresponds to the well known condensed phase diagram and is quantitatively expressed by equation 1). For reasons of symmetry the diagram is invariant with respect to the exchange of x with (1 - x). The horizontal line at high temperature represents the vapor-liquid equilibrium: vaporization in this case has no effect on the existence of the other phases. T_{L1} is the temperature at which pressure along the AL line of Figure 1 reaches the value p_1.

The T-x diagram at an intermediate pressure p_2 is reported in Figure 2b: the lower part coincides with Figure 2a, but at $T = T_{L2}$, corresponding to the intersection of curve QL with line p_2 in Figure 1, the vapor phase appears. For compositions close to the racemate we simply observe the evaporation of the liquid phase, for samples having a higher enantiomeric purity, the solid-liquid mixture converts into a solid-vapor system. At temperatures higher than T_{L2} we observe the sublimation of the enantiomer in excess and a

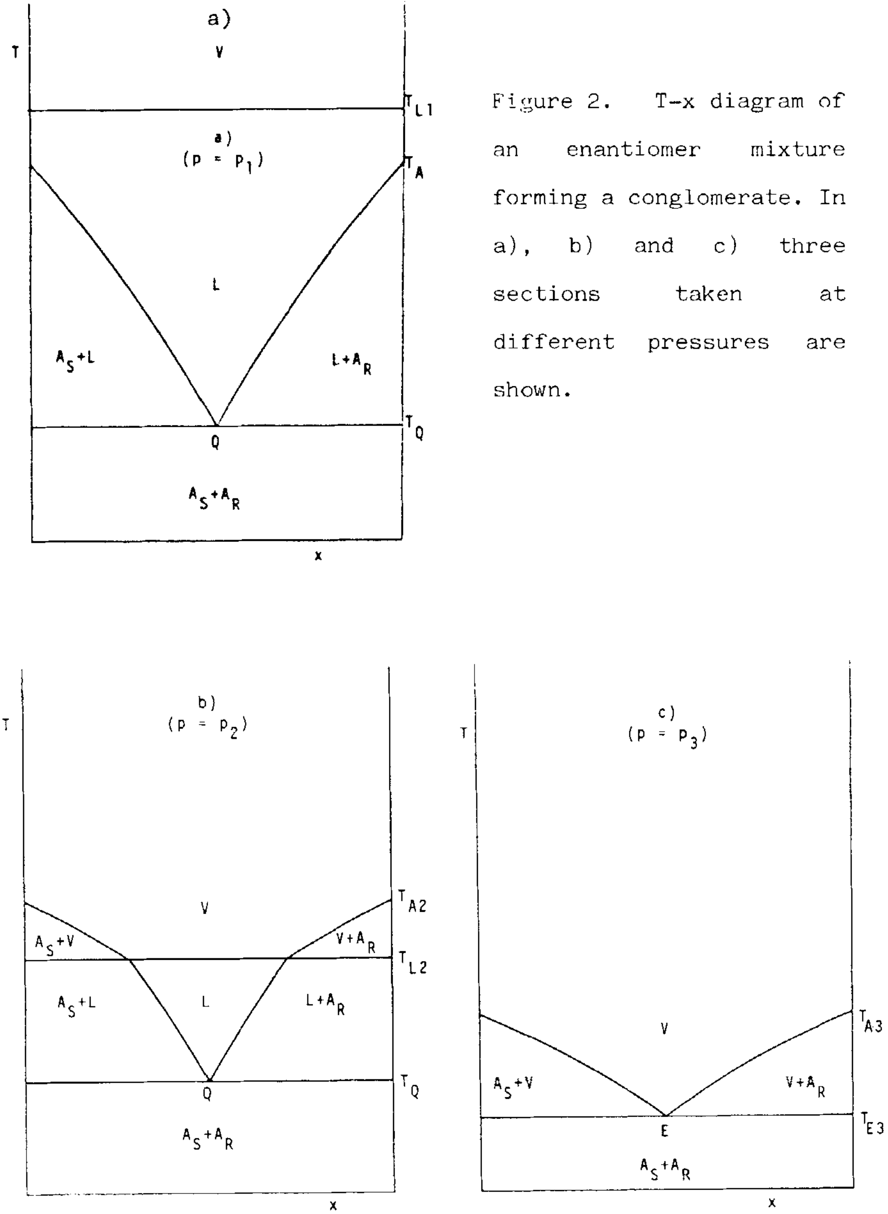

Figure 2. T-x diagram of an enantiomer mixture forming a conglomerate. In a), b) and c) three sections taken at different pressures are shown.

continuous change in composition of the vapor phase. T_{A2} represents the sublimation temperature of pure A at $p = p_2$. The slope of the solid-vapor equilibrium line (equation 11)) is lower than that of the solid-liquid transition, since the sublimation enthalpy is higher than that of melting.

At a lower pressure (p_3) the liquid is no longer stable and the diagram contains only two solid phases and the vapor (Figure 2c). The solid-vapor transition is described by equation 11).

The p-x diagram at high temperature (e.g., T_1)consists of a single horizontal line placed at $p = p_{L1}$, the pressure at which line T_1 intersects the AL curve of Figure 1. The only existing phases are the superheated vapor below p_{L1} and the liquid above.

The phase diagram changes greatly with decreasing temperature and exhibits a very peculiar aspect at temperatures between T_Q and T_A. Figure 3a shows the fields of existence of the various phases at $T = T_2$. Systems having a moderate enantiomeric purity undergo a simple vapor-liquid transition at p_{L2}, whereas at the extremes of the diagram the solid phase is also present: the pure crystalline A is in equilibrium with the liquid above p_{L2}, and with the vapor between p_{L2} and p_{A2}, i.e., at a pressure between the vapor pressure of the liquid and that of the pure solid at temperature T_2. The solid-vapor equilibrium is calculated using equation 11).

The vertical lines which divide the homogeneous

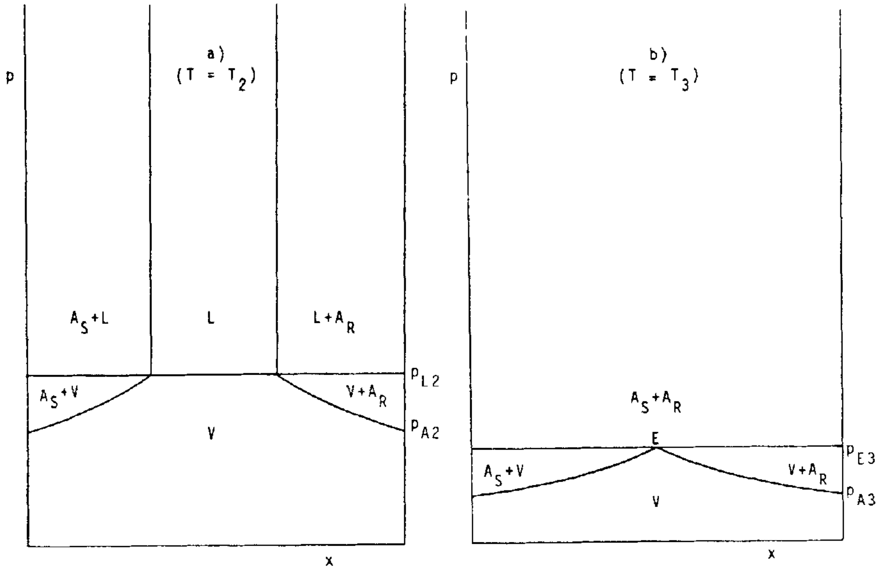

Figure 3. p-x phase diagram of an enantiomer mixture forming a conglomerate. In a) and b) two sections taken at different temperatures are shown.

solution from the biphasic (solid + liquid) regions indicate that no or very little dependence of solubility on external pressure is expected, at least in the pressure range considered in this paper (below 1 atm).

A more usual diagram is observed at T = T_3 (Figure 3b): above p_{E3}, only the two crystalline phases A_R and A_S exist. Between p_{E3} and p_{A3} the equilibrium involves the vapor and one of the solid phases, and is expressed by equation 11). It should be noted that $p_{E3} = 2\ p_{A3}$, in agreement with Meyerhoffer[14].

b) Systems forming a racemic compound

Two examples of a p-T diagram, concerning a high-melting and a low-melting racemic compound, were briefly discussed in a previous paper.[12] In the present article we consider only the high-melting adduct; the discussion can be applied with only minor changes to the other case.

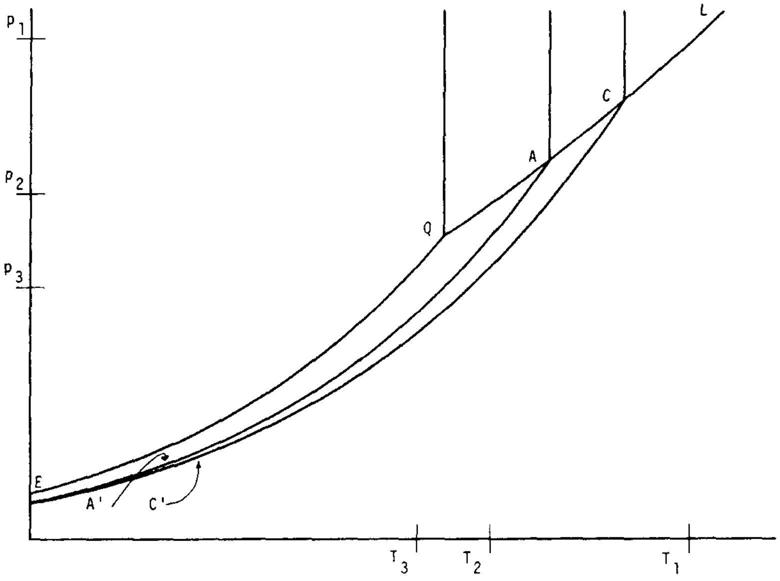

Figure 4. p-T projection diagram of an enantiomer system forming a racemic compound.

Figure 4 contains, in addition to the liquid-vapor curve Q-L (equation 1), three solid-vapor curves: C'C refers to the pure racemic compound (equation 8), A'A to the pure enantiomer (equation 5) and EQ to the eutectic mixture (equation 9) . The vertical lines starting from C, A and Q represent the solid-liquid transition of the pure racemic compound, of the single enantiomers and of the eutectic mixture. These transitions are considered, as a first approximation, independent of pressure. The regions of existence of the various phases can be determined along the lines discussed in the previous section.

The condensed phase diagram is reported in Figure 5a: the pressure at which this section has been obtained (p_1) is higher than that corresponding to point C of Figure 4. The liquidus curve in equilibrium with solid A is calculated by means of equation 1), that in equilibrium with the racemic compound C by means of equation 3). The possible presence of a liquid-vapor transition at higher temperature does not interfere with this diagram.

At a lower pressure (p_2) a horizontal line, corresponding to the vaporization of the liquid, intersects the diagram (Figure 5b). The composition of the liquid phase in equilibrium either with A or C below T_{L2} is obtained from equations 1) and 3): above T_{L2} the vapor replaces the liquid and the equations to be used are 11) and 12). At an even lower pressure (p_3), only the vapor and the crystalline phases are present, and the diagram takes the form shown in Figure 5c, in agreement with equations 11) and 12). Points E_R and E_S are not quadruple (invariant) points, as Q_R and Q_S are in Figure 5a, because only two solid phases and the vapor are present: moreover, unlike point E of Figure 2c,

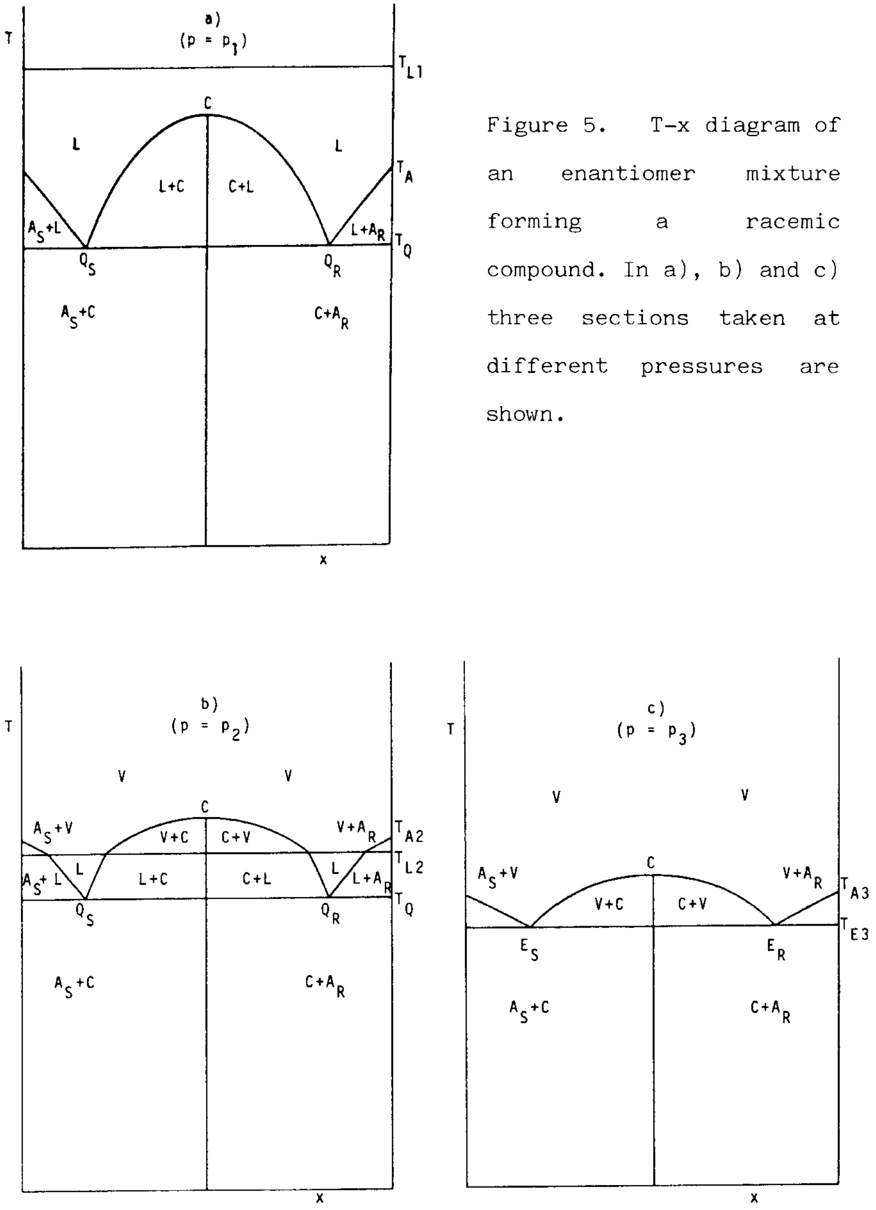

Figure 5. T–x diagram of an enantiomer mixture forming a racemic compound. In a), b) and c) three sections taken at different pressures are shown.

their composition varies with pressure and temperature according to equation 10).

The last point of this discussion concerns the p-x diagrams at constant temperature. If a section of Figure 4 is taken at temperature T_1, higher than T_C (and T_A), the only observed phenomenon is the distillation of the liquid. The phase diagram consists simply of a horizontal line, as observed in the previous case.

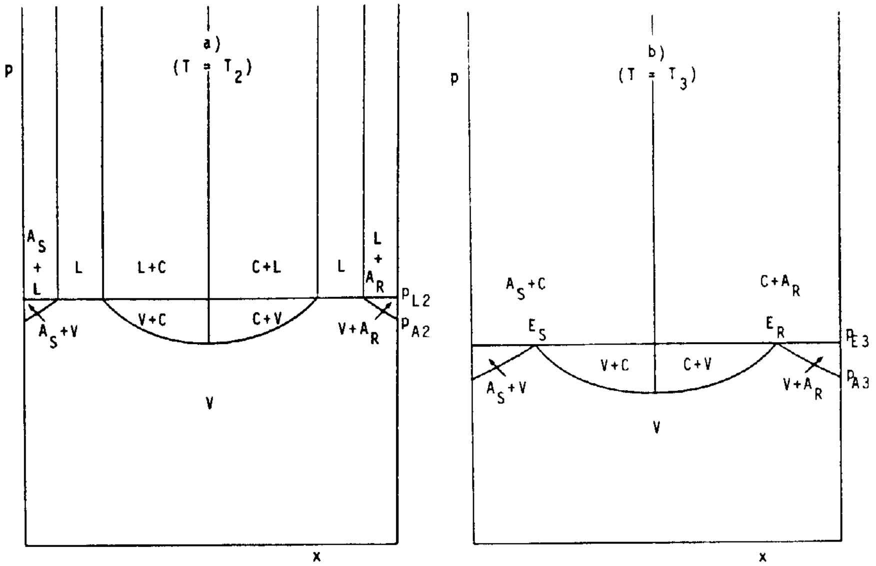

Figure 6. p-x phase diagram of an enantiomer mixture forming a racemic compound. In a) and b) two sections taken at different temperatures are shown.

At temperature T_2 we obtain the diagram reported in Figure 6a. It looks like that reported in Figure 3a, but is more complicated due to the existence of the racemic compound. However, its explanation is analogous to that already discussed. The corresponding equations are 11) and 12)

The diagram corresponding to temperature T_3 is shown in Figure 6b. Phase equilibria are calculated using equations 11) and 12). The position of points E_R and E_S derives from the intersection of the two curves and can be directly obtained using equation 10).

CONCLUSIONS

The p-T diagrams of chiral compounds can be obtained from vapor pressure measurements carried out on a pure enantiomer and on the racemate, either when this forms a conglomerate or a racemic compound. From these data all the diagrams discussed in the previous sections are easily deduced and a general knowledge of the system can be obtained.

An almost complete lack of information exists in this field, due in part to the little attention paid in the past to this subject and in part to experimental difficulties. Highly volatile chiral compounds rarely present simple behavior in the solid state (they easily form solid solutions, plastic crystals, etc.) and are not suited for testing the above reported equations. The vapor pressure of compounds showing simple melting diagrams is, at the most, of the order of some Pa (about 10^{-5} atm or 10^{-2} Torr), a pressure range where specifically designed methods should be used, e.g. high-sensitivity Bourdon type gauges[15,16], effusion techniques[2,17] or indirect methods such as that devised by Chickos[3,18,19].

Dimethyl tartrate represents the only chiral compound for which these measurements have been done[2]. The equations derived from effusion experiments are:

$$\text{d (solid): } \log p = -5903.2/T + 16.6104 \qquad 13)$$

$$\text{d (liquid): } \log p = -3993.1/T + 10.7296 \qquad 14)$$

$$\text{dl (solid): } \log p = -5941.3/T + 16.1268 \qquad 15)$$

p_{DL} (solid) is lower than 2 p_D (solid), thus indicating the existence of a racemic compound. From these data the following values for the parameters used in our equations are obtained: L = 4398.1; A = 13.5411; K = 4485.8; C = 11.7344; V = 9194.5; B = 24.7058. Comparison of equation 14) with 13) and 15) allows the calculation of T_A (324.8 K = 51.6°C) and T_C (361.0 K = 87.8°C). These values agree very well with those obtained experimentally (t_A = 48°C and t_C = 89°C)[2]. However, even in this case, the complete description of the phase diagrams is not simple, due to the possible presence of polymorphism.

Further research is required in order to ascertain the general validity and the usefulness of this method.

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REFERENCES

1. J. Jacques, A. Collet and S. H. Wilen, Enantiomers, Racemates and Resolutions (Wiley, New York, 1981); a) p. 46-47 and 52; b) p. 91; c) p. 165.
2. T. I. Crowell and G. L. Jones Jr., J. Phys. Chem., 58, 666 (1954).
3. J. S. Chickos, D. L. Garin, M. Hitt and G. Schilling, Tetrahedron, 37, 2255 (1981).
4. H. Kwart and D. P. Hoster, J. Org. Chem., 32, 1867 (1967).
5. D. L. Garin, D. J. Cooke Greco and L. Kelley, J. Org. Chem., 42, 1249 (1977).
6. D. L. Garin and D. J. Cooke, J. Chem. Soc., Chem. Commun., 33 (1972).
7. L. A. Paquette and C. J. Lau, J. Org. Chem., 52, 1635 (1987).
8. M. Farina and G. Di Silvestro, J. Chem. Soc., Perkin II, 1406 (1980).
9. M. Farina and G. Di Silvestro, Gazz. Chim. Ital., 112, 91 (1982).
10. M. Farina, in Inclusion Compounds, edited by J. L. Atwood, J. E. D. Davies and D. D. MacNicol (Academic Press, London, 1984), Vol. 2, Chapt. 3, p. 69-95.
11. M. Farina, G. Di Silvestro and A. Colombo, Mol. Cryst. Liq. Cryst., 137, 265 (1986).
12. M. Farina, J. Chem. Soc., Chem. Commun., 1121 (1987).
13. I. Prigogine and R. Defay, Chemical Thermodynamics (Longmans Green, London, 1954), p. 375.
14. W. Meyerhoffer, Berichte, 37, 2604 (1904).
15. C. G. de Kruif, T. Kuipers, J. C. van Miltenburg, R. C. F. Schaake and G. Stevens, J. Chem. Thermodyn., 13 1081 (1981).
16. W. Y. Lee and L. J. Slutsty, J. Phys. Chem., 79, 2602 (1975).
17. C. G. de Kruif and C. H. D. van Ginkel, J. Chem. Thermodyn., 9, 725 (1977).

18. J. S. Chickos, *J. Chem. Educ*, **52**, 1324 (1975).

19. D. J. Sandman, A. J. Epstein, J. S. Chickos, J. Ketchum, J. S. Fu and H. A. Sheraga, *J. Chem. Phys.*, **70**, 305 (1979).