

SOME SOLID STATE PROPERTIES OF ENANTIOMERS AND THEIR RACEMATES

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(Received in U.S.A. 21 July 1980)

Abstract—Heats of sublimation and fusion for *l* and *dl*-menthol, *d* and *dl*-carvoxime and *d* and *dl*-dimethyl tartrate were measured. Values of 22.9, 18.8, 21.7, 24.3, 18.5 and 26.9 kcal/mole and 18.2, 15.7, 24.3, 30.9, 23.3 and 36.2 cal/g were obtained for heats of sublimation and fusion respectively. Heats of sublimation are believed known to $\pm 5\%$ while heats of fusion are believed qualitatively correct. Generally good agreement was observed with literature values when available. Higher heats of fusion and sublimation are observed for the enantiomer or racemate with the higher fusion temperature. Correlation of these physical properties with the phase diagram for fusion and solubility suggest that differences in the temperature dependence of vapor pressure and solubility might be useful diagnostic tests for discontinuities in molecular packing and phase behavior in the solid state. Prediction of the temperature where racemic mixture to conglomerate transitions occur would be extremely useful for resolving racemates.

It is generally recognized that depending on the phase diagram, the physical properties of enantiomorphs can differ markedly from those of the racemate.¹ In many instances, the physical properties of the two forms are sufficiently different that fractionation^{2,3} and even resolution^{1,4} can be achieved without the need of a chemical resolving agent. These systems are referred to as racemic mixtures or conglomerates. About 200 such examples are now presently known. Even in the instances where "unassisted" resolution cannot be achieved, the physical properties of the enantiomer and enantiomeric pair in the majority of instances do differ. Only in the cases where a solid solution is formed is the crystal lattice unable to discriminate. Recent studies of solid solutions such as the *d,dl*-camphor system have in some instances attributed this to rotational motion in the solid.⁵ At temperatures where this molecular motion ceases, the system no longer exists as a solid solution. In some rarer instances, such as the *d,dl*-carvoxime system which is described as a solid solution exhibiting a maximum in the freezing point curve, the physical properties are a function of composition.⁶ Yet despite the practical importance of obtaining pure enantiomorphs, until recently, very few systematic studies of the physical properties of both enantiomorph and racemate have been reported. The work of Collet and Jacques *et al.* is certainly the most prominent in this area. Recent interest in this area, has been prompted in part by advances in analytical instrumentation, notably the availability of differential scanning calorimeters capable of a precision of a few percent.

Leclercq *et al.*⁷ have systematically studied the free energy change for the process $D(\text{solid}) + L(\text{solid}) \rightarrow DL(\text{solid})$. They found that ΔG° varied in the range 0 to -2 kcal for some 40 systems studied and that the magnitude of the free energy change was roughly proportional to the difference in m.p. between enantiomer and racemate. In addition they examined the thermodynamic factors which control transitions between racemic mixture—racemic compound formation. On the basis of their measurements and calculations, they concluded that only a

small number of systems were likely to exhibit such transitions as a function of temperature. Their estimates of the transition temperature between racemic compound and mixture required measurements of heat capacities, and fusion enthalpies for enantiomer and racemate, both in the solid and liquid states.

Our interest in this area was stimulated by recent reports of the possibility of enhancement of optical purity by fractional sublimation.² In order to learn more about the origin and magnitude of this effect we initially decided to measure the heats of sublimation of a variety of enantiomorphs and racemates to see how the results correlated to the appropriate phase diagram. As a guide in identifying those systems expected to exhibit substantial differences in physical behavior, we chose systems with large differences in m.p. between racemate and enantiomer. As demonstrated below our results suggest that the vapor pressures of enantiomer and racemate can differ substantially.

Heats of sublimation. The heats of sublimation of *d,dl*-dimethyl tartrate, *l,dl*-menthol and *d,dl*-carvoxime were measured by a technique previously described.^{8,14} The results are shown in Figs. 1–3 and the data is tabulated in Table 1. The results reported are believed accurate to $\pm 5\%$. However, the comparisons between enantiomer and racemate are relative numbers since the same experimental technique was employed in measuring the vapor pressures. Therefore we believe that the differences in ΔH_s reported are qualitatively significant.

In the case of *d*-dimethyl tartrate, the very low observed vapor pressure coupled with the small temperature range experimentally accessible may subject this result to a somewhat larger uncertainty. Previous studies⁸ have shown that when vapor pressures of the order of 10^{-6} atm or less are encountered in the method we used, adsorption effects have a tendency of lowering the observed heat of sublimation and in extreme cases can lead to curvature in the $\log p$ vs $1/T$ plot. Since curvature was not observed in this case we would conclude the ΔH_s for measured *d*-dimethyl tartrate is probably low by about 5%. Heats of sublimation for *dl* and *d*-dimethyl tartrate have previously been determined. Our result of

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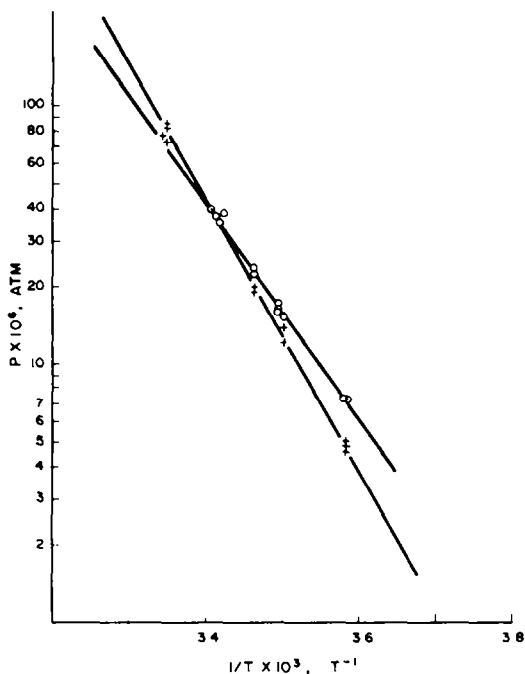


Fig. 1. Log P vs $1/T$. (a) *dl*-menthol (\circ). (b) *l*-menthol (+).

26.9 kcal/mole for *dl*-dimethyl tartrate is in excellent agreement with the results of Crowell and Jones⁹ who report 27.19 kcal/mole as determined by effusion. Their results reported for the *d* enantiomer however does not compare well with our own. Their determination of ΔH_f for *d*-dimethyl tartrate however, was based on only three measurements covering a total temperature span of 10°. In view of the consistency observed in Table 1, regarding the relationship of m.p. to ΔH_f , we believe that the ΔH_f of *d*-dimethyl tartrate to be substantially lower than for the *dl* form.

Heat of fusion. The heat of sublimation can be estimated from the following relationship

$$\Delta H_s = \Delta H_f + \Delta H_v. \quad (1)$$

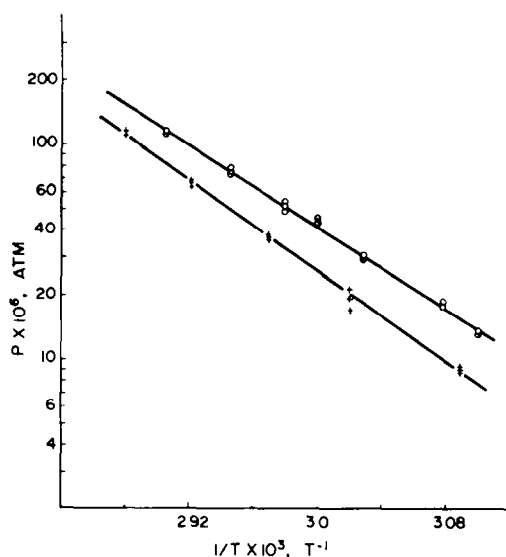


Fig. 2. Log P vs $1/T$. (a) *dl*-carvoxime (+). (b) *d*-carvoxime (\circ).

This relationship is rigorously correct only for enthalpies obtained at the same temperature. However, if it is assumed that the heat capacity for the pure enantiomer and for the *dl* form are comparable, then differences in ΔH_f between *d* and *dl* can only arise from differences in ΔH_f or ΔH_v . The different m.ps observed in Table 1 coupled with the work of Leclercq *et al.* suggested that ΔH_f is the most important term.⁷ However, it should be pointed out that very few heats of vaporization for both enantiomer and racemate have been reported. To confirm that the ΔH_f term does differ significantly, heats of fusion of the compounds previously mentioned as well as for some additional samples of some particular interest were determined by differential thermal analysis. These results, including those values previously available in the literature, are compiled in Table 2. Examination of Table 2 clearly reveals that quantitative agreement with literature values was not achieved in each case. However we do find qualitative, even semiquantitative agreement and most important, our data does appear to reproduce

Table 1. Heats of sublimation of some optical isomers

Compound	mp	²⁵ ΔH_{sub} (kcal/mole)	Correl. coeff.	Intercept (ln b)
<i>l</i> - menthol	43	22.9	.9986	29.15
<i>dl</i> - menthol	28	18.8	.9966	22.2
<i>d</i> - dimethyl tartrate	49	18.5	.9936	18.0
<i>dl</i> - dimethyl tartrate	87	26.86	.9973	30.05
<i>d</i> - carvone oxime	71	21.7	.9982	22.8
<i>dl</i> - carvone oxime	91	24.3	.9991	26.2

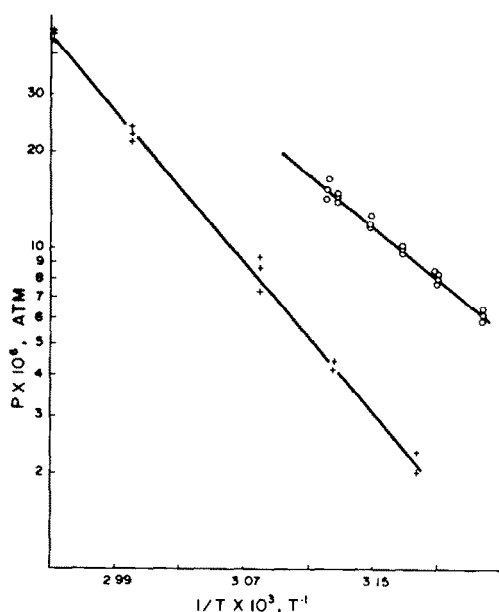


Fig. 3. Log P vs $1/T$. (a) dl -dimethyl tartrate (+). (b) d -dimethyl tartrate (O).

the same trend observed between enantiomer and racemate as a function of m.p. as reported by Leclercq *et al.*⁷ We therefore feel that the relative values observed for enantiomer and racemate are qualitatively correct and that some discussion of the relative values is warranted by the data.

The typical phase diagrams exhibited by enantiomeric pairs are shown in Fig. 4. Figure 4(A) represents the typical phase diagram representing compound formation. Menthol is an example in which the pure enantiomer melts higher than the dl form while ephedrine and dimethyl tartrate are examples where the reverse is true. In all cases that were determined, the form with the lowest m.p. appears to exhibit the smallest ΔH_f° and ΔH_s° . Examples of the rarer and often sought after phase diagram in which the dl composition corresponds to a eutectic (Fig. 4B), include dl -menthyl 3,5-dinitrobenzoate. In this instance ΔH_f for dl -menthyl 3,5-dinitrobenzoate at the eutectic composition appears lower than for the pure enantiomer.

The results reported in Table 2 appear internally consistent with the ΔH_f results reported in Table 1. They demonstrate that, depending upon the phase diagram,

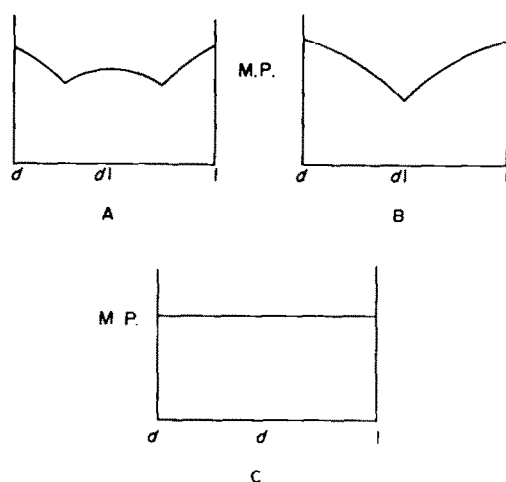


Fig. 4. M.p. vs d,l composition for: (A) racemic compound (B) racemic mixture; (C) solid solution.

significant differences in a variety of physical properties may be observed which depend upon optical purity. In addition to the obvious precautions that must be exercised to avoid fractionation when dealing with optically impure materials, the significance of these results can further be demonstrated as follows. Consider a phase diagram similar to that observed for menthol. The vapor pressure curves for dl and l -menthol are observed to diverge as the temperature is lowered. Assuming continuity in the vapor pressure curves, extrapolation to a temperature at which the vapor pressure of dl -menthol is equal to twice that of l -menthol, must correspond to the transition temperature between racemic compound and racemic mixture since a lowering of temperature will produce the condition, $vp_{dl} > 2vp_l$. Under these conditions separate crystals of d and l should be observed to form. Thus vapor pressure measurements over a range of temperatures are likely to be a good diagnostic tool for systems with the potential of undergoing racemic compound to racemic mixture interconversions.

Yet to be experimentally demonstrated but implied by the discussion above is that an evacuated chamber consisting of physically separate seed crystals of d and l should grow at the expense of racemic compound (dl) at a temperature where the vapor pressure of the dl is greater than twice the vapor pressure of d or l . This statement is similar in nature to the double solubility rule

Table 2. Heats of fusion of various chiral systems

Compound	mp(°C)	ΔH_f (cal/g)	ΔH_f (cal/g)(11t) ^a
l -menthol	43	18.2 \pm .1	18.6
dl -menthol	28	15.7	
d -carvoxime	71	24.3 \pm 1.1	23.3
dl -carvoxime	91	30.9 \pm 1.1	23.6
d -dimethyl tartrate	49	23.3 \pm .2	21.5
dl -dimethyl tartrate	87	36.2 \pm .5	35.1
l -menthyl 3,5-dinitrobenzoate	154	23.5 \pm .7	
dl -menthyl 3,5-dinitrobenzoate	128	20.9 \pm .7	

^a reference 10;

of Meyerhoffer^{15,16} used to identify conglomerates in solution.

An alternative diagnostic method closely related to the above and perhaps simpler than measuring vapor pressures, requires a study of the difference in solubility of the active and *dl* form as a function of temperature. The dependence of both solubility and vapor pressure on temperature assuming ideal behavior are similar in form and are given by the Schröder-Van Larr (in its simplified form) and Clapeyron-Clausius equation shown below.¹¹

$$\ln S = \frac{\Delta H_f}{R} \left(\frac{1}{T_f} - \frac{1}{T} \right) \quad (2)$$

$$\ln P_2/P_1 = \frac{\Delta H_s}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \quad (3)$$

For solubility, the slope of the line is primarily dependent on the heat of fusion, ΔH_f ; whereas for vapor pressure the slope is dependent on the heat of sublimation, ΔH_s . We have previously shown that differences in heats of sublimation are qualitatively paralleled by the heats of fusion (Tables 1 and 2).

If the solubility behavior of the active vs the *dl* form diverge sufficiently as a function of temperature and interactions between the *d* and *l* forms in solution can be neglected, then for a compound which does not dissociate in solution, the temperature at which the solubility of the *dl* form is twice that of the active form should correspond to the phase transition temperature (racemic compound = conglomerate). At temperatures where the solubility of the *dl* is greater than twice the *l* (or *d*) form, the stable phase diagram should be represented by a racemic mixture (Fig. 4B); solubility of the *dl* form less than twice the active form should be represented by Fig. 4(A). On the basis of the relationship observed between heats of fusion and m.p.,⁷ if the m.p. of the active form lies above the racemic material then decreasing the temperature should generally favor formation of the conglomerate. Alternatively, if the m.p. of the racemic material is greater than that of the active form it is reasonable to assume that the conglomerate will be favored at higher temperatures (this will depend on whether the solubility curves for enantiomer and racemate intersect and on the position of intersection). Systems prone to exhibit this behavior are those compounds exhibiting large differences in m.ps between racemic compound and pure enantiomer dissolved in achiral solvents in which both forms show limited solubility.

In order to illustrate how the above can be used to predict changes in phase behavior between conglomerate and racemic compound in the solid state, we have plotted in Fig. 5 $\ln S$ (solubility in mole fraction) vs $1/T$ for *d* and *dl* rubidium tartrate¹⁷ and *l* and *dl* histidine hydrochloride.¹⁶ Yamanari *et al.*^{18,19} have shown for electrolytes of the general formula AX_n which dissociate, the double solubility rule takes the form

$$S_{(\text{racemic compound})} = n+1 \sqrt{(2)(S_E - K_s)} + 2K_s$$

where S and S_E is the solubility in mole fraction of racemic compound and enantiomer respectively, n is the number of achiral ligands which are released upon dissociation and K_s is the amount of undissociated salt. If rubidium tartrate and histidine hydrochloride are assumed to be 100% dissociated ($K_s = 0$), this leads to the

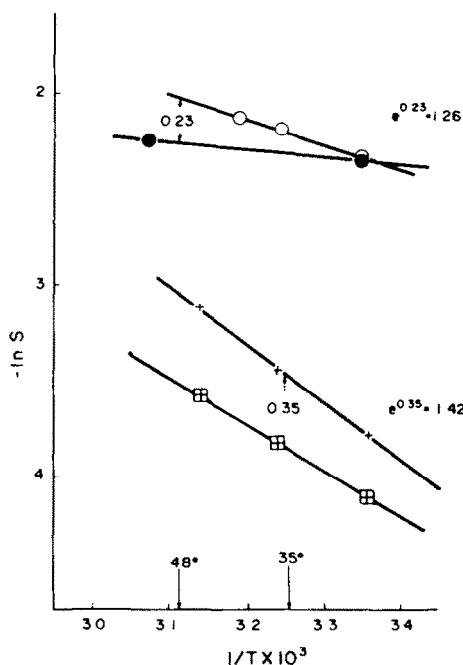


Fig. 5. $\ln S$ vs $1/T$. (a) *d, dl*-rubidium tartrate ●, ○. (b) *l, dl*-histidine hydrochloride ■, +.

conclusion that the conglomerate will be more stable when S (racemic compound) $\geq 1.26 S_E$ for rubidium tartrate and S (racemic compound) $\geq 1.42 S_E$ for histidine hydrochloride. The temperatures at which these conditions are met can be estimated from Fig. 5 as 48 and 35° respectively. Experimentally, racemic compound to conglomerate transitions are observed at 41° and between 35–45°C respectively. Unfortunately very few other systems have been studied in which the solubility of both enantiomer and racemate are known as a function of temperature. Therefore it is difficult to predict how successful plots of $\ln S$ vs $1/T$ will be in predicting these type of phase changes in the solid state. It is known that curvature is observed in $\ln S$ vs $1/T$ plots at low solubilities. This curvature is reproduced by the Schröder-Van Larr equation by taking into account the differences in heat capacity of the solid and liquid phases.[†] These heat capacity differences may be greater for the *d(l)* or *dl* form thereby causing the solubility curves to diverge faster or slower with temperature than anticipated by the simplified form of this equation. Since the heat capacity data is not generally available, plots of $\ln S$ vs $1/T$ can only be expected to yield an estimate of the phase transition temperature.

A measure of a system's propensity to exist as a conglomerate based on the differences in m.p. between *dl* and *d(l)* has previously been proposed by Peterson.¹³ Collet *et al.*,²⁰ have used the simplified form of the

[†]The complete form of the Schröder-Van Larr equation is given below.¹¹

$$\ln S = \frac{\Delta H_f}{R} \left(\frac{1}{T_f} - \frac{1}{T} \right) - \frac{C_1 - C_2}{R} \left(\ln \frac{T_f}{T} + 1 - \frac{T_f}{T} \right)$$

where S = solubility in mole fraction; T_f is the fusion temperature of the pure material; $C_1 - C_2$ is the difference in heat capacity of the liquid and solid.

Schröder-Van Larr equation to identify potential conglomerates. These workers used eqn (2) to calculate the m.p. expected for the racemate ($S = 0.5$) given the m.p. of the enantiomer, T_f , and an estimate of its heat of fusion, typically found to be between 5 and 12 kcal for most organics. Comparison of the calculated value with the reported literature value for the racemate permitted these workers to assess potential conglomerates. This led to a success rate of about 50%. It should be noted that those systems suspected to be conglomerates but found to exhibit other phase behavior are, according to eqn (2), likely candidates to exhibit racemic compound to racemic mixture (conglomerate) phase changes at temperatures other than those studied.

Despite the importance of identifying conglomerates, very little information has been gathered on the physical properties of enantiomers and what is available has mainly been determined over a narrow temperature range. It is quite likely that many other systems form racemic mixtures in addition to the 200 already known. In these instances however the temperature range where the racemic mixture is stable may differ from that previously studied. Measurements of vapor pressure or solubility as a function of temperature is a reasonable means of estimating the temperature for such a phase change. It is also clear that considerably more systems must be studied to explore the practicability of the above.

EXPERIMENTAL

Heats of sublimation. Heats of sublimation were determined by measuring vapor pressures as a function of temp. as previously described⁸ using a modified apparatus.¹⁴ Concentrations of dimethyl tartrate and menthol were determined by IR spectroscopy on a Beckman IR spectrophotometer using the CO (1750 cm^{-1} , CHCl_3) and C-H stretch (2960 cm^{-1} , CCl_4) respectively as the diagnostic frequencies. Carvoxime was analyzed by UV spectroscopy on a Perkin Elmer model 202 spectrophotometer at 2370 Å in absolute alcohol. All compounds were found to obey the Lambert-Beer law within the range 0.6–0.05. Heats of fusion were measured on a Rigaku D.T.A. using the heat of fusion of indium metal (m.p. 156° , ΔH_f , 6.8 cal/g) as the standard.

Acknowledgements—We would like to thank the Office of Research, University of Missouri-St. Louis for their continuous financial support and Profs. Alan Berndt and William Pirkle for helpful discussions, Dr. Dale Panter and the McDonnell-Douglas Corporation for allowing us the use of the DTA apparatus, and

Dr. H. M. Fales (N.I.H.) for providing us with samples of the dimethyl tartarates. We also gratefully acknowledge preprints of articles and comments provided by Prof. A. Collet (C.N.R.S.) and S. H. Wilen (C.U.N.Y.).

REFERENCES

- ¹R. M. Secor, *Chem. Rev.* **63**, 297 (1963); S. H. Wilen, A. Collet and J. Jacques, *Tetrahedron* **33**, 2725 (1977).
- ²D. L. Garin, D. J. Greco and L. Kelley, *J. Org. Chem.* **42**, 1249 (1977).
- ³H. Kwart and D. P. Hoster, *J. Org. Chem.* **32**, 1867 (1967); H. M. Fales and G. J. Wright, *J. Am. Chem. Soc.* **99**, 2339 (1977); U. I. Zahorsky and H. Musso, *Chem. Ber.* **106**, 3608 (1973); G. Pracejus, *Liebigs Ann.* **622**, 10 (1959).
- ⁴A. Collet, M. J. Brienne and J. Jacques, *Bull. Soc. Chem. Fr.* **494**, (1977); H. E. Zaugsy, *U.S. Pat.* **2**, 983, 757, May 6 (1961).
- ⁵J. E. Anderson and W. P. Slichter, *J. Chem. Phys.* **41**, 1922 (1964). C. Mjojo, *Chem. Soc. Faraday Trans. II* **75**, 692 (1979).
- ⁶F. Baert and R. Fouret, *Crystal Structure Communications* **4**, 307 (1975). H. A. J. Oonk and J. Kroon, *Acta Cryst.* **B32**, 500 (1976). J. Kroon, P. R. E. Van Gurp, H. A. J. Oonk, F. Baert and R. Fouret, *Ibid.* **B32**, 2561 (1976).
- ⁷M. Leclercq, A. Collet and J. Jacques, *Tetrahedron* **32**, 821 (1976).
- ⁸J. S. Chickos, *J. Chem. Ed.* **52**, 134 (1975).
- ⁹T. I. Crowell and G. L. Jones, Jr., *J. Phys. Chem.* **58**, 666, (1954).
- ¹⁰R. Loebl, *Handbook of Chemistry and Physics*, 62 Ed. R. C. Weast, pp. C-717-9. The Chemical Rubber Co., Cleveland, Ohio (1972).
- ¹¹I. Schröder, *Z. Phys. Chem.* **11**, 449 (1893); J. J. Van Larr, *Arch. Neerland*, **118**, 264 (1903); I. Prigogine and R. Defay, *Chemical Thermodynamics*, p. 357. Longman and Green, London (1967); S. Gladstone and D. Lewis, *Elements of Physical Chemistry* (2nd Edn) pp. 240, 385-6. Van Nostrand, New York, N.Y. (1960).
- ¹²*Stereochemistry of Carbon Compounds* (Edited by E. L. Eliel) pp. 44-45. McGraw-Hill, New York (1962).
- ¹³K. Peterson, *Ankio Kemi.* **10**, 297 (1956), as discussed by Leclercq, *et al.*⁷
- ¹⁴D. J. Sandman, A. J. Epstein, J. S. Chickos, J. Ketchum, J. S. Fu and H. A. Scheraga, *J. Chem. Phys.* **70**, 305 (1979).
- ¹⁵W. Meyerhoffer, *Ber. Dtsch. Chem. Ges.* **37**, 2604 (1904).
- ¹⁶J. Jacques and J. Gabard, *J. Bull. Soc. Chem. Fr.* **342** (1972).
- ¹⁷J. H. Van't Hoff and W. Muller, *Ber. Dtsch. Chem. Ges.* **31**, 2206 (1898).
- ¹⁸K. Yamanari, J. Hidaka and Y. Shimura, *Bull. Chem. Soc. Japan* **46**, 3724 (1973).
- ¹⁹A. Collet, M.-J. Brienne and J. Jacques, *Chem. Rev.* **80**, 217 (1980).
- ²⁰A. Collet, M.-J. Brienne and J. Jacques, *J. Bull. Soc. Chem. Fr.* **127** (1972).