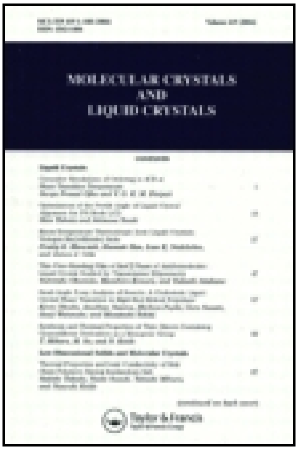

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Simulation of Calorimetric Melting Processes—A Useful Tool for Enantiomeric Purity Determination

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Simulation of Calorimetric Melting Processes — A Useful Tool for Enantiomeric Purity Determination

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Simulation of calorimetric fusion curves was introduced as a new technique in calorimetric purity analysis and has now been tested for its applicability to enantiomeric purity determination. The system investigated was the enantiomeric pair (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol. The racemic form of this system either exists as a conglomerate or as a racemic compound. The binary fusion diagrams of both forms of enantiomeric mixtures were built up from melting investigations and were compared with calculations. The results obtained show that the simulation method is suitable to determine enantiomeric purities by an accuracy of better than 10% within a concentration range 80...100% *ee* which is the important range for purity analysis.

Keywords: Enantiomeric purity; phase diagram; calorimetry; simulation; DSC

1. INTRODUCTION

Monitoring the composition of enantiomeric mixtures is an essential procedure in organic synthesis, pharmacology, physiology and food chemistry and a variety of methods has been developed to determine this important property [1]. To define the composition of the mixture with

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respect to the two optical antipodes the quantities optical purity and enantiomeric purity are used.

Optical purity, *o.p.*, is defined as the optical rotation α of a mixture divided by the specific rotation, $[\alpha]$, of the pure enantiomer:

$$o.p. = \frac{\alpha}{[\alpha]} \tag{1}$$

Since the values of α and $[\alpha]$ relate to the experimental conditions such as wavelength, solvent and concentration, the enantiomeric excess, *ee*, which is equivalent to the enantiomeric purity p describes the composition of an enantiomeric substance and is defined without recourse to any physical measurement:

$$ee = \frac{[R] - [S]}{[R] + [S]} \tag{2}$$

$[R]$ and $[S]$ are the concentrations of the two enantiomers with $[R]$ being the predominant isomer for convenience. A relationship between the mole fraction of the predominant enantiomer x and the enantiomeric excess is given by:

$$x = \frac{1 + ee}{2} \tag{3}$$

The magnitude of the enantiomeric excess may range from zero, in which case the compound is said to be racemic, to 1 in which case the substance is called a pure enantiomer. Assuming a linear relationship between α and concentration, which is true for most systems, the optical purity is equal to the percent excess of one enantiomer over the other.

If the laboratory synthesis or industrial manufacturing merely produces racemates or racemic mixtures, a separation of the enantiomers is involved in the course of the manufacturing process if a pure enantiomer is finally required. Hence, a quick and reliable method for monitoring the enantiomeric purity of the product is of high importance. If the pure enantiomer is available or the value of the absolute rotation $[\alpha]$ can be calculated from structural considerations, the optical purity can be determined by polarimetry using Eq. (1). The methods which do not involve separation require simultaneous analysis of the enantiomeric components and include techniques like chromatography, NMR spectroscopy and Differential Scanning Calorimetry, DSC. The latter is the subject of the present study.

2. CALORIMETRIC PURITY DETERMINATION

The absolute purity determination of organic compounds by means of DSC is an established practice in science and industry. The method consists of a quantitative analysis of the sample's fusion peak and is based on the fact that small amounts of impurities broaden the melting range of a substance and lower its melting temperature. The general evaluation procedure of a melting curve, depending on the application of van't Hoff's law of freezing temperature depression, includes several steps and has been described elsewhere [2–4].

A new method of purity determination which takes into account both calorimeter and substance properties gives more precise results than the classical method and is based on the comparison between experimental and computed DSC curves [5, 6]. The latter were obtained by calculating the enthalpy production during melting of a binary mixture. For this purpose a suitable mathematical model describing the heat flows in the calorimeter has been developed. After the model parameters have been adapted to the employed calorimeter, purity determinations can be performed by simulation of DSC curves: Both the experimental and the calculated melting curves are plotted in one diagram and compared. The total impurity concentration x_2^* is varied together with the fusion temperature until the deviations between the two curves exhibit a minimum. In this case the impurity concentration x_2^* used for the calculated curve corresponds to the impurity of the sample investigated, including a relative error $(x_{2,\text{real}}^* - x_{2,\text{exp}}^*)/x_{2,\text{real}}^*$ in the order of 10%.

The reliability of the simulation method has been shown in former studies using different calorimeters and several binary systems forming eutectic mixtures. e.g., naphtalene/*trans*-azobenzene. Recently, the method has also been extended to mixed crystals [7]. Since compositions of optical antipodes behave like eutectic mixtures the determination of enantiomeric purities may also be performed by simulation of calorimetric curves [8].

3. CALCULATION OF THE ENTHALPY PRODUCTION

The calculation of the molar enthalpy production during melting $\mathrm{d}H/\mathrm{d}t$ represents the essential step in the simulation of calorimetric curves. For the model presented in this study the enthalpy of fusion at a certain temperature, $\Delta H(T)$, may be expressed as:

$$\Delta H(T) = F_1(T)\Delta_{\text{fus}}H_1 + F_2(T)\Delta_{\text{fus}}H_2 \tag{4}$$

The molten fraction is subdivided into the main component and the sum of impurities present in the sample. Because the amount of impurities and, consequently, its influence on the enthalpy of fusion is negligible in most cases, only the enthalpy of fusion of the main component, $\Delta_{\text{fus}}H_1$, is considered leading to the simplified Eq. (5).

$$\Delta H(T) = F(T)\Delta_{\text{fus}}H_1 = \frac{x_2^*}{x_2(T)}\Delta_{\text{fus}}H_1 \tag{5}$$

In this equation, $F(T)$ is the fraction melted, x_2^* is the total mole fraction of impurities in the initial mixture and $x_2(T)$ is the fraction of impurities in the liquid phase. However, in the case of enantiomeric mixtures this assumption is actually correct because the enthalpy of fusion is the same for both enantiomers.

A relationship between the composition of a eutectic mixture and its final melting temperature T is given by the equation of Schröder-Van Laar:

$$\ln x_1 = \frac{\Delta_{\text{fus}}H_1}{\text{R}}\left(\frac{1}{T_{\text{fus},1}} - \frac{1}{T}\right) - \frac{C_{lq,1} - C_{s,1}}{\text{R}}\left(\ln\frac{T_{\text{fus},1}}{T} + 1 - \frac{T_{\text{fus},1}}{T}\right) \tag{6}$$

The validity of Eq. (6) is based upon immiscibility of the enantiomers in the solid state and ideality of the enantiomeric mixture in the liquid state which is very nearly true since the energy differences between homochiral and heterochiral interactions are very small relative to the enthalpies of fusion. The second term which takes into account the difference in specific heats between liquid $C_{lq,1}$ and solid $C_{s,1}$ is generally negligible compared to the first term and Eq. (6) may be written as:

$$\ln x_1 \approx \frac{\Delta_{\text{fus}}H_1}{\text{R}}\left(\frac{1}{T_{\text{fus},1}} - \frac{1}{T}\right) \tag{7}$$

If ln x_1 is replaced by $\ln(1-x_2)$ the combination of Eq. (5) and Eq. (7) yields:

$$\Delta H(T) = \frac{x_2^*\Delta_{\text{fus}}H_1}{1 - \exp\left[-\frac{\Delta_{\text{fus}}H_1}{\text{R}}\left(\frac{T_{\text{fus},1} - T}{T_{\text{fus},1}T}\right)\right]} \tag{8}$$

Finally, Eq. (8) is differentiated with respect to time:

$$\frac{\mathrm{d}H}{\mathrm{d}t}=\left(\frac{\mathrm{d}H}{\mathrm{d}T}\right)\left(\frac{\mathrm{d}T}{\mathrm{d}t}\right)=x_2^*\frac{\Delta_{\mathrm{fus}}H_1^2}{\mathrm{R}\,T^2}\;\frac{\exp\left[-\frac{\Delta_{\mathrm{fus}}H_1(T_{\mathrm{fus,1}}-T)}{\mathrm{R}\,T_{\mathrm{fus,1}}\,T}\right]}{\left[1-\exp\left(-\frac{\Delta_{\mathrm{fus}}H_1(T_{\mathrm{fus,1}}-T)}{\mathrm{R}\,T_{\mathrm{fus,1}}\,T}\right)\right]^2}\left(\frac{\mathrm{d}T}{\mathrm{d}t}\right) \tag{9}$$

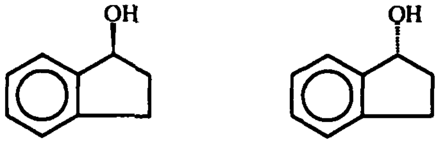
Equation (9), combined with the non-linear system of four coupled differential equations describing the heat flows in the calorimeter, enables the calculation of the enthalpy production with the temperature T being the actual temperature of the sample and $\mathrm{d}T/\mathrm{d}t$ being the constant heating rate [5]. The result is a fusion curve the shape of which depends on the value of the initial impurity concentration x_2^*.

4. EXPERIMENTAL

4.1. A Model Substance for Monitoring Enantiomeric Purities

The application of both the classical and the simulation technique for calorimetric purity analysis includes the melting behaviour of the sample and is consequently restricted by the properties of the substance. Melting should take place within a temperature range accessible with the employed equipment. That means measurements on liquid enantiomers have to be carried out either at low temperatures if possible or they have to be converted into crystalline derivatives. Furthermore, compounds which exhibit additional phenomena overlapping with the melting such as decomposition, racemization or phase transitions can obviously not be analyzed by differential scanning calorimetry.

To validate the simulation method for monitoring enantiomeric compositions the system (*S*)-(+)-1-Indanol (**a**)/(*R*)-(−)-1-Indanol (**b**) has been chosen:



(a) (b)

FIGURE 1 (*S*)-(+)-1-Indanol (**a**) and (*R*)-(−)-1-Indanol (**b**).

Mixtures of the two enantiomers were prepared by adding defined amounts of *rac*-Indanol to the pure (*S*)-enantiomer (both obtained from Aldrich). To avoid the purity determination being distorted by unknown impurities, the materials had been zone-refined yielding purities ≥ 99.95%. Their melting temperatures and enthalpies of fusion determined by DSC are 51.1°C and 16.5 ± 0.2 kJ mol^{-1} for the *rac*-Indanol, respectively 72.5°C and 19.5 ± 0.2 kJ mol^{-1} for the pure enantiomer.

Measurements were performed using a dynamic heat flux calorimeter Heraeus TA 500 which had been calibrated with respect to temperature and calorimetric sensitivity according to the procedure described in [9]. Samples of 3 – 5 mg were weighed into aluminium crucibles and heated at a scanning rate of 1 K min^{-1}. The computer program for the simulation of DSC curves was implemented with a Turbo-Pascal compiler. Calculations of the fusion peaks were performed on a standard Personal Computer taking 10 – 15 seconds of computing time.

4.2. Determination of Phase Diagrams

The racemic composition of 1-Indanol belongs to one of two different classes. In the first, the crystalline racemate exists as a conglomerate, a mechanical mixture of small crystals of the pure enantiomers. The second and, in this case, the more stable type is that in which both enantiomers are present in equal quantities in a defined arrangement within the crystal lattice. The resulting homogeneous solid phase corresponds to a true crystalline addition compound which is also called a racemic compound. A continuous series of solid solutions is rarely formed by enantiomers and was not observed for 1-Indanol.

According to [10] the conglomerate of 1-Indanol can be prepared from the racemic compound by heating up to 120°C and subsequent recrystallization from petroleum ether. The results of our DSC measurements show that the conglomerate can also be obtained by crystallizing the liquid racemic compound if it is kept at 80°C for some minutes before further cooling. If, on the other hand, the racemic compound was molten, but only heated up to approx. 55°C, recrystallization again yields the racemic compound. This indicates that well-ordered regions which consist of molecule pairs of the racemate remain in the liquid. As the mobility of the molecules is still limited at this temperature, these ordered regions act as centres of crystallization which enable the racemic compound to crystallize instead of the conglomerate.

The melting behaviour of mixtures of the two Indanol enantiomers can be seen from the melting curves in the figures below. Racemic compounds were used as initial samples before the first melting. From these melting curves eutectic peaks can be located at 49.5°C which finally disappear and the melting temperature rises to 52.1°C, observed for the equimolar composition (Fig. 2):

If the mixtures had been heated up to 80°C the conglomerate crystallizes from the liquid which is proved by the melting curves obtained from the second melting. In this case the eutectic composition is equal to the racemic one and the final melting point is lowered to 37.2°C (Fig. 3):

Keeping the samples at room temperature for two weeks causes the racemic compositions to be formed again.

The binary phase diagrams of 1-Indanol can be derived from the two series of fusion curves. The phase diagram of a mechanical mixture of enantiomers is given in Figure 4. It shows a simple eutectic, and the eutectic temperature corresponds to the melting point of the racemic conglomerate. In contrast to this behaviour, there are two eutectic points in the phase diagram of a racemic compound, see Figure 5. The melting point of the racemate is always located above the eutectic temperature though it generally may be either above or below the melting point of the pure enantiomers, depending on the system investigated. In the case of 1-Indanol the difference in melting points between the eutectic and the racemic compound is only 2.5 K which in Figure 2 causes the two overlapping peaks.

It is evident from the derivation of the enthalpy production given in Chapter 3 that the simulation method requires the composition of the

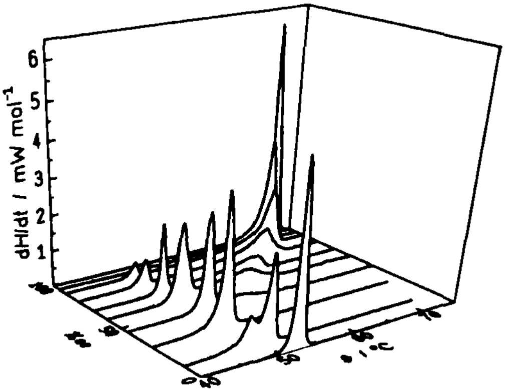


FIGURE 2 Melting curves of (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol mixtures. Racemic compositions exist as racemic compounds.

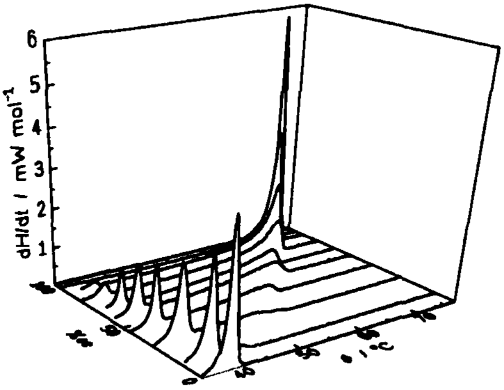


FIGURE 3 Melting curves of (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol mixtures. Racemic compositions exist as conglomerates.

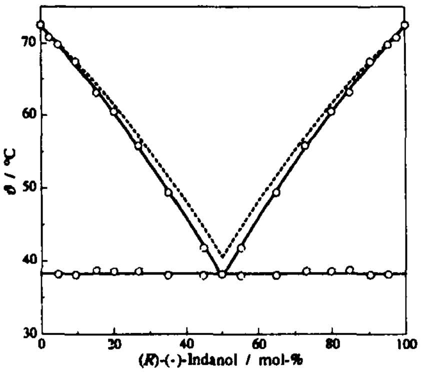


FIGURE 4 Phase diagram of the system (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol forming conglomerates. Experimental —O— and calculated ---- liquidus curves.

sample to be located in a range described by the equation of Schröder-Van Laar. In the case of a conglomerate this equation permits the calculation of the entire liquidus curve only from the melting point and the enthalpy of fusion of a pure enantiomer. In the case of a racemic compound, the same equation may be applied to that part of the liquidus found between the pure enantiomers and the corresponding eutectic (enantiomeric branch), whereas the region between the two eutectics including the dystectic point corresponding to the racemate (racemic branch) may be calculated by the equation of Prigogine-Defay:

$$\ln 4x\,(1-x) = \frac{2\Delta_{\text{fus}}H_R}{\mathrm{R}}\left(\frac{1}{T_{\text{fus},R}} - \frac{1}{T}\right) \tag{10}$$

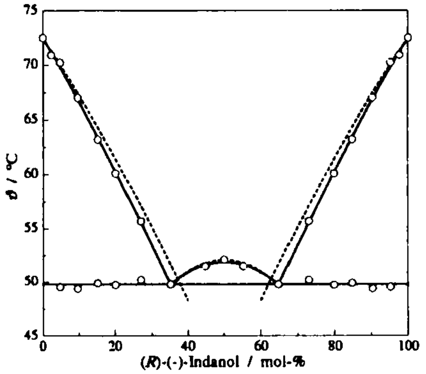


FIGURE 5 Phase diagram of the system (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol forming racemic compounds. Experimental —O— and calculated ---- liquidus curves.

In this equation x represents the mole fraction of one of the enantiomers in the mixture whose melting terminates at the temperature T. $T_{\mathrm{fus},R}$ and $\Delta_{\mathrm{fus}} H_R$ are melting temperature and the enthalpy of fusion of the racemic compound [11].

To prevent the arduous construction of phase diagrams from a series of measurements on well defined enantiomeric mixtures the range of compositions applicable to the simulation method should also be calculated by means of Eqs. (7) and (10). This has been done for 1-Indanol. A comparison between experimental and calculated phase diagrams is given in Figures 4 and 5.

5. DETERMINATION OF ENANTIOMERIC PURITIES BY SIMULATION OF DSC CURVES

It is obvious from the phase diagrams that the simulation method for calorimetric purity determination is applicable to mixtures of the two 1-Indanol enantiomers. If conglomerates are formed, any composition may in principle be analyzed whereas the validity of Eq. (7) is given only in the range 30 − 100% *ee* if racemic compounds are present. However, the real applicability is limited further more by the fact that melting of a composition having a melting temperature close to the eutectic temperature results in a DSC curve in which the fusion peak of the main component overlaps with the fusion peak of the eutectic. From thereon, an unambiguous adaptation of the calculated to the experimental curve is very difficult since it is the ascending part of a DSC peak from which the purity of a sample is inferred.

In our opinion this restriction is of little significance because purity determinations usually become important if substances have to be classified using attributes like 'pure', 'very pure' or 'ultrapure' corresponding to an enantiomeric excess of at least 90% *ee*.

The experimental results of purity determinations on different (*S*)-(+)-1-Indanol/(*R*)-(−)-1-Indanol mixtures performed by the simulation method are given in Table I:

TABLE I Compositions of the samples compared with calculated amounts of the (*R*)-enantiomer

x_2^*	*ee*	$x^*_{2,calc.}$	*Deviation*
mol-%	%	*mol-%*	%
0.75	98.50	0.69	−8.0
1.43	97.14	1.29	−9.8
2.33	95.34	2.40	3.0
4.78	90.44	4.50	−5.9
9.68	80.64	9.30	−3.9

Compositions of 80...98.50% *ee* containing (*S*)-(+)-1-Indanol as the main component have been analyzed. The impurity concentration x_2^* given by the simulation software always belongs to those calculated curves for which the sum of deviations exhibits a minimum with respect to the corresponding experimental peak. Further experiments on samples containing more than 10 mol-% of the (*R*)-enantiomer in the present case did not come to any satisfying results because melting of the main component starts immediately after the eutectic became liquid and the two peaks could not be separated. Finally, the result of an experiment is given in Figure 6 as an example:

It shows the fusion curve of a (*S*)-(+)-1-Indanol sample containing 0.75 mol-% of (*R*)-(−)-1-Indanol and its optimized simulated curve. Since the calculation of a calorimetric curve results in a temperature difference between sample and reference the comparison of the two curves is simplifyed by converting the output of the calorimeter using the Pt 100 temperature function.

Considering the maximum relative error of 10% referring to the employed impurity concentration the simulation method can be regarded as a reliable method for enantiomeric purity determination. In addition the technique can be managed using small amounts of sample material (at least 1−3 mg) which can even be reclaimed if no decomposition takes place immediately after melting.

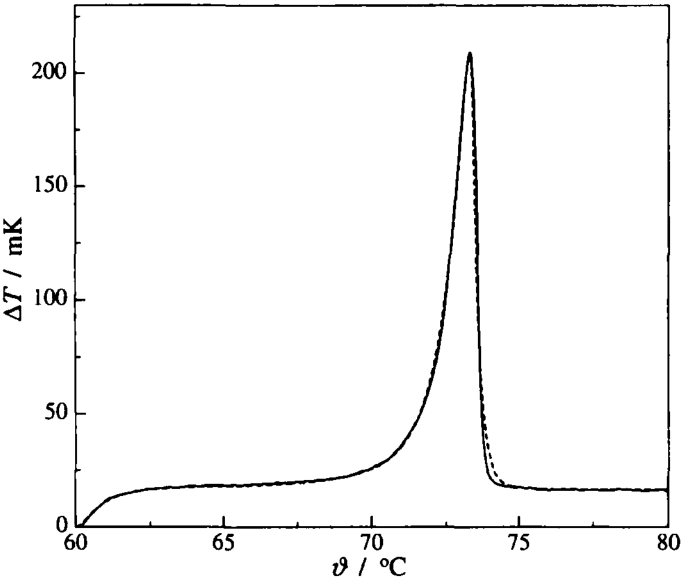


FIGURE 6 Measured — and calculated ---- melting curve of a (*S*)-(+)-1-Indanol sample containing 0.75 mol-% (*R*)-(−)-1-Indanol.

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