Organic Branched-Chain Compounds, 4[+]

A New Racemic Conglomerate and Its Characterization by the Melting Point Diagram – Formation of the Metastable Racemic Compound

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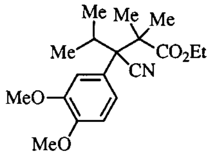
The highly branched ester *rac*-**1** has been prepared. It exists in the form of a conglomerate (m.p. 90–92 °C) in which the two enantiomers are present in separate crystal lattices, as indicated by the melting point diagram. Both enantiomers of **1** have been isolated by crystallization [m.p. 112–114 °C, $[\alpha]_D^{22} = +24.4 \pm 0.7$ ($c = 0.45$, Et_2O), -25.4 ± 0.8 ($c = 0.44$, Et_2O)]; mechanical manipulation of the conglomerate provided samples enriched in one or the other enantiomer and subsequent recrystallization of these partially resolved samples furnished the isolated enantiomers. The high value of the enthalpy of fusion of enantiomers **1** ($\Delta H_f^{enant} = 8.8 \pm 1.4$ kcal mol^{-1}) and the moderate value of the corresponding entropy ($\Delta S_f^{enant} = 23 \pm 4$ cal K^{-1} mol^{-1}), both derived from the melting point diagram, are ascribed to the relative compactness of the highly branched molecule and to its reduced conformational flexibility, respectively. Ester *rac*-**1** has been serendipitously obtained in the form of a racemic compound (m.p. 82–84 °C) by crystallization of the racemate. The racemic compound transforms into the conglomerate at 70 °C. This transformation may be regarded as a spontaneous optical resolution occurring in the solid crystalline state.

Introduction

Solid organic racemates can exist in various crystalline forms, the most common being the conglomerate, the racemic compound, and the solid solution.[1] In the conglomerate, the two enantiomers are present in separate crystal lattices. The formation of a conglomerate is often referred to as "spontaneous resolution" since a single crystal contains only one optical antipode. In the racemic compound, the two enantiomers, present in a 1:1 ratio, are arranged in a single lattice. When there is no preference for one or the other enantiomer in the different sites of a lattice, the distribution of the two enantiomers in the lattice is random and a solid solution results. The form that will be obtained by crystallization under thermodynamic control is that for which the lattice is more stable. Most known crystalline organic racemates are racemic compounds, while conglomerates (which represent only about 5% of the racemates) and solid solutions are unusual.[1a–1c,2,3]

A means of identifying the type of a crystalline racemate is to use a melting point diagram.[1,4] Such a diagram is constructed from the temperatures of onset and of termination of fusion (the melting range) of mixtures of the racemate with an added constituent enantiomer, or of mixtures of the enantiomers obtained by partial resolution. As first described by Roozeboom,[5] the shape of the melting point diagram is characteristic for each racemate type. Using this method, the racemate type can in many cases be unambiguously determined.

Over the past years, we have been interested in the synthesis of branched-chain organic compounds.[6] In relation to a project on certain carboxylic amides of biological interest,[7] we required the highly branched ester *rac*-**1**. We report herein on the preparation of this racemate and its characterization as a conglomerate by means of a melting point diagram. In order to permit construction of the diagram, we isolated both enantiomers in the racemate. This isolation was accomplished by recrystallization of mixtures previously enriched in one or the other enantiomer by means of mechanical manipulation of the conglomerate. In addition, we serendipitously obtained the ester *rac*-**1** in the form of a racemic compound by crystallization of the racemate. We have found that this form is thermodynamically unstable with respect to the conglomerate, into which it transforms.



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Results and Discussion

The highly branched ester *rac*-**1** was prepared in low yield (26%) by alkylation of the carbanion derived from nitrile **2** with α-bromo ester **3** as depicted in Scheme 1. LDA was used as base in THF/hexane to form the strongly basic carbanion, and HMPA was subsequently added as a co-solvent

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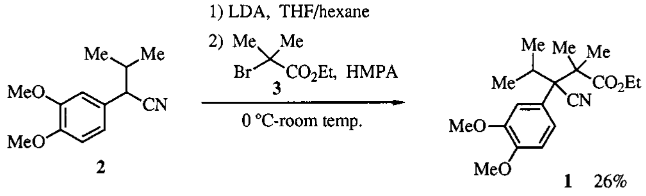


Scheme 1. Synthesis of highly branched ester *rac*-**1**

to facilitate the carbanion alkylation. The yield was even lower (8%) using $NaNH_2$ as base and DME as solvent.

In order to gain a preliminary idea of the crystalline form of the pure racemate obtained, the melting points of several tiny samples, randomly taken from the bulk of the crystals, were visually determined using a hot-stage microscope. The samples included fragments of crudely broken crystals. The samples melted over different, wide temperature intervals, beginning at 90°C in every case and ending at various temperatures above 95°C. However, a sample truly representative of the racemate, obtained by thorough homogenization of a substantial portion, melted completely at 90−92°C. These findings were fully consistent with the existence of two different crystalline solids in the racemate, occurring either in separate single crystals or aggregated in twin crystals. Since the eutectic mixture of the two solids (the lowest melting point observed) coincided with the racemate, the results strongly suggested that the racemate was a conglomerate. The higher melting points observed corresponded to samples containing excess enantiomer. A preliminary crystallographic examination confirmed the occurrence of multiple twinning in the crystals. However, this prevented a determination of the nature of the racemate by X-ray analysis. Thus, the melting point diagram method was undertaken.

Isolation of the Enantiomers

The isolation of the enantiomers in ester *rac*-**1**, needed to construct the melting point diagram, was accomplished in the following manner. A large crystal (34 mg) was obtained by recrystallization of pure *rac*-**1** from Et_2O/petroleum ether. The crystal grew from a tiny crystal of the racemate added as a seed. The crystal was made up of two plates, which were carefully separated from each other providing two fragments of almost equal weight. The broad melting ranges of the two fragments (90−96 and 90−98°C) indicated that both contained excess enantiomer. The enantiomeric excesses in the fragments could later be quantified from the respective melting ranges using the subsequently constructed melting point diagram, and were found to be 20 and 25% for these two fragments. The mixed melting point of the two fragments in a 1:1 ratio (90−93°C) was narrower than the melting range of either of the unmixed fragments. Therefore, it was evident that the excess enantiomers in the two unmixed fragments were actually the antipodes of opposite rotation. Thus, the mechanical fragmentation of the crystal gave a partial optical resolution of the two antipodes. Single recrystallizations of the two fragments from Et_2O/petroleum ether directly furnished the two pure enantiomers, each one from one of the fragments. Both isolated enantiomers melted at 112−114°C and had specific optical rotations in agreement with each other within experimental uncertainty $\{[\alpha]_D^{22} = +24.4 \pm 0.7$ (c = 0.45, Et_2O), -25.4 ± 0.8 (c = 0.44, Et_2O)$\}$.[8]

We concluded that the enantiomeric purities of the isolated enantiomers were high based on the following. No partial fusion below 112°C could be detected visually with a microscope for either isolated enantiomer. On the other hand, addition of only 5% of the isolated opposite antipode to one of the isolated enantiomers produced a drastic depression of the onset of fusion temperature to well below 112°C, which was clearly perceived with the microscope.

Melting Point Diagram

To construct the melting point diagram for ester *rac*-**1**, mixtures of the racemate with one or the other constituent enantiomer were used. The temperatures were determined visually using a hot-stage microscope. Figure 1 shows the diagram, which is typical for a conglomerate, as distinct from the diagrams for other racemate types.[1,4,5] Thus, the diagram exhibits a single eutectic point, the composition at which is that of the racemate. Furthermore, the different mixtures always begin to melt at the melting point of the eutectic, and their termination of fusion temperature is higher the larger is the enantiomeric excess.

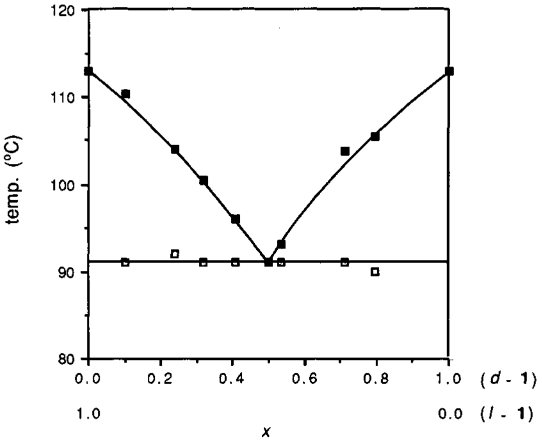


Figure 1. Melting point diagram for ester *rac*-**1** in the form of a conglomerate; x: mol fraction of ester *d*-**1** or *l*-**1**; open squares: temperature of beginning of fusion; solid squares: temperature of termination of fusion

Further evidence supporting the conglomerate formation is provided by the fit of the experimental data in Figure 1 to the theoretical, thermodynamic Schröder−Van Laar equation, which describes the symmetrical branches in the diagram for a racemic conglomerate (Equation 1).[1a,1b] In this equation, T_{end}^{mixt} is the temperature of termination of fusion (on the absolute scale) of the conglomerate mixture, the mol fraction of which for the predominant enantiomer is x ($x > 0.5$); otherwise T_{end}^{mixt} is the melting point of the racemic conglomerate ($x = 0.5$). T_f^{enant}, ΔH_f^{enant}, and R are constants representing the melting point of the pure enantiomers, the enthalpy of fusion of the pure enantiomers, and the gas constant, respectively. The fit is illustrated by the linear regression shown in Figure 2.[9]

$$\ln x = \frac{\Delta H_f^{\text{enant}}}{R}\left(\frac{1}{T_f^{\text{enant}}} - \frac{1}{T_{\text{end}}^{\text{mixt}}}\right) \quad \text{(eq. 1)}$$

$$T_f^{\text{enant}} = 386.2\ \text{K}\ (113.0\ ^\circ\text{C})$$

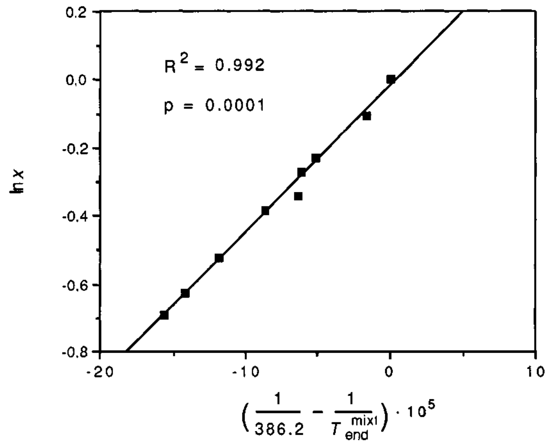
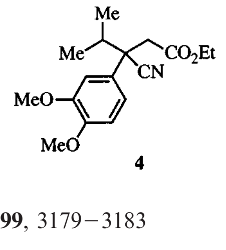


Figure 2. Linear regression of the experimental data in Figure 1 as applied to the Schröder−Van Laar equation for a racemic conglomerate (Equation 1)

Application of the Schröder−Van Laar equation to each experimental $x-T_{\text{end}}^{\text{mixt}}$ pair in Figure 1 provides a set of eight values for the enthalpy of fusion of enantiomers **1** ($\Delta H_f^{\text{enant}}$), furnishing a mean value of 8.8 ± 1.4 kcal mol^{-1}. Hence, for the entropy of fusion of enantiomers **1** ($\Delta S_f^{\text{enant}} = \Delta H_f^{\text{enant}}/T_f^{\text{enant}}$) we obtain a value of 23 ± 4 cal K^{-1} mol^{-1}.[10]

For most organic compounds, the enthalpy of fusion has a value between 5 and 10 kcal mol^{-1}.[1b] The enthalpy of fusion of enantiomers **1** (8.8 kcal mol^{-1}) thus lies in the upper range. We attribute this to the molecular compactness arising from the highly branched molecular backbone. This molecular compactness is favorable for a close, compact packing in the crystal.[11] Such a packing, in which the interactions between molecules are favored, should correspond to a high enthalpy of fusion. It is worth noting that ester *rac*-**4**, which is a less branched and less compact close analogue of ester *rac*-**1**, is liquid at room temperature.[12] As for the entropy of fusion, values in excess of 30 cal K^{-1} mol^{-1} can be obtained for simple elongated organic molecules that are conformationally flexible in the liquid state.[13] The entropy of fusion of enantiomers **1** (23 cal K^{-1} mol^{-1}) does not reach such a value. Steric constraints in **1** should be high owing to the presence of two adjacent quaternary carbon atoms. These constraints will decrease the conformational flexibility in the liquid state.



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The Racemic Compound

Ester *rac*-**1** was serendipitously obtained in the form of a racemic compound by crystallization of the racemate from Et_2O/petroleum ether, from which crystallizations of the racemate generally afforded the conglomerate. Conditions allowing the formation of the racemic compound in this solvent system could not be found. Even a controlled crystallization of the racemate with added seeds of the racemic compound failed to give the racemic compound. The seeds of the racemic compound grew into crystals of the conglomerate. Entrainment was however effective in the absence of a solvent. Thus, a molten undercooled sample of the racemate crystallized to give the racemic compound when seeds of the racemic compound were added. In the absence of seeds, the liquid undercooled racemate always crystallized to the conglomerate.

Characterization of racemic compound **1** by the melting point diagram method is not feasible because its melting point is lower than that of the corresponding conglomerate (82−84°C versus 90−92°C). The Gibbs free energy of this racemic compound is higher than that of the corresponding conglomerate at the melting point of the former. Therefore, the racemic compound is thermodynamically unstable at its melting point with respect to the conglomerate, and it will spontaneously tend to transform into the latter at this temperature. This thermodynamically necessary transformation of the racemic compound will prevent the observation of the thermodynamically controlled melting processes in the melting point diagram. Furthermore, the crystals of the racemic compound were found to be multiple twin crystals, which prevented their X-ray analysis.

The characterization of racemic compound **1** is based on the nonidentity of its melting point and IR spectrum in the solid state with the corresponding data for the pure constituent enantiomers, as expected for a racemic compound.[1] The IR spectrum of each pure enantiomer in the solid state is identical to that of the conglomerate, in agreement with the nature of the latter. The IR spectrum of the racemic compound differs from those of the enantiomers and the conglomerate, most notably in the fingerprint region (Figure 3).

We observed the thermodynamically expected transformation of the racemic compound into the conglomerate, as mentioned above, using a hot-stage microscope. When the liquid melt obtained by fusion of the racemic compound was kept at a temperature above 84°C and below 90°C, it slowly crystallized as the conglomerate. The conglomerate thus formed was, in turn, found to melt at the correct temperature of 90−92°C on increasing the temperature after the crystallization was complete. When fusion of the racemic compound was carried out in the presence of added conglomerate, which acted as a seed, the entrained crystallization of the liquid melt to give the conglomerate was so quick that the transition from one crystalline form to the other was difficult to observe with a microscope. In this case, only a superficial, transient fusion and slight changes

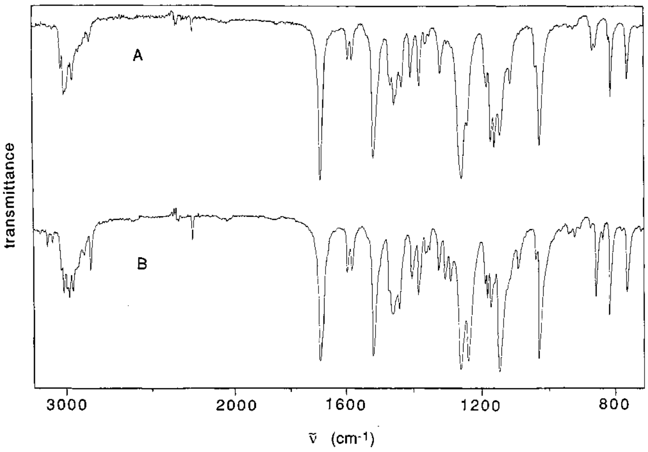

Figure 3. Infrared spectra (KBr): A: ester *rac*-**1** in the form of conglomerate, m.p. 90−92°C; B: ester *rac*-**1** in the form of racemic compound, m.p. 82−84°C

in the crystals could be detected at the melting point of the racemic compound.

Conversion of the racemic compound to the conglomerate was also observed below the melting point of the former. Thus, a sample of the racemic compound heated at 70°C for 20 h underwent complete transformation into the conglomerate, as ascertained by the melting point and solid-state IR spectrum of the resulting material. In this case, and in contrast to the above cases, the transformation does not take place through the liquid molten racemate but directly in the solid state. Hence, this transformation may be classified as a spontaneous resolution occurring in the solid crystalline state.

The preceding experiment shows that the racemic compound is thermodynamically unstable with respect to the conglomerate below the melting point of the former, at least down to 70°C. It should be noted that the racemic compound nevertheless retained its identity when it was stored at −25°C for several months. Since the racemic compound is less stable than the conglomerate, it follows that the crystal lattice of the former is less stable than that of the enantiomers. Normally, two organic enantiomers are able to arrange together in a lattice, forming a racemic compound, in a manner which is energetically favorable in comparison with the arrangement of only one enantiomer.[1a−1c] The present case is an example of the contrary and less common situation. Finally, we suggest that the natural instability of the racemic compound with respect to the conglomerate may be responsible for the difficulty encountered in obtaining the former crystalline form

Experimental Section

General: THF was distilled from $LiAlH_4$, HMPA from CaO in vacuo, and $i\mathrm{Pr_2NH}$ from KOH. A commercial solution of *n*BuLi in hexane was titrated prior to use. $3,4\text{-}(MeO)_2C_6H_3C(i\mathrm{Pr})HCN$ was prepared according to a literature procedure.[14] Transfers of solvents and reagents were effected by means of syringes. Petroleum ether of boiling range 40−60°C was used for the crystallizations. − M.p.: Reichert-Jung Thermovar hot-stage microscope, calibrated. To obtain reliable results, the conglomerate, either racemic or nonracemic, was first thoroughly homogenized and pulverized by grinding to give a sample that was representative of the entire amount. The sample was melted, and the undercooled melt was quickly crystallized by scratching so as to obtain a thoroughly homogenized microcrystalline conglomerate. This was melted again at a heating rate of $\approx 1\,°C\ min^{-1}$ under crossed Nicols in order to determine the melting range. − IR: Perkin−Elmer 681. − NMR: Varian Gemini (200 MHz for ^1H), Varian Inova (100 MHz for ^{13}C). For ^1H NMR, TMS as internal standard; for ^{13}C NMR, $CDCl_3$, $\delta_C = 77.0$. − Optical rotation: Perkin−Elmer 241MC polarimeter. [α] values were calculated from the average of three experimental determinations of α at the sodium D line (λ = 589 nm). − Microweighing: Sartorius 4504 microbalance. − Statistical calculations: StatView II program. Values of [α], ΔH_f^{enant}, and ΔS_f^{enant} are given with their standard deviations.

Ester *rac*-1 in the Form of a Conglomerate: To a solution of *n*BuLi in THF/hexane [2.5 mL of 2.0 M *n*BuLi (5.0 mmol) in hexane, 4 mL of THF] at 0°C under N_2 was added 0.67 mL (4.8 mmol) of $i\mathrm{Pr_2NH}$. A solution of 1.048 g (4.78 mmol) of $3,4\text{-}(MeO)_2C_6H_3\text{-}C(i\mathrm{Pr})HCN$ in THF (3.5 mL) was then slowly added, which resulted in a bright-yellow solution of the carbanion of the nitrile, to which HMPA (8 mL) followed by 0.71 mL (4.8 mmol) of Me_2CBrCO_2Et were added. After 4.5 h at room temp., workup was accomplished by Et_2O/H_2O extraction, thorough washing with H_2O to remove the HMPA from the ethereal phase, drying with Na_2SO_4, and evaporation of the solvent. The crude oil thus obtained was stirred with 30 mL of petroleum ether, which led to the formation of a solid. This was separated by filtration and recrystallized from Et_2O/petroleum ether by cooling from the boiling temperature to 4°C to give 0.278 g of *rac*-**1** in the form of a conglomerate (17%); white crystals, m.p. 90−92°C. From the combined supernatant mother liquors, several similar recrystallizations yielded an additional 0.177 g of the racemic conglomerate (9%); m.p. 88−91°C. − IR (KBr): $\tilde{\nu} = 2230\ cm^{-1}$ (C≡N), 1730 (C=O), 1260, 1180, 1160, 1150. − ^1H NMR ($CDCl_3$): δ = 0.82 [d, *J* = 7 Hz, 3 H, $CH(CH_3)_2$], 1.24 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.29 [d, *J* = 7 Hz, 3 H, $CH(CH_3)_2$], 1.36 [s, 6 H, 2,2-$(CH_3)_2$], 2.67 [sept., *J* = 7 Hz, 1 H, $CH(CH_3)_2$], 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 4.00 (m, 2 H, CH_2CH_3), 6.81 (d, *J* = 9 Hz, 1 H, aromatic H), 7.00 (br. s, 2 H, aromatic H). − ^{13}C NMR ($CDCl_3$): δ = 13.78, 19.89, 21.23, 23.77, 24.22, 33.81, 48.76, 55.76, 55.92, 58.94, 61.11, 110.3, 111.5, 119.9, 120.2, 129.5, 148.2, 148.4, 174.8 (C=O). − $C_{19}H_{27}NO_4$ (333.0): calcd. C 68.47, H 8.11, N 4.20; found C 68.79, H 8.01, N 4.11.

Ester *rac*-1 as Racemic Compound: A similar reaction with $3,4\text{-}(MeO)_2C_6H_3C(i\mathrm{Pr})HCN$ and Me_2CBrCO_2Et, but using $NaNH_2$ as the base (1 mmol of each reagent) and DME as the solvent, followed by purification by PLC [silica gel, petroleum ether/Et_2O (70:30)] gave 25 mg of *rac*-**1** (8%) as an oil, which solidified on standing; R_f and ^1H NMR were identical to those of *rac*-**1** above. Recrystallization from Et_2O/petroleum ether by cooling from boiling to room temperature gave 9 mg of *rac*-**1** in the form of a racemic compound as off-white crystals; m.p. 82−84°C. − IR (KBr): $\tilde{\nu} = 2240\ cm^{-1}$ (C≡N), 1730 (C=O), 1260, 1240, 1150.

Esters *d*-1 and *l*-1: 165 mg of pure ester *rac*-**1**, in the form of a conglomerate, m.p. 90−92°C, was dissolved in 6.4 mL of Et_2O/petroleum ether (60:40) at room temp. The solution was filtered through cotton wool, seeded with a tiny crystal of the conglomerate, and the solvent was slowly allowed to evaporate at room temp. (≈20°C). After several days, the added crystal had grown considerably and was separated from the mother liquor and the rest of crystals. This crystal, 34 mg, was found to be composed of two colorless hexagonal plates. Separation of the two plates using a spatula with the aid of a magnifying lens gave two fragments: one of 17 mg, m.p. 90−98°C, and the other of 16 mg, m.p. 90−96°C, mixed m.p. (1:1) 90−93°C. Each fragment was recrystallized by dissolving it in 0.7 mL of Et_2O/petroleum ether (70:30) at room temp. in a small test tube and slowly allowing the solvent to evaporate at room temp. (ca. 20°C). After several days, 6 mg of *d*-**1** and 5 mg of *l*-**1** were obtained from the 17 mg and 16 mg fragments, respectively. *d*-**1:** m.p. 112−114°C. − $[\alpha]_D^{22} = +24.4 \pm 0.7$ (c = 0.45, Et_2O). *l*-**1:** m.p. 112−114°C. − $[\alpha]_D^{22} = -25.4 \pm 0.8$ (c = 0.44, Et_2O). Both *d*-**1** and *l*-**1** gave R_f and IR (KBr) data identical to those for *rac*-**1** in the form of a conglomerate

Melting Point Diagram: Mixtures of the ester *rac*-**1** in the form of a conglomerate with ester *d*-**1** or *l*-**1**, with a total weight of ca. 1.000 mg, were employed. The mixtures were prepared and their melting ranges determined as described under General. Each melting range was determined by two independent workers. The difference between the temperature measurements by the two workers was ≤ 1.5°C in every case, both for the temperature of onset and the temperature of termination of fusion; the average of the two measurements was employed to construct the melting point diagram presented in Figure 1. The temperatures of beginning of fusion refer to the mean temperature of the estimated melting range of the eutectic contained in the sample; the termination of fusion of the eutectic was distinguishable from the beginning of fusion of the remaining excess enantiomer because the latter melted at a slower rate.

Acknowledgments

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[8] On the basis of the enantiomeric excesses derived from the melting point diagram, the amount of each isolated enantiomer obtained by recrystallization is somewhat larger than the amount of excess enantiomer contained in the respective, partially resolved mixture being recrystallized. For instance, in the case of *d*-**1**, 17 mg with an enantiomeric excess of 25% was subjected to recrystallization, and 6 mg of *d*-**1** was obtained rather than only 4 mg (25% of 17 mg). Therefore, once the expected amount of excess enantiomer crystallized (4 mg), the crystallization continued in a preferential manner with entrainment.

[9] This fit also indicates that the system conforms to the conditions under which Equation 1 is valid (see ref.[1b]). First, the enthalpy of fusion of the pure enantiomers is constant from their temperature of fusion under thermodynamic equilibrium [i.e. from their proper melting point, T_f^{enant} = 386.2 K (113.0°C)] to the temperature at which the racemic conglomerate melts [T_f^{congl} = 364.2 K (91.0°C)]. Second, the molten liquid mixtures of the two enantiomers are ideal solutions over this temperature interval. This ideality implies that the enthalpy and entropy of mixing of the pure liquid enantiomers are zero and $-R \ln x$, respectively. Ideality or near ideality is expected for liquid mixtures of enantiomers.[1a−1c] In the liquid state, the molecules are translating and rotating, and an enantiomer will discern its antipode only with difficulty, especially as the opposite enantiomers are so similar. In the solid state, the molecules are nearly static, and the opposite enantiomer can be more easily recognized. Non-ideal solid solutions of enantiomers are known (see ref.[1b]).

[10] Owing to the adherence of the system to Equation 1 (see note[9]), the enthalpy of fusion of racemic conglomerate **1** should coincide with that of the enantiomers, taking into consideration the uncertainty for the latter value. On the same basis, the entropy of fusion of racemic conglomerate **1** should be: $\Delta S_f^{congl} = (\Delta H_{T(f)}^{congl,enant}/T_f^{congl}) - R \ln x = (8800/364.2) - R \ln 0.5 = 25.6$ cal K^{-1} mol^{-1}. It should thus coincide with the entropy of fusion of the enantiomers (23 ± 4 cal K^{-1} mol^{-1}) within the limits of experimental uncertainty.

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