A Compact and Lipophilic Enantiomer Showing a Bilayer Crystal Structure − Free Energy of Spontaneous Resolution of the Racemic Compound into the Crystalline Enantiomers[‡]

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In memory of Dr. Mandred Stud[†]

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The melting points and the enthalpies and entropies of fusion of (*R*)-**1** and *rac*-**1**, with the racemate both as the conglomerate and as the true racemic compound, were determined by differential scanning calorimetry: the melting points were 113.2 ± 0.3, 90.7 ± 0.4, and 80.5 ± 0.6 °C, respectively, the ΔH_{fus} values 8.82 ± 0.03, 7.94 ± 0.27, and 5.98 ± 0.59 kcal·mol^{-1}, respectively, and the ΔS_{fus} values 22.8 ± 0.1, 21.8 ± 0.7, and 16.9 ± 1.7 cal·deg^{-1}·mol^{-1}, respectively. The specific heat of fusion (ΔC_{fus}) of the pure enantiomer **1** calculated from these data is 39.1 cal·deg^{-1}·mol^{-1}. The ΔH_{fus}, ΔS_{fus}, and ΔC_{fus} values of these enantiomers are consistently high relative to average values for organic compounds. The enthalpy, entropy, and free energy of formation of the racemic compound from the crystalline enantiomers are 1.56 kcal·mol^{-1}, 3.8 cal·deg^{-1}·mol^{-1}, and 0.22 kcal·mol^{-1}, as calculated from the above data. The positive sign of the free energy of formation bears out the observed spontaneous resolution of the racemic compound into the crystalline enantiomers. A statistical thermodynamic model of melting, weighing the different mechanical contributions to the crystalline and the liquid states, is described in conjunction with the interpretation of the data. It is concluded that both the interaction potential energy of the crystal of the pure enantiomer **1** and the vibrational mobility of the crystal structure are low, features pertinent to a low enthalpy and entropy of the crystal, respectively. X-ray crystallography of (*R*)-**1** revealed a simple bilayer arrangement of the roughly ellipsoidal molecules: a characteristic bilayer consists of two monomolecular layers with interactions between the lipophilic groups in between, featuring a methyl–phenyl interaction, while the cyano groups project towards the outsides of the bilayer, which stacks by means of dipolar interactions to a constant distance.

Introduction

Organic racemates usually crystallize in the form of true racemic compounds, their crystal structures consisting of the interpenetrated substructures of the enantiomers.[1] The conglomerate, in which the enantiomers are present in separate crystals, is seldom formed. The racemic compound is usually thermodynamically stable with respect to the conglomerate (i.e., the isolated crystalline enantiomers; $\Delta G <$ 0).[1a] Few racemic compounds are recognized as the unstable form.[2] The factors determining the relative thermodynamic stabilities of racemic compounds and conglomerates, factors relevant to the enthalpies and entropies of the crystals ($\Delta G = \Delta H - T\Delta S$), are not yet well understood.[3]

We had previously obtained ester **1** both as conglomerate and as racemic compound.[2a] This racemic compound is seldomly encountered, unlike the conglomerate, and is the unstable form. Its instability was confirmed by its lower melting point and by its spontaneous transformation into the conglomerate.[2a,4]

We also isolated the crystalline enantiomers from the conglomerate and have now carried out a calorimetric investigation on the crystalline enantiomers, the conglomerate, and the racemic compound by differential scanning calorimetry (DSC). We have thus determined the enthalpies and entropies of fusion of these solids. From these data we have calculated an approximate specific heat of fusion of

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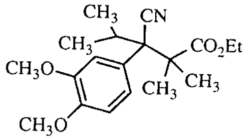
the enantiomers (the difference between the specific heats of the liquid and of the crystalline phases at fusion), a quantity of interest in regard to the molecular motions. In addition, we have calculated an approximate free energy of formation of the racemic compound from the crystalline enantiomers. Interpretation of the data with the aid of a statistical thermodynamic model of melting, with which the different enthalpic or entropic mechanical contributions to the crystalline and liquid states can be evaluated, suggests that both the interaction potential energy of the crystal of enantiomer **1** and the vibrational mobility of the crystal structure are low, features pertinent to low enthalpy and entropy of the crystal, respectively. By X-ray crystallography we found a structure in which the molecules form a bilayer structure consolidated by lipophilic forces within bilayers and by dipole forces between bilayers.



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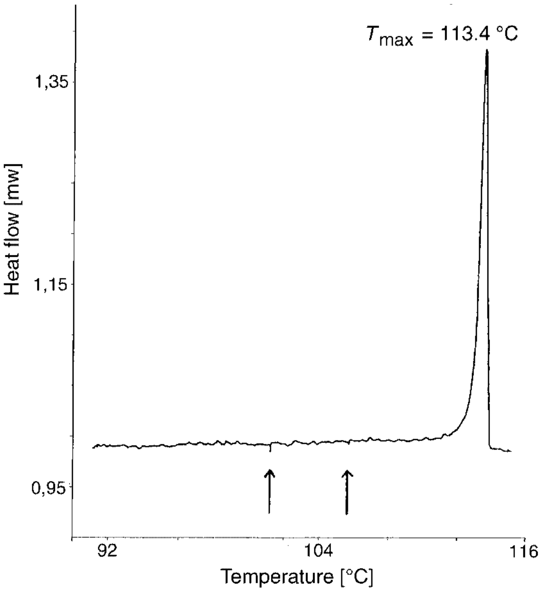

Figure 1. Fusion DSC trace for crystalline (*R*)-**1**; sample weight: 0.221 mg; heating rate: 0.010 °C·s^{-1}; minute exothermal projections are indicated by arrows

Results and Discussion

Thermodynamic Data of Fusion of Ester 1; Free Energy of Formation of the Racemic Compound

1The melting points and the enthalpies of fusion of ester **1** as its crystalline (*R*) enantiomer, the racemic conglomerate (eutectic mixture), and the racemic compound were directly measured by DSC. A DSC trace for the single enantiomer is shown in Figure 1. A fusion DSC trace records the rate of absorption of heat during the transition from the crystalline to the liquid state as a function of the temperature, which is gradually increased at a constant rate, the area under the sharp projection corresponding to the heat for the transition. The values obtained are shown in Table 1. The entropies of fusion were computed from the melting points and the enthalpies of fusion, taking into account that the free energy of fusion is zero ($\Delta S_{fus} = \Delta H_{fus}/T_{fus}$). The melting points of the enantiomer and of the conglomerate are in agreement with those determined earlier with a hot-stage microscope: 112−114 and 90−92 °C.[2a] The melting point of the racemic compound is slightly lower than the previously measured one (82−84 °C) and similarly the measured purity of the particular racemic compound specimen was not very high (98%), probably because of contamination by extraneous material, as the appearance of the colored specimen, obtained only with difficulty, was not very good. The enthalpy and entropy of the enantiomer are in agreement with those derived from the melting-point diagram of the enantiomers by means of the Schröder−Van Laar equation: 8.8 kcal·mol^{-1} and 23 cal·deg^{-1}·mol^{-1}.[2a]

Very weak exothermal transitions occurred before the onset of melting of the enantiomer (Figure 1) but were not reproducible in the recrystallized sample. We attribute these transitions to removal of lattice defects, resulting in a better crystal.[5] From the small magnitudes of the transitions we conclude that this crystal structure should be highly ordered. On cooling of the melt obtained from the conglomerate, a weak exothermal transition occurred at −10 °C (Figure 2, a), and the reverse transition occurred on increasing the temperature (Figure 2, b). In addition, this melt exists as a liquid at −20 °C. We attribute this exothermal transition − weak and unprecedentedly taking place in the liquid state as much as 100 °C below the melting point − to incipient ordering in the chaotic condition of the liquid (tentatively a glass-like transition). The thermodynamically

Table 1. Melting points and enthalpies and entropies of fusion of ester **1** in the forms of crystalline (*R*) enantiomer, racemic conglomerate, and racemic compound

Form[a]	M.p. [°C]	ΔH_{fus} [kcal·mol^{-1}]	ΔS_{fus} [cal·deg^{-1}·mol^{-1}]
Crystalline (*R*) enantiom.	113.2 ± 0.3	8.82 ± 0.03	22.8 ± 0.1
Racemic conglom.	90.7 ± 0.4	7.94 ± 0.27	21.8 ± 0.7
Racemic compd.	80.5 ± 0.6	5.98 ± 0.59	16.9 ± 1.7

[a] The values shown were determined by DSC and are the average with standard deviation for at least two measurements.

spontaneous transformation of the racemic compound into the conglomerate mentioned in the introduction was not detected in this case; this was not unexpected as it had previously been shown that the transformation occurs only sluggishly (20 h at 70 °C),[2a] indicating that this transformation in the crystalline solid state is hindered by kinetic factors.

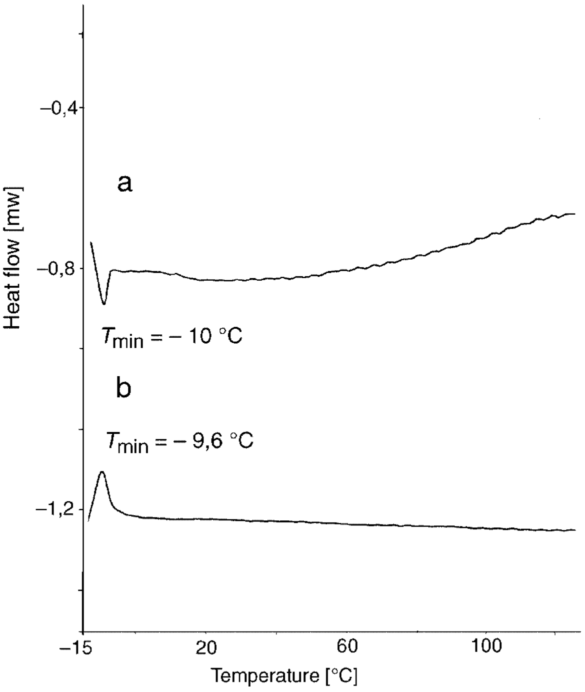

Figure 2. DSC traces for the melt obtained from ester **1** in the form of racemic conglomerate; sample weight: 5.199 mg; a: cooling run at 10 °C/min; b: heating run at 10 °C/min; for the two peaks at ca. −10 °C, $|\Delta H| \approx 40$ cal·mol^{-1} ($|\Delta S| \approx 0.2$ cal·deg^{-1}·mol^{-1})

From the melting point and the enthalpy of fusion of the conglomerate and those of the enantiomers, the specific heat of fusion of the enantiomers can be calculated as a matching mean ($\overline{\overline{\Delta C}}{}^{en}_{fus}$) for the temperature interval between the two melting points (T^{con}_{fus}, T^{en}_{fus}) in the following manner. The enthalpy of fusion of the conglomerate equals the enthalpy of fusion of the separate enantiomers at the melting point of the conglomerate plus the enthalpy of mixing of the melted enantiomers (such melting of the enantiomers represents a physically impossible melting below the melting point; i.e., $\Delta G > 0$). The enthalpy of mixing would be zero if the mixture were ideal, which would mean that the interactions between molecules of the same enantiomer and between molecules of the opposite enantiomers were the same in the liquid mixture. Liquid mixtures of enantiomers are generally practically ideal,[1a] and furthermore, these enantiomers adhere sufficiently well to the Schröder−Van Laar equation,[2a] which requires such ideality. Therefore, if the enthalpy of mixing is disregarded, the relationship between the enthalpy of fusion of the conglomerate and that of the enantiomers can be expressed as in Equation (1) (recall that $C = \mathrm{d}q/\mathrm{d}T$). Application of the pertinent values in Table 1 to the equation affords $\overline{\overline{\Delta C}}{}^{en}_{fus}$ (Table 2).

Table 2. Various thermodynamic quantities relative to ester **1** in the solid or liquid state

ΔC^{en}_{fus} [a]	39.1 cal·deg^{-1}·mol^{-1}
ΔS_{mix}	1.35 cal deg^{-1}·mol^{-1}
$\Delta H^{con,Tfusrac}_{fus}$	7.54 kcal·mol^{-1}
$\Delta S^{con,Tfusrac}_{fus}$	20.7 cal·deg^{-1}·mol^{-1}
ΔH_{Φ}	1.56 kcal·mol^{-1}
ΔS_{Φ}	3.8 cal·deg^{-1}·mol^{-1}
ΔG_{Φ}	0.22 kcal·mol^{-1}

[a] The quantities referred to are: mean specific heat of fusion of the enantiomers for the interval 90.7−113.2 °C; entropy of mixing of the liquid enantiomers in a 1:1 ratio at 90.7 °C; enthalpy and entropy of fusion of the conglomerate at the melting point of the racemic compound, 80.5 °C; enthalpy, entropy, and free energy of formation of the racemic compound from the conglomerate at 80.5 °C. The values shown were calculated from data in Table 1 as described in the text.

$$\Delta H^{en}_{fus} - \Delta H^{con}_{fus} = \overline{\overline{\Delta C}}{}^{en}_{fus}(T^{en}_{fus} - T^{con}_{fus}) \tag{1}$$

Having found $\overline{\overline{\Delta C}}{}^{en}_{fus}$, we can provide support for the ideality of the liquid mixture of the enantiomers as follows. If the mixture were ideal, the entropy of mixing would consist only of the spatial entropy of mixing (i.e., $\Delta S_{mix} = R\ln 2 = 1.38$ cal·deg^{-1}·mol^{-1}; the volume is doubled), to the exclusion of the thermal entropy of mixing. This entropic component would result from the intermolecular interactions not being the same in the mixture as in the separate enantiomers, which implies a difference in the *number* of energy states for the molecular motions. Whether the mixture is ideal or not, the entropy of mixing at the melting point of the conglomerate can be calculated by Equation (2) (recall that $\mathrm{d}S = \mathrm{d}q/T = C\mathrm{d}T/T$; also, compare the equation with the preceding one).

$$\Delta S^{en}_{fus} - (\Delta S^{con}_{fus} - \Delta S_{mix}) = \int_{T^{con}_{fus}}^{T^{en}_{fus}} \frac{\Delta C^{en}_{fus}}{T}\mathrm{d}T = \overline{\overline{\Delta C}}{}^{en}_{fus} \ln\frac{T^{en}_{fus}}{T^{con}_{fus}} \tag{2}$$

Through the use of the known value of $\overline{\overline{\Delta C}}{}^{en}_{fus}$, arithmetically deduced from the enthalpy rather than from the entropy, as an approximation, a ΔS_{mix} of 1.35 cal·deg^{-1}·mol^{-1} results, and is very close to that of the ideal mixture.

From the fusion data on the racemic compound and the conglomerate, together with $\overline{\overline{\Delta C}}{}^{en}_{fus}$, it is possible to calculate the enthalpy and entropy of formation of the racemic compound from the conglomerate as approximate values, and hence the free energy of formation of the racemic compound. Firstly, the enthalpy and entropy of fusion of the conglomerate at the melting point of the racemic compound (again a hypothetical melting) are calculated from Equations (3) and (4). These imply constancy of the enthalpy and entropy of mixing of the liquid enantiomers over the temperature interval (or the ideality of the mixture), with the above value of $\overline{\overline{\Delta C}}{}^{\mathrm{en}}_{\mathrm{fus}}$ for a higher temperature interval being used as an approximation (the resulting values are shown in Table 2).

$$\Delta H^{con}_{fus} - \Delta H^{con,T^{rac}_{fus}}_{fus} = \overline{\overline{\Delta C}}{}^{en}_{fus}(T^{con}_{fus} - T^{rac}_{fus}) \tag{3}$$

$$\Delta S^{con}_{fus} - \Delta S^{con,T^{rac}_{fus}}_{fus} = \overline{\overline{\Delta C}}{}^{en}_{fus} \ln \frac{T^{con}_{fus}}{T^{rac}_{fus}} \tag{4}$$

From these quantities for the conglomerate, together with the enthalpy and entropy of fusion of the racemic compound, the enthalpy and entropy of formation of the racemic compound can be computed, taking into account that the conglomerate and the racemic compound give the same mixture on melting [Equations (5) and (6), Table 2].

$$\Delta H_{\Phi} = \Delta H^{con,T^{rac}_{fus}}_{fus} - \Delta H^{rac}_{fus} \tag{5}$$

$$\Delta S_{\Phi} = \Delta S^{con,T^{rac}_{fus}}_{fus} - \Delta S^{rac}_{fus} \tag{6}$$

As calculated by the preceding method, the free energy of formation of ester **1** in the form of the racemic compound from the crystalline enantiomers is 0.22 kcal·mol^{-1}. This free energy of formation − formation here representing a physical rather than a chemical change − is of course related to the melting point of the racemic compound (80.5 °C) and not to 25 °C; in view of the variation of the free energy with the temperature ($\mathrm{d}\Delta G_{\Phi}/\mathrm{d}T = -\Delta S_{\Phi}$), it should be larger at 25 °C, but of the same order of magnitude. The absolute value of this free energy is consistent with what might be expected for the transformation of a conglomerate into the racemic compound[1a] but its plus sign is not quite so: the reverse transformation is a rare example of spontaneous resolution of a racemic compound into the crystalline enantiomers, as pointed out above.

Interpretation of the Data

According to Jacques, Collet, and Wilen,[1a] the ΔH_{fus} values of many organic compounds lie between 5 and 10 kcal·mol^{-1}, ΔS_{fus} about 17 cal·deg^{-1}·mol^{-1}, and ΔC_{fus} between 20 and 40 cal·deg^{-1}·mol^{-1}. The three quantities for enantiomer **1** (8.82, 22.8, and 39.1) are above average, whereas the ΔH_{fus} and ΔS_{fus} values for the racemic compound (5.98 and 16.9) are below and at the average, respectively. In order to interpret the ΔH_{fus} and ΔS_{fus} data in simple and fundamental terms we employ a basic statistical thermodynamic model which allows evaluation of the different enthalpic or entropic mechanical contributions to the crystalline and liquid states, quantitatively in the case of the entropy.

Statistical Thermodynamic Model of Melting

In the crystalline state, only the lattice vibrations are taken into account, the internal vibrations of the molecule being excluded. Lattice vibrations (cooperative oscillations of the molecules about their equilibrium positions in the crystal structure) have frequencies lower than those of internal vibrations of the molecule (say, 0 to 100 cm^{-1}, 0 to 3×10^{12} Hz), their energy levels being more closely spaced. The internal vibrations of the molecule are all assumed to be at their lowest energy levels. In addition, the interaction between lattice and internal vibrations is disregarded since its influence on the enthalpy and the entropy, unlike the specific heat, is not very important. Three mechanical degrees of freedom of the molecule are allotted to the lattice vibrations, with regard to the three Cartesian axes of the crystal lattice. As far as the liquid state is concerned, the molecules undergo free translational motions in the bulky potential energy box for the intermolecular cohesion forces in the liquid and, furthermore, undergo free rotations about the molecular center of mass. The vibrations of the molecule are assumed not to differ from those in the crystal and also remain at the lowest levels. Now, through application of the elementary principle of equipartition of the energy, the total energy of the translational plus rotational motions in the liquid equals the total energy of the lattice vibrations in the crystal: the contribution of each translational or rotational degree of freedom to the internal energy (U) is $RT/2$, while that of each vibrational degree of free freedom is twice RT.

Enthalpy of Fusion

In the above model, ΔH_{fus} is a function only of the increase in the negative potential energy for the cohesion forces on passing from the crystalline to the liquid state (disregarding the volume of fusion: $\Delta H_{\mathrm{fus}} = \Delta U_{\mathrm{fus}} + p\Delta V_{\mathrm{fus}}$; $\Delta V_{\mathrm{fus}} \approx 0$). The model does not take into account the hindered internal rotations of the molecule (conformers) that take place in the liquid. Internal rotations would arise from torsional oscillations in the crystal, but would not be able to take place in the crystal because of the higher potential energy barriers. The torsional oscillations in a hindered internal rotation, each one characteristic of one of the conformers involved in the hindered internal rotation, have frequencies lower (energy levels more closely spaced) than those of a torsional oscillation in the crystal as a result of the smaller potential energy humps. Hindered internal rotations may be evaluated as a secondary factor in ΔH_{fus}. As an illustration, the increase in internal energy on going from a torsional oscillation with a frequency of 500 cm^{-1} (1.5×10^{13} Hz) to a hindered internal rotation is 0.3 kcal·mol^{-1},[6] only 4% of ΔH_{fus} (taken as 7.5). For conformationally mobile or complex molecules (not the case with ester **1**) the contribution of hindered internal rotations may be significant. In summary, it may be adequate for qualitative estimations to take the increase in the interaction potential energy on melting for ΔH_{fus}.

With regard to enantiomer **1**, ΔH_{fus} − which is above average (8.82 vs. 7.5) − suggests that the interaction potential energy of the crystal is low. To be correct, the interaction potential energy of the liquid ought not to be high, as it would be for a liquid alkane and would not be for a liquid hydrogen-bonded compound; the DSC data discussed above suggest that the liquid in question is an average liquid. The suggested low interaction potential energy for the enantiomer crystal is underlined by the smaller ΔH_{fus} value obtained for the racemic compound (5.98), which melts to give the same liquid as the enantiomer (regarding the enthalpy as discussed above), or by the positive enthalpy of formation for the racemic compound (1.56). Note in this respect, however, that the interaction potential energy for the enantiomer will confidently be lower than for the racemic compound only if the zero-point vibrational energies of the two crystals are not too different, which may be barely possible − not certain − considering the similarity of the IR spectra.[2a]

Entropy of Fusion

In terms of the model, ΔS_{fus} is the result of the translational and rotational entropies of the liquid less the entropy of the lattice vibrations [Equation (7)]. These three terms can be quantitatively dealt with by using the general statistical thermodynamic expression for entropy: $S = R\ln Q + U/T + R(1 - \ln N_{\mathrm{Av}})$;[7a] in this expression Q represents the partition function for the energy states of molecular motion ($Q = \Sigma e^{-\varepsilon i/kT}$) and the last term applies only to $S_{\mathrm{tr}}^{\mathrm{liq}}$ (it accounts for the quantum indistinguishability of the molecules; the rotational and vibrational partition functions, $Q_{\mathrm{rot}}^{\mathrm{liq}}$, $Q_{\mathrm{latt.vib.}}^{\mathrm{cr}}$, refer beforehand to a single molecule).

$$\Delta S_{fus} = S_{tr}^{liq} + S_{rot}^{liq} - S_{latt.vib.}^{cr} \tag{7}$$

The three worked-up partition functions are shown in Table 3. For $Q_{\mathrm{tr}}^{\mathrm{liq}}$, the elementary translational partition function for a molecule in a box ($Q_{\mathrm{tr}}^{\mathrm{gas}}$)[7] is applied, for which the size of the box (i.e., the volume of the liquid) is reduced directly to the ratio of the kinetic pressure of the molecules in the liquid − which is taken as equal to the vapor pressure − to the pressure of a gas under the same volume as the liquid; this reduction in the volume parallels the reduction of kinetic pressure by cohesion forces on going from the gas to the liquid (the translational energy is unaffected: $U_{\mathrm{tr}}^{\mathrm{gas}} = U_{\mathrm{tr}}^{\mathrm{liq}} = 3RT/2$[7]). As it has to do with the spatial entropy and not the energy, the size of the above potential energy box for the model liquid is smaller than the volume of the liquid. $Q_{\mathrm{latt.vib.}}^{\mathrm{cr}}$ features three degrees of freedom, allotted as above to the lattice vibrations (accordingly, $U_{\mathrm{latt.vib.}}^{\mathrm{cr}} = 3RT$). As a test to this approach to ΔS_{fus}, the entropy of vaporization at the normal boiling point can readily be derived to compare the value with that of the Trouton rule: $\Delta S_{\mathrm{vap}} \approx 20.7$ cal·deg^{-1}·mol^{-1}, when $p_{\mathrm{vap}} = 1$ atm. ΔS_{vap} is simply the difference between the translational entropies of the gas and the liquid ($\Delta S_{\mathrm{vap}} = S_{\mathrm{tr}}^{\mathrm{gas}} - S_{\mathrm{tr}}^{\mathrm{liq}}$; rotations and vibrations are the same for the two states according to the model). As noted, $Q_{\mathrm{tr}}^{\mathrm{gas}}$ differs from $Q_{\mathrm{tr}}^{\mathrm{liq}}$ in Table 3 only in regard to the volume ($V_{\mathrm{gas}} = RT/p_{\mathrm{gas}}$), and the expression for ΔS_{vap} follows directly by subtraction [i.e. $\Delta S_{\mathrm{vap}} = R\ln Q_{\mathrm{tr}}^{\mathrm{gas}} - R\ln Q_{\mathrm{tr}}^{\mathrm{liq}} = 2R\ln(d_{liq}RT_{\mathrm{vap}}/Mp_{\mathrm{vap}})$; ($p_{\mathrm{vap}} \equiv p_{\mathrm{gas}}$)]. A ΔS_{vap} value of 22 cal·deg^{-1}·mol^{-1}results,[11] consistently with the Trouton rule.

Table 3. Translational, rotational, and vibrational partition functions relative to the statistical thermodynamic model of melting and corresponding entropies

Partition function	Entropy[a]
$Q_{tr}^{liq} = V_{liq}\dfrac{p_{vap}}{p_{gas}^{*}}\left(\dfrac{2\pi m\mathbf{k}T}{\mathbf{h}^2}\right)^{3/2} = \dfrac{M^2 p_{vap}}{d_{liq}^2\mathbf{R}T}\left(\dfrac{2\pi M\mathbf{k}T}{\mathbf{N}_{\mathbf{Av}}\mathbf{h}^2}\right)^{3/2}$ [b]	$S_{tr}^{liq} = 10$ cal deg^{-1}mol^{-1}
$Q_{rot}^{liq} = 8\pi^2\left(\dfrac{2\pi\bar{\bar{I}}\mathbf{k}T}{\mathbf{h}^2}\right)^{3/2} \approx 8\pi^2 M d_{liq}\mathbf{N}_{\mathbf{Av}}\left(\dfrac{2\pi M\mathbf{k}T}{\mathbf{N}_{\mathbf{Av}}\mathbf{h}^2}\right)^{3/2}$ [c]	$S_{rot}^{liq} = 40$ cal deg^{-1}mol^{-1}
$Q_{latt.vib.}^{cr} = \left(\dfrac{\mathbf{k}T}{\mathbf{h}\bar{\bar{\nu}}_{latt.vib.}}\right)^{3}$ [d]	$S_{latt\cdot vib}^{cr} = 39$ cal deg^{-1}mol^{-1}

[a] Derived by use of the parameter values in ref.[8] [b] $p_{\mathrm{gas}}{}^{*} = RT/V_{\mathrm{liq}}$; m and M are the mass of the molecule and the mole weight, $m = M/N_{\mathrm{Av}}$; $V_{\mathrm{liq}} = M/d_{\mathrm{liq}}$. [c] By use of Q for the rigid rotator,[9] $\bar{\bar{I}}$ is a matching mean moment of inertia of the molecule: $I = (I_x I_y I_z)^{1/3}$; $\bar{\bar{I}} = m\bar{\bar{r}}^2 \approx mv^{2/3}$; v (molecular volume) $\approx V_{\mathrm{liq}}/N_{\mathrm{Av}} = M/d_{\mathrm{liq}}N_{\mathrm{Av}}$. [d] Using Q for the harmonic oscillator,[10] $\bar{\bar{\nu}}_{\mathrm{latt.vib.}}$ is a matching mean frequency: $\bar{\bar{\nu}}_{\mathrm{latt.vib.}} = (\nu_{x-\mathrm{latt.vib.}}\nu_{y-\mathrm{latt.vib.}}\nu_{z-\mathrm{latt.vib.}})^{1/3}$.

Hindered internal rotations contribute significantly to ΔS_{fus}, in contrast to their minor impact on ΔH_{fus} as discussed above. The increase in entropy on passing from a torsional oscillation with a frequency of 500 cm^{-1} (1.5 × 10^{13} Hz) to a hindered internal rotation of 50 cm^{-1} (1.5 × 10^{12} Hz, a sort of mean frequency for the torsional oscillations involved in the hindered internal rotation) is 4 cal·deg^{-1}·mol^{-1},[12,13] which represents 25% of ΔS_{fus} (taken as 17). It is recognized that ΔS_{fus} values for conformationally mobile compounds are high because of the large numbers of conformers in the molten liquid.[4,14] Because of the importance of hindered internal rotations for the entropy, the ΔS_{fus} value of 11 cal·deg^{-1}·mol^{-1} determined by this approach [Equation (7) and Table 3; note that $S_{\mathrm{rot}}^{\mathrm{liq}}$ is approximately canceled by $S_{\mathrm{latt.vib.}}^{\mathrm{cr}}$] is of course deficient. It should be noted that Walden provided an early empirical average ΔS_{fus} value of 13.5 cal·deg^{-1}·mol^{-1} relative to simple organic compounds,[15] which is not far from the above value.

With regard to enantiomer **1**, ΔS_{fus} is above the average (22.8 vs. 17 cal·K^{-1}·mol^{-1}),[16] which suggests that the entropy of the crystalline enantiomer is low. The entropy of the molten liquid should not be high, since the parameters involved in $S_{\mathrm{tr}}^{\mathrm{liq}}$ and $S_{\mathrm{rot}}^{\mathrm{liq}}$ for the enantiomer in the model (see Table 3) are not unreasonable. Furthermore, conformers should not contribute to elevate the entropy of the molten liquid since the molecule is compact and densely branched, and we have previously provided NMR support for restricted conformational mobility in this compound.[2a,4,17] From the expression for $S^{cr}_{latt.vib.}$ in the model [i.e., $S^{cr}_{latt.vib.} = R\ln(kT/h\bar{\bar{\nu}}_{latt.vib.})^3 + 3R$], a low entropy for the lattice vibrations implies either that their mean frequency is high, or their mean amplitude is small; that is to say, the vibrational mobility of the crystal structure is restricted. Consistent with the high vibrational frequency, cohesion forces in the crystal will be strong. Thus, the ΔS_{fus} value for enantiomer **1** once more suggests, additionally to ΔH_{fus}, that the interaction potential energy of the enantiomer crystal is low. The entropy of the enantiomer crystal is less than that of the racemic compound because the entropy of formation of the racemic compound is positive (3.8 cal·K^{-1}·mol^{-1}) and so the interaction potential energy for the enantiomer should be below that for the racemic compound. Note, however, that the absolute level of the potential energy for the enantiomer cannot be gauged by this simple comparison.

Specific Heat of Fusion

The specific heat, *C*, is very sensitive to interactions between internal degrees of freedom of the molecule (vibrations and rotations, such as the interaction between lattice and molecular vibrations disregarded above). These interactions bring about combination of the energy states. In general, the larger the spacing of energy levels, the smaller is *C* and, in simple terms, the stronger the interaction between lattice and molecular vibrations, the larger is the spacing of the energy levels in the crystal structure, the strength of the interaction depending on the cohesion forces. Thus, ΔC_{fus} of enantiomer **1**, which lies in the upper range for organic compounds (39.1 with reference to 20−40 cal·K^{-1}·mol^{-1}), reinforces the view that the interaction potential energy of the crystal is low.

We underline the consistency of the ΔH_{fus}, ΔS_{fus}, and ΔC_{fus} values for enantiomer **1** in regard to a low interaction potential energy of the crystal. We performed an X-ray crystallography of this crystal to obtain information on the crystal structure.

Crystal Structure of Enantiomer 1

An enantiomer monocrystal was employed for X-ray crystallography. This showed the (*R*) configuration for the enantiomer constituting the crystal. The configuration of the enantiomer specimen used for the calorimetry was hence also revealed to be (*R*) by the undepressed mixed melting point of the specimen and the crystal. Crystallographic details have been reported to the Cambridge Crystallographic Data Center. The molecule (Figure 3) represents a dense packing of atoms. The existence of numerous interatomic contacts is consistent with restricted conformational mobility as cited above.

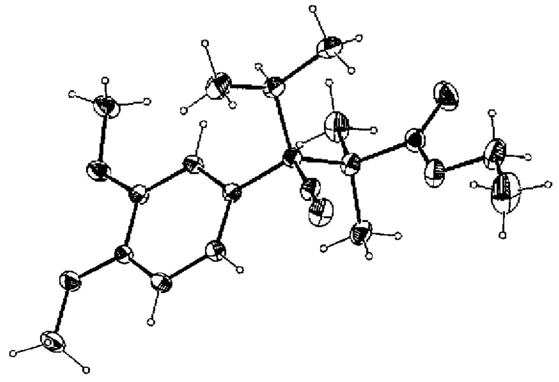

Figure 3. Molecular structure of (*R*)-**1** as determined by X-ray crystallography; the displacement ellipsoids are drawn at an occupation probability level of 30%

The crystal belongs to the monoclinic system (Table 4), which is common for organic crystals but not quite so for enantiomer crystals, which would instead prefer the orthorhombic system.[1a] In the crystal the molecules align according to their major axis (the molecule being visualized as an elongated spheroid; Figure 4, a). This molecular axis corresponds to the *b* side of the crystal unit cell, while the minor molecular axis corresponds to the *a* and shorter side of the unit cell (Figure 4, b). Each site of the space lattice is occupied by a pair of molecules (primitive space lattice, $Z = 2$). The two molecules in these pairs are displaced slightly with respect to one another, according to the oblique angle of the unit cell, which results in the crystal being monoclinic rather than orthorhombic. Furthermore, the pairs of molecules at the lattice sites separate from each other along the *c* and longest side of the unit cell, resulting in a bilayer crystal structure. For the actual chiral molecules, the structure is also characterized by a single bilayer. The binary screw axis superposed to side *a* in Figure 4 (c) is useful support for the packing of the molecules being analogous to the close packing of spheres. The packing coefficient of the crystal is reasonable for an organic crystal (Table 4, 0.74 for the close packing of spheres) and so is the density of the crystal. The crystallographic analysis showed that there is no room in the crystal for a water molecule.

The thermal factors, which underlie the size of the vibrational displacement ellipsoids (Figure 3) and are presented in Table 4 as the average value ($\bar{B}$), are consistent both with restricted vibrational mobility of the crystal structure and with the compactness of the molecule. As far as the vibrational mobility is concerned, the closer to the center of gravity of the molecule − about which the molecule as a whole vibrates in the crystal structure − an atom is situated, the more properly the thermal factor, *B*, represents the lattice vibrations, such as the mean frequency of the lattice vibrations for the above model (Table 3). For C-3 and C$_{Ar}$-1 of enantiomer **1**, both of which are situated close to the center of the molecule, the measured *B* values are 3.1 Å^2, at the lower edge of the typical 3.2−3.9 Å^2 range for crystalline organic compounds. With regard to the compactness of the molecule, the *B* values for a number of per-

Table 4. X-ray crystal data for (*R*)-**1**

Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.46768 Å b = 9.33868 Å c = 12.04531 Å α = 100.4°
Z	2
$v^{[b]}$	304 $Å^3$
Packing coefficient[c]	0.649
D	1.182 g cm^{-3}
$B^{[d]}$	4.9 ± 1.9 $Å^2$

[a] Number of molecules per unit cell. [b] Volume of the molecule. [c] Quotient of the volume of the molecule by the volume allotted to one molecule in the unit cell, $v/(v_{cell}/Z)$. [d] Average thermal factor with standard deviation for all non-hydrogen atoms; $B = 8\pi^2 \cdot \overline{(r - r_{equil})^2}$, for the sphere equivalent to the displacement ellipsoid.

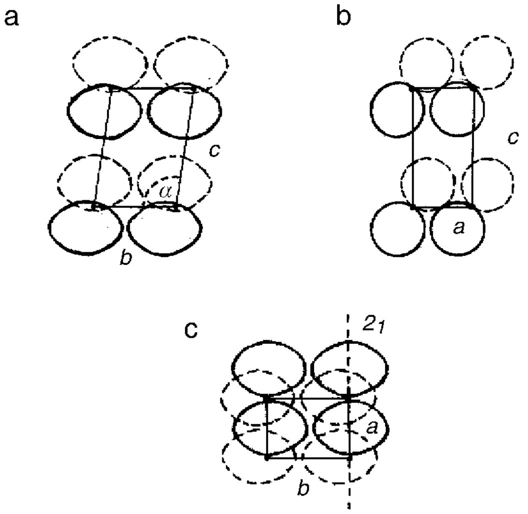

Figure 4. Illustration of the crystal unit cell for enantiomer **1**; a: view along side *a*; b: view along side *b*; c: view along side *c*

ipheral atoms in this molecule are significantly larger than this, 6.8 $Å^2$ on average, which we attribute to the compactness of the molecule, since, for illustration, the increase would be large for a homogeneously solid sphere, with its center of gravity at a maximal distance from the surface. The smaller size of the displacement ellipsoids about the center of the enantiomer molecule additionally indicates that positional disorder in the crystal (static displacements of molecules from their regular positions in the crystal structure) should not be high, which is consistent with the DSC data regarding the orderliness of the crystal structure discussed above.

Paying attention to the molecular details of the crystal structure, the molecules arrange in bilayers in such a manner that interactions between lipophilic groups predominate on the inside of the bilayers (Figure 5). In this respect, one remarkable feature is an interaction between the methyl group of a 3-methoxyphenyl group and a phenyl group, belonging to adjacent layers. The methyl group lies between two phenyl groups, which form a dihedral angle of 80.4° and are not in contact; the top of the methyl group is situated above the neighboring phenyl ring so that the distances of the three hydrogen nuclei from the center of the ring are almost the same: 3.4 ± 0.1 Å. The cyano groups project on the outsides of the bilayers, dipolar interactions predominating between bilayers.

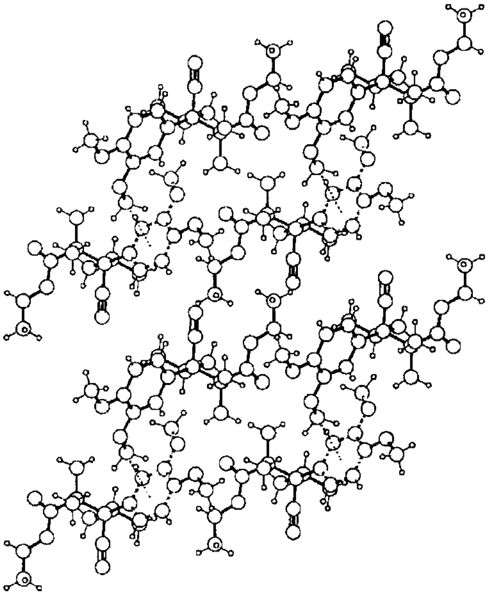

Figure 5. Crystal packing of (*R*)-**1** as viewed along axis *a*

Conclusion

In conclusion, the lipophilic and dipolar forces existing in the crystal of enantiomer **1** may be of consequence in the interaction potential energy of the crystal, which is probably low as suggested by the enthalpy, entropy, and specific heat of fusion of the crystal. Furthermore, this energy is probably lower than that for the racemic compound, as suggested by the enthalpy and entropy of formation of the racemic compound. These structural features of the enantiomer crystal, as pertinent to the enthalpy, may be relevant to the higher thermodynamic stability of these crystalline enantiomers with respect to the racemic compound.

Experimental Section

General: The crystalline (−)-(*R*) enantiomer, the racemic conglomerate, and the racemic compound for ester **1** had been obtained previously.[2a] DSC: Perkin−Elmer Pyris 1 calorimeter, calibrated for the temperature and power scales with recommended high-purity reference materials;[18,19] Mettler AT21 microbalance for weighing of samples. X-ray crystallography: Seifert XRD diffractometer. DSC: Samples of about 200 to 5000 μg contained in sealed aluminum pans were heated at a rate of 0.010 °C·s^{-1}. Melting points were taken as the temperatures corresponding to the maxima of the fusion peaks. The purities of the crystalline (*R*) enantiomer, the racemic conglomerate, and the racemic compound, determined by the fractional-fusion technique,[20] were 99.6, 99.6, and 98%, respectively.

X-ray Crystallography: A colorless monocrystal prism of enantiomer **1** of dimensions 0.46 × 0.38 × 0.09 mm was selected from the racemic conglomerate. The lattice constants were obtained by a least-squares fit (LSUCREB program)[21] on the settings of 70 reflections measured at room temp. with Θ up to 35°. The dimensions of the spectrum corresponded to a monoclinic lattice. The Laue symmetry confirmed the crystal system. The systematic absences (just the $0k0$ spots with odd k values) in addition to the unit cell constants corresponded to space group symmetry $P2_1$ according to literature reference data.[22] The intensities of 3590 reflections, obtained with monochromated Cu-K_α radiation ($\lambda = 1.54180$ Å), were collected in scan-mode ω-2Θ (ω at 0.06°/s) with Θ between 4 and 67°. No decay was observed in two reference reflections (113, $-1-1-3$) measured every 100 min. A total of 3117 reflections were considered as observed at the $2\sigma(I)$ level (σ from counting statistics). Spherical atomic scattering factors were taken from the literature.[22] Since the compound crystallizes in a polar, non-centrosymmetric space group, polar axis restraints were applied by a literature method,[23] by keeping the centroid of the molecule fixed. The structure of the molecule was resolved by direct probabilistic methods with the aid of the SHELX97 program[24] and refined by least squares on F^2 with SHELXL-97. No absorption correction was applied, since the linear absorption coefficient was low ($\mu = 0.655$ mm^{-1}). All non-hydrogen atoms were refined with anisotropic vibrational parameters, employing standard default values of 0.04 to 0.05 Å^2 at the start (corresponding B values: 3.2−3.9 Å^2). The hydrogen atoms were geometrically assigned and treated by use of appropriate riding models. The refinement converged to the following final indices: for observed reflections, $R_1 = 0.050$, and $wR = 0.144$; for all data, $R_2 = 0.052$, and $wR = 0.149$. No cavities suitable to include a virtual water molecule of 0.7 Å radius were left in the crystal structure, as assessed by use of the program HOLES.[25] The volume of the molecule was estimated by use of HOLES. Geometric calculations were carried out with the program PARST.[26] CCDC-185429 [crystalline (*R*)-**1**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[6] As calculated from the equation for the energy of the harmonic oscillator, $U = N_{\mathrm{Av}}h\nu[1/2 + (e^{h\nu/kT} - 1)^{-1}]$,[7a] in regard to the torsional oscillation, along with the assumption of the principle of equipartition of the energy in regard to the hindered internal rotation, RT (27 °C); this principle implies that the oscillator is harmonic (parabolic potential energy curve), which is not the case for a hindered internal rotation (potential energy humps).

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[8] For $S_{\mathrm{tr}}{}^{\mathrm{liq}}$ and $S_{\mathrm{rot}}{}^{\mathrm{liq}}$, three liquids with molecular weights of 50, 300, and 500, p_{vap} values of 10 Torr at 127 °C, 1 Torr at 127 °C, and 0.1 Torr at 227 °C, respectively, and a d_{liq} value of 1 g·ml^{-1}; 40 and 10% average deviations, respectively. For $S_{\mathrm{latt.vib.}}{}^{\mathrm{cr}}$, three crystals with $\bar{\bar{\nu}}_{\mathrm{latt.vib.}}$values of 0.1, 1, and 10 cm^{-1} (3×10^{12}, 3×10^{13}, and 3×10^{14} Hz); 20% average deviation.

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[11] Average for three liquids with molecular weights of 50, 300, and 500, normal b.p.s of 77, 327, and 577 °C, respectively (T_{vap} values; $p_{\mathrm{vap}} = 1$ atm), and a d_{liq} of 1 g·ml^{-1}; 10% average deviation.

[12] As calculated from $S = R\ln Q + U/T$: with regard to the torsional oscillation, Q and U refer to the equations in ref.[6,10] (ordinary quantum Q) and, in regard to hindered internal rotation, they refer to Q at the classical limit[10] and the principle of equipartition of the energy, RT (27 °C); for more rigorous calculations, see ref.[9]

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