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Overall Stability for the Ibuprofen Racemate: Experimental and Topological Results Leading to the Pressure–Temperature Phase Relationships between Its Racemate and Conglomerate

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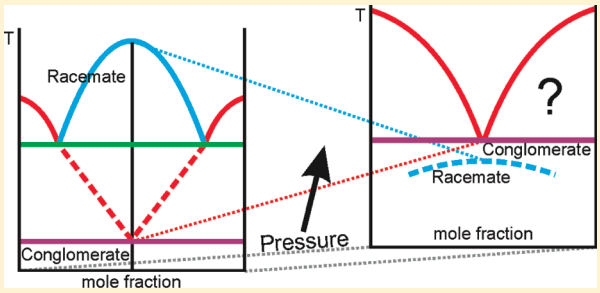
ABSTRACT: Enantiomer resolution is much sought after for pharmaceutical applications, because many optically active drug molecules have only one pharmaceutically active enantiomer. Although it is always possible to force separation, it will come at a cost. The present method, based on thermodynamics, provides a relatively easy approach to investigate whether separation can be thermodynamically spontaneous. A topological phase diagram of the binary enantiomer system at 0.5 mol-fraction is constructed as a function of temperature and pressure after analysis of pressure and heat related quantities. It is demonstrated that for ibuprofen, an optically active analgesic, the racemate is the only stable solid form; the phase relationship between the racemate and the conglomerate is analogous to dimorphism with overall monotropy in pure chemical compounds.



INTRODUCTION

Ibuprofen is a nonsteroidal anti-inflammatory analgesic and antipyretic compound. It is generally recognized that (+)- or (*S*)-ibuprofen (cf. Figure 1) is the pharmaceutically active enantiomer.[1] Many more active pharmaceutical ingredients (API's) are optically active, and in many cases, only one of the two enantiomers is active pharmaceutically. Synthesis often produces a racemic mixture, and even if it is not always necessary to separate the enantiomers, the knowledge whether a racemic mixture can separate spontaneously is valuable information for production purposes.

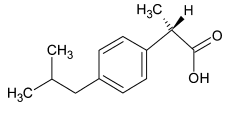


Figure 1. Chemical structure of (*S*)-ibuprofen.

There exists many ways to separate enantiomers, some of which are specifically tailored to a particular molecule. Thermodynamics is a general tool providing direct insight into spontaneous enantiomer separation by the variation of thermodynamic variables, generally pressure and temperature. Its application will be demonstrated by the investigation whether the conglomerate [R + S] consisting of separate (*S*)- and (*R*)-ibuprofen crystallites has a stable domain in the pressure–temperature phase diagram with respect to the racemate (*RS*)-ibuprofen.

To this aim, the system will be studied at 0.5 mol-fraction, the composition of the racemate, but also the composition of the eutectic equilibrium between the two enantiomers, as a result of the symmetry of the system. The two mixed enantiomers existing as a conglomerate "melt" at the eutectic temperature and not at their pure melting point; nonetheless, the vapor pressure and the enthalpy of fusion, which are thermodynamic quantities, do not change with respect to the pure enantiomer because of the (assumed) ideality of the vapor and the liquid phase. Hence at 0.5 mol-fraction, the phase relationship between the racemate and the conglomerate can be considered equivalent to dimorphism of a single compound.[2] Therefore, the topological approach, which has been applied successfully to dimorphism,[3−5] can be used to study the stability hierarchy between the conglomerate and the racemate.

The first step in the topological approach is to review the literature to gather all the heat-related and pressure-related data on the ibuprofen system. In addition, missing data needs to be supplied by measurements and the pressure–temperature

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Table 1. Crystallographic Data from Literature for (*S*)- and (*RS*)-Ibuprofen

T (K)	a (Å)	b (Å)	c (Å)	β	V (Å^3)	Z	ρ (g cm^{-3})	ref
(*S*)-Ibuprofen, Monoclinic $P2_1$								
291	12.462(3)	8.035(3)	13.539(4)	112.89	1248.8	4	1.097	6
RT[a]	12.46	8.03	13.53	112.95	1246.6	4	1.099	1
298	12.456(4)	8.0362 (11)	13.533 (3)	112.86 (2)	1248.2 (5)	4	1.098	7−9
(*RS*)-Ibuprofen Form I, Monoclinic $P2_{1/c}$								
RT[a]	14.67	7.88	10.73	99.3	1224.1	4	1.119	1
RT[a]	14.667	7.886	10.730	99.362	1224.5	4	1.119	10
100	14.397(8)	7.818(4)	10.506(6)	99.70(3)	1165.6	4	1.176	11,12
(*RS*)-Ibuprofen Form II, Monoclinic $P2_{1/c}$								
258	12.3794(9)	5.8723(5)	17.5615(15)	94.873(4)	1272.03(18)	4	1.077	13

[a]because no temperature is mentioned in the original publication, room temperature (RT) has been assumed.

dependence of selected equilibria must be measured to verify the topological results.

The solid state of ibuprofen has been thoroughly studied as can be seen in Table 1, in which the crystallographic data has been summarized, and in Table 2, in which the temperatures

Table 2. Calorimetric Data from Literature for (*S*)- and (*RS*)-Ibuprofen

T_{fus} (K)	$\Delta_{fus}H$ (kJ mol^{-1})	ref
(*S*)-Ibuprofen		
327	17.9	1
322.2	18.7 ± 0.1	14
319.4		15
323 ± 4	18.3 ± 0.6	average
(*RS*)-Ibuprofen, Form I		
349	25.5	1
351.6		16
349.8		17
348.6	25.7	14
344.2	26.9 ± 1.0	15
349	25.8 ± 0.5	18
348.6	25.7 ± 0.2	14
347.2 ± 0.4	23.1 ± 0.4	19
348.0[a]	26.6[a]	20
348.4 ± 0.1	25.0 ± 0.1	20
348.86 ± 0.14	26.5 ± 2.4	21
349.16	26.3	21
350	44.8	22
337−346		23
349 ± 2[b]	25.7 ± 1.0[c]	average
(*RS*)-Ibuprofen, Form II		
290	7.0 ± 0.5	18

[a]Adiabatic calorimeter. [b]Without the value of ref 23. [c]Without the value of ref 22.

and enthalpies of fusion are compiled. The averages of the crystallographic density of the racemate and of the pure enantiomer have a relatively small standard deviation. The melting data are more dispersed, but with averages of 323 ± 4 K and 18.3 ± 0.6 kJ mol^{-1} for the melting point and the melting enthalpy of (*S*)-ibuprofen and 349 ± 2 K and 25.7 ± 1.0 kJ mol^{-1} for the melting point and melting enthalpy of (*RS*)-ibuprofen, the values are reasonably well-defined, except for the relatively large error over the melting point of the pure enantiomer.

Less agreement is found for the data of the eutectic equilibrium between the pure enantiomer and the racemate (ε1). Romero et al. found the eutectic temperature to be close to 321 K and its composition at 10.0% pure enantiomer.[1] This coincides with the eutectic temperature found by Burger et al. at 321.2 K, but their eutectic composition was found somewhat lower at 7%.[14] Dwivedi et al. found the eutectic temperature at 310 K, which is very low in comparison with the other results, whereas the eutectic composition is found at 18% pure enantiomer; however, the latter value may be due to too steep an extrapolation of the Prigogine−Defay equation, as can be judged from the phase diagram in the original paper.[15] Furthermore, a questionable feature of their phase diagram is that, at the pure-enantiomer-rich side of the eutectic composition, the eutectic transition is not observed. The authors claim that this is due to its closeness to the side of the phase diagram (and thus close to a pure enantiomer), whereas it is nonetheless also close to the eutectic point (and thus the eutectic transition should be observed). Moreover, the eutectic remains visible up to 50%; that is at the composition of the racemate, where no eutectic transition can be visible, because the racemate is one of the "pure" compounds that make up the eutectic equilibrium. Without speculating on the origin of the transition observed by Dwivedi et al., one can conclude using simple thermodynamic equilibrium arguments that the transition observed at 310 K cannot be the eutectic equilibrium between the pure enantiomer and the racemate.

Interestingly, Burger et al. observed a second eutectic temperature about 5° lower than the value they have chosen to report as the correct eutectic temperature; they ascribe this to polymorphism even though they failed to find polymorphs for either the pure enantiomer or for the racemate.[14] A polymorph of (*RS*)-ibuprofen has been found later on, although it is doubtful that it could have been the cause of the observed eutectic transition by Burger et al. It was found by quenching molten ibuprofen at 143 K; this leads first to a glass with a glass transition temperature at 228 ± 1 K.[18] Annealing the glass at 143 K for an hour and subsequent annealing of the undercooled liquid at 258 K for five hours results in a different solid phase, form II, which melts at 290 K. The dimorphism of this (*RS*)-ibuprofen system is most likely monotropic and form I is the single stable solid phase following a Gibbs-energy-versus-temperature analysis.[18]

Burger et al. have determined the density by direct measurement of (*S*)-ibuprofen, 1.093 g cm^{-3}, and (*RS*)-ibuprofen, 1.110 g cm^{-3};[14] the values coincide with the densities obtained by X-ray diffraction. They also have obtained the heat capacities of (*RS*)- and (*S*)-ibuprofen and the respective liquids by DSC.[14] In addition, the heat capacity has been measured for the racemate in an adiabatic calorimeter

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by Xu et al. in combination with its melting point and its melting enthalpy.[20] Unfortunately, there is no agreement between the heat capacities of Burger and Xu.

Ertel et al. found an enthalpy of sublimation for racemic ibuprofen of 121 kJ mol^{-1} measured by the Knudsen effusion technique.[24] Perlovich et al. have measured the saturation vapor pressure (P) of both the racemate and the pure enantiomer as a function of temperature (T) resulting in the following expressions:

$$\ln(P(\mathrm{Pa})) = (40.4 \pm 0.2) - (13\,927 \pm 73)/T(\mathrm{K}) \quad (1)$$

for the racemate and

$$\ln(P(\mathrm{Pa})) = (38.1 \pm 0.2) - (12\,920 \pm 60)/T(\mathrm{K}) \quad (2)$$

for crystals of the pure enantiomer.[9] The resulting enthalpies of sublimation are 115.8 ± 0.6 and 107.4 ± 0.5 kJ mol^{-1}, respectively. The enthalpy of the racemate coincides reasonably well with the value found by Ertel et al.

The activation energy of vaporization, which in principle can be taken equal to the enthalpy of vaporization, has been determined with thermal gravimetric analysis based on the rate of weight loss and was found to be 81.8 kJ mol^{-1} for isothermal experiments and 83.8 kJ mol^{-1} for ramping experiments. The boiling point of racemic ibuprofen was found ranging from 485 to 524 K depending on the heating rate.[25] Xu et al. determined the activation energy for the vaporization of liquid racemic ibuprofen and found 80.3 ± 1.4 kJ mol^{-1} comparable to the value found by Lerdkanchanaporn.[20,25] The reason for the high energy of vaporization was ascribed to the existence of dimers in solution that break up upon evaporation.[25] ACD/Laboratories provides an enthalpy of vaporization of 59.25 ± 3.0 kJ mol^{-1} and a calculated boiling point of 593 K.[26] The enthalpy of vaporization calculated by ACD/Laboratories seems too low in comparison with the measured values; however the boiling point found experimentally appears to depend on the heating rate of the TGA. It may be possible that the sample was simply depleted by vaporization before it had even reached the real boiling point. Therefore, the calculated boiling point from ACD/Laboratories will be used in this paper. For the vaporization enthalpy, the experimental average of 81.96 kJ mol^{-1} will be used, because of the agreement between the values from different literature sources.

Ibuprofen comes in many different crystal habits, which caused the scientific community to suspect polymorphism. Although the melting point and the associated enthalpy appear to fluctuate considerably, no evidence for polymorphism has been found, except for the case mentioned above (Tables 1 and 2). The fluctuations in melting point and enthalpy may be due to the relatively high vapor pressure of ibuprofen. Camphor, another compound with a high vapor pressure, exhibits large fluctuations too in its melting enthalpy.[27,28] That ibuprofen's different crystal habits represent one and the same crystal structure has been convincingly demonstrated by Rasenack et al.[29] and has been confirmed by Lee et al.[22]

EXPERIMENTAL SECTION

Materials. Ibuprofen (2-[4-(2-methylpropyl)phenyl] propanoic acid, $C_{13}H_{18}O_2$) has a molecular weight of 206.27 g mol^{-1}. (*RS*)- and (*S*)-Ibuprofen (CAS nos. 15687-27-1 and 51146-56-6, respectively, 99%) were purchased from Acros Organics and were used as such.

High Resolution X-ray Powder Diffraction. X-ray powder diffraction was performed on a transmission mode diffractometer using Debye−Scherrer geometry equipped with a cylindrical position-sensitive detector (CPS120) from INEL (France) containing 4096 channels (0.029° 2θ angular step)[30] with monochromatic Cu Kα_1 (λ = 1.54061 Å) radiation. A liquid nitrogen 700 series Cryostream Cooler from Oxford Cryosystems (U.K.) was used to control the temperature during the measurements.

Gently ground specimens were introduced in a Lindemann capillary (0.5 mm diameter) rotating perpendicularly to the X-ray beam during the experiments to improve the average over the crystallite orientations. For the temperature dependent measurements in the range from 100 K up to the melting point, the sample temperature was equilibrated for about 10 min followed by an acquisition time of ca. 1 h. The heating rate in between data collection was 1.33 K min^{-1}.

Differential Scanning Calorimetry. Differential scanning calorimetry (DSC) was performed at 10 K min^{-1} with a Q100 thermal analyzer from TA-Instruments calibrated with indium (T_{fus} = 429.75 K, $\Delta_{fus}H$ = 3267 J mol^{-1}) as standard for temperature and enthalpy. Specimens were weighed with a balance sensitive to 0.01 mg.

High-Pressure Differential Thermal Analysis. To measure the transition temperatures as a function of the pressure, an in-house constructed high-pressure differential thermal analyzer (HP-DTA) was used, similar to the apparatus previously built by Würflinger.[31] Its temperature and pressure range from 203 to 473 K and 0 to 300 MPa. The temperature of fusion of (*S*)-ibuprofen, (*RS*)-ibuprofen, the liquidus transition at 75% (*S*)-ibuprofen and the temperature of the eutectic equilibrium (*RS*) + (*S*) + L (ε1) have been determined. To make sure that in-pan volumes were free from residual air, specimens were mixed with an inert perfluorinated liquid (Galden, from Bioblock Scientifics, France) before the pans were closed. HP-DTA scans were conducted with heating rates ranging from 1 to 2 K min^{-1}. In addition, DSC runs at ordinary pressure (i.e. in standard aluminum pans) with mixtures of ibuprofen and perfluorinated liquid demonstrated that the latter was inert.

RESULTS

The melting point of (*S*)-ibuprofen was found at 323.8 ± 0.1 K with a melting enthalpy of 94 ± 1 J g^{-1} (19.4 ± 0.2 kJ mol^{-1}). The melting point of (*RS*)-ibuprofen was found at 347.9 ± 0.2 K with a melting enthalpy of 126.7 ± 0.8 J g^{-1} (26.1 ± 0.2 kJ mol^{-1}). This leads to an average value for the melting temperature of (*S*)-ibuprofen of 323 ± 3 K in combination with the literature data and for the enthalpy of fusion 18.7 ± 0.8 kJ mol^{-1}. In the case of (*RS*)-ibuprofen, the average melting point becomes 348.6 ± 1.6 K and the enthalpy of fusion 25.7 ± 1.0 kJ mol^{-1}. The temperature of the liquidus (peak maximum) and the temperature of the eutectic equilibrium ε1 (onset) for a mixture with 75% (*S*)-ibuprofen were found to be 347.7 and 321.2 K, respectively. It can be seen that the eutectic equilibrium is very close to the melting point of the pure enantiomer and that the liquidus temperature only slightly differs from the congruent melting point of the racemate. The temperature of the eutectic transition coincides very well with those found previously.[1,14]

The dependence of the specific volume on the temperature, $v_{spec}(T)$ was obtained by X-ray diffraction, and for solid (*S*)-ibuprofen it is given by

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$$v_{spec}(cm^3\ g^{-1}) = 0.8670(0.0024) + 1.4(2.5) \times 10^{-5} T(K) + 4.9(0.6) \times 10^{-7} (T(K))^2 \quad (3)$$

and for solid (*RS*)-ibuprofen

$$v_{spec}(cm^3\ g^{-1}) = 0.8488(0.0018) + 2.7(1.8) \times 10^{-5} T(K) + 4.1(0.4) \times 10^{-7} (T(K))^2 \quad (4)$$

The experimental data, the fitted curves, and data from literature can be found in Figure 2.

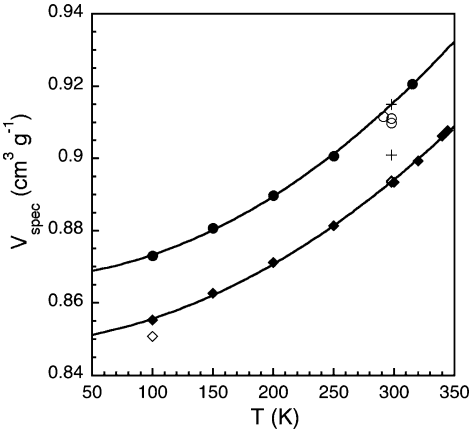

Figure 2. Specific volume of (*S*)- and (*RS*)-ibuprofen (filled circles and filled diamonds respectively) as a function of temperature together with the values determined with X-ray diffraction from literature (open circles and diamonds, if no temperature was mentioned, 298 K was assumed; cf. Table 1). The plus signs are from direct measurement of the density (cf. Introduction).[14]

The evolution of the melting transitions for (*S*)- and (*RS*)-ibuprofen as a function of pressure have been obtained by high-pressure differential thermal analysis together with the temperatures of the liquidus peak and of the eutectic equilibrium at 0.75 mol-fraction. Examples of the high-pressure curves can be found in Figure 3. The pressures as a function of the transition temperatures have been plotted in Figure 4.

The melting equilibria of the pure enantiomer and the racemate in the *P*−*T* diagram are described by the two following expressions:

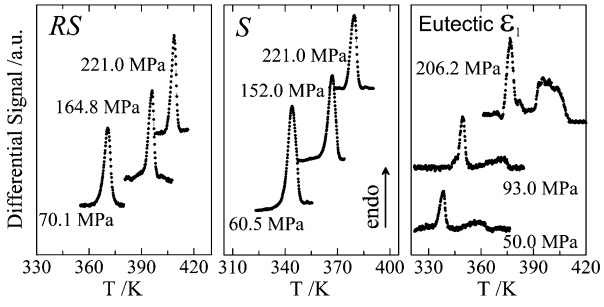

Figure 3. Curves from the high-pressure differential thermal analysis. Left, congruent melting of the racemate *RS*. Center, melting of the pure enantiomer *S*. Right: the eutectic equilibrium $\varepsilon 1$ (*RS*−*S*−L), the liquidus peaks can be observed too. Peaks have been vertically shifted for clarity.

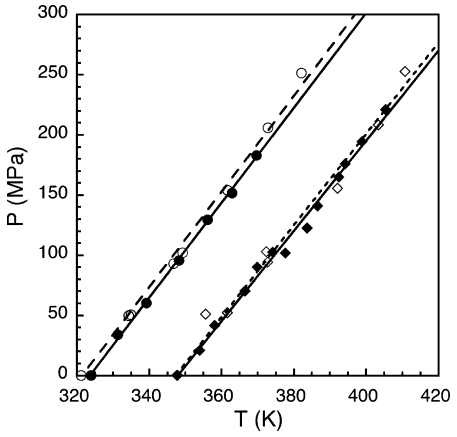

Figure 4. Dependence on the pressure and the temperature of the melting of (*S*)-ibuprofen (filled circles), the congruent melting of the racemate (filled diamonds), the eutectic equilibrium between the racemate and (*S*)-ibuprofen (open circles), and the maximum of the liquidus peak of the racemate (0.75 mol fraction (*S*)-ibuprofen). The lines are fits to the data: solid lines for the melting transitions, broken lines for the eutectic equilibrium and the liquidus.

$$\text{enantiomer: } P(\text{MPa}) = -1279(12) + 3.952(0.034) T(\text{K}) \quad (5)$$

$$\text{racemate: } P(\text{MPa}) = -1303(23) + 3.745(0.063) T(\text{K}) \quad (6)$$

It can be seen that the slope of the melting equilibrium of the pure enantiomer is slightly steeper than the one of the racemate; thus, the two equilibria are diverging with increasing temperature and pressure (eqs 5 and 6). Moreover, the intercept with the *y* axis is slightly higher (less negative) for the pure enantiomer than for the racemate indicating that the extrapolated lines of the two solid−liquid equilibria do not cross at any positive temperature. As can be seen in Figure 4, the eutectic equilibrium and the liquidus follow the melting equilibria closely. The slopes obtained by linear regression are respectively 3.98 ± 0.05 and 3.80 ± 0.09 MPa K^{-1}; they fall exactly in between the slopes of the melting equilibria, indicating that all equilibria are diverging with pressure.

DISCUSSION

Specific Volume of the Liquid. The slope of an equilibrium in a *P*−*T* diagram is given by the Clapeyron equation

$$\frac{dP}{dT} = \frac{\Delta H}{T \Delta v} \quad (7)$$

ΔH is the enthalpy change associated with the equilibrium shift, Δv is the volume change, and *T* the equilibrium temperature at a given pressure. The slope of the equilibrium between the solid enantiomer and its liquid has been measured and so is the slope for the melt of the racemate. Because the enthalpy and the equilibrium temperature are known, the volume change, Δv, can be calculated, which in turn allows for the calculation of the liquid volumes making use of the measured specific volumes of the solid phases.

For (*S*)-ibuprofen the slope of the solid−liquid equilibrium is 3.952 MPa K^{-1} (eq 5). With the calorimetric data given at the beginning of the Results section, this leads to a Δv between solid (*S*)-ibuprofen and its liquid of 0.0709 $cm^3 g^{-1}$ at the melting temperature. For the solid, the specific volume is equal

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to 0.9232 $cm^3\ g^{-1}$ (eq 3), and this leads to a specific volume for the liquid of 0.9941 $cm^3\ g^{-1}$ at the melting point. The ratio v_{liquid}/v_{solid} is 1.08. Adding this to the ratios already found for other APIs, paracetamol 1.15, biclotymol 1.13, progesterone 1.09, lidocaine 1.06, ternidazole 1.05, and benfluorex−HCl form I 1.06, the average volume ratio between the liquid and the solid for APIs remains 1.09, as found in the publication on benfluorex−HCl.[3−5,32−34] This ratio is smaller than 1.17, which is the ratio for organic compounds in general as found by Goodman et al.[35]

In the case of the racemate, the slope of the solid−liquid equilibrium in the $P-T$ diagram is 3.745 MPa K^{-1} (eq 6). With the thermal data from the first part of the Experimental Section, this leads to a variation in the specific volume over the melting transition Δv of 0.09562 $cm^3\ g^{-1}$. The racemate has a specific volume of 0.9083 $cm^3\ g^{-1}$ at its melting point (eq 4), and this results in a specific volume of the liquid of 1.004 $cm^3\ g^{-1}$. The higher melting point of the racemate gives rise to a higher specific volume of its liquid in comparison to the pure enantiomer. The ratio of the specific volumes for the liquid and the solid is in this case 1.105; even though the crystal is a racemate, this ratio is still very close to the value calculated for APIs.

Recently, the glass transition temperature of racemic ibuprofen, 225 K, has been obtained by dielectric measurements.[36] An estimate of the dependence of the specific volume of the liquid on the temperature can be obtained by setting the volume of the liquid equal to that of the crystalline solid at the glass transition.[37] A liquid volume of 1.004 $cm^3 g^{-1}$ at 347.9 K and a solid volume for the racemic compound of 0.876 $cm^3\ g^{-1}$ at 225 K lead to a slope for the specific volume of the racemic liquid of 1.04×10^{-3} $cm^3\ g^{-1}\ K^{-1}$. This is similar in magnitude to the slope found for ternidazole: 5.09×10^{-4} $cm^3\ g^{-1}\ K^{-1}$.[33] An empirical ratio of 2/3 between the glass transition temperature and the temperature of fusion of an organic compound has once been proposed by Tammann. It can be seen that for racemic ibuprofen the ratio of T_g/T_{fus} = 0.65 is close to 2/3. Because the pressure dependence of the glass transition has been determined too,[36] it is even possible to investigate if this 2/3 ratio can be extended to the slopes as a function of the pressure: $(dT_g/dP)/(dT_{fus}/dP)$. For the slope of the glass transition temperature 0.195 K/MPa has been found[36] and for the melting temperature of the racemate 0.267 K/MPa is found (eq 6). It leads to a ratio of 0.73, which is higher than the value for the ratio of the temperatures alone, but still reasonably close to the value of 0.67 suggested by Tammann.

Comparison between the Solid−Liquid Equilibria of the Racemate and the Conglomerate. It is clear that the racemate in the case of ibuprofen is the stable phase in relation to the conglomerate under ordinary pressure. To investigate whether enantiomer resolution can be spontaneous, the enantiomer−racemate system at 0.5 mol-fraction is treated like a dimorphic system.[2] However, it is not the pure enantiomer, but the conglomerate of the pure enantiomers that is the second phase in this dimorphism analogue and the temperature of this eutectic equilibrium $[R + S] + L$ ($\varepsilon 2$) needs to be determined. Because the liquid phase containing the two optical antipodes is generally ideal, the Schröder equation[38,39] can be used to calculate the eutectic temperature at 0.5 mol-fraction,[40,41] as the system is completely symmetric

$$\ln(1 - x) = \frac{\Delta H}{R}\left(\frac{1}{T_{fus}} - \frac{1}{T}\right) \quad (8)$$

ΔH is the enthalpy of fusion of the pure enantiomer, R is the gas constant (8.31451 J K^{-1} mol^{-1}), T_{fus} is the melting point of the pure enantiomer, and T is the temperature of the liquidus at mole fraction x. To calculate the eutectic temperature, the measured values for the enthalpy and temperature of fusion were used as mentioned in the Results section to maintain consistency with the values measured at higher pressures. For the pressure dependence of the transition temperature, the fit to the melting equilibrium of the pure enantiomer is used together with the melting entropy determined at ordinary pressure (57.8 J K^{-1} mol^{-1}), which is assumed constant within the pressure range under consideration.[2,27]

Table 3. Temperature of the Eutectic Equilibrium Formed by the Conglomerate ($\varepsilon 2$) Calculated with the Schröder Equation (eq 8)

P (MPa)	T_{fus} (K)	T_{eut} (K)
0.1	323.8	294.5
25	330.0	300.1
50	336.3	305.8
100	349.0	317.3
150	361.6	328.8
200	374.3	340.3
250	386.9	351.8

The temperatures calculated with the Schröder equation (eq 8, Table 3) for $\varepsilon 2$ lead to the following expression as a function of the pressure

$$\varepsilon 2:\ P(\text{MPa}) = -1281(2) + 4.352(0.003)T(\text{K}) \quad (9)$$

Equation 9 does not cross eq 6, which is the fit to the congruent melting temperature of the racemate as a function of pressure, at any positive absolute temperature. The slope of $\varepsilon 2$ is larger than that of eq 6 and with increasing pressure and temperature both equilibria diverge. In other words, the racemate becomes more stable with increasing pressure.

Enthalpy of Sublimation. Sublimation enthalpies have been obtained by Ertel et al. and by Perlovich et al.[9,24] Furthermore, vaporization enthalpies have been obtained by two other groups.[20,25] Applying a thermodynamic cycle, starting with solid (*RS*)-ibuprofen, melting, evaporation, and condensation back into the solid form, brings the ibuprofen back into its initial state and thus the enthalpy variation should equal zero. The problem is that, although in both cases the sublimation enthalpy and the vaporization enthalpy have been determined by different groups and consistently the same values have been found, applying the thermodynamic cycle leads to a final value of −10.7 kJ mol^{-1} instead of zero. This can be due to the temperature dependence of the transition enthalpies or due to experimental uncertainties, but it means that a choice has to be made as to which data to use. The sublimation data of Perlovich at al. appear to be the most suitable, because the data is obtained directly from equilibrium vapor pressures, which are a direct result of thermodynamic equilibrium. All of the other data have been measured with steady state methods that according to theory should lead to thermodynamic quantities.

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Final Pressure−Temperature Phase Diagram. With the use of expression 1, the sublimation pressure of the racemate, the pressure at the congruent melting point of the racemic crystal, 347.9 K can be calculated resulting in 1.45 Pa. The same can be done for the eutectic equilibrium between pure (*R*)- and (*S*)-ibuprofen, which occurs at 294.5 K, using expression 2 for the pure enantiomers. The pressure at this point is 0.0031 Pa for the eutectic mixture, whereas the pressure for the racemate at the same temperature (using eq 1) is 0.0010 Pa, which is lower, indicating that the racemate is indeed the stable form. The stable invariant racemate−liquid−vapor (*RS*−L−V) and the metastable invariant conglomerate−liquid−vapor ([*R* + *S*]−L−V) are now defined in the *P*−*T* diagram (cf. Figure 5). They are the two invariants that can be found on the curve of the liquid−vapor equilibrium.

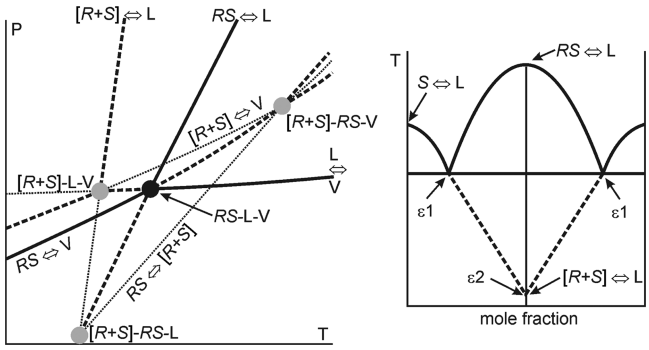

Figure 5. Left-hand side: The topological pressure−temperature phase diagram of ibuprofen at 0.5 mol-fraction (the diagram is not to scale). *RS* is the racemate, [*R* + *S*] is the conglomerate, L is the liquid phase, and V is the vapor phase. Solid lines are stable equilibria, broken lines are metastable equilibria, and dotted lines are supermetastable equilibria. This phase diagram has only one stable invariant point marked with a solid circle, where *RS*, L, and V are in equilibrium. The metastable invariants are marked with gray circles. For the coordinates of the invariant points in the *P*−*T* diagram, see text. Right-hand side: A schematic temperature−composition phase diagram for ibuprofen valid over the entire pressure range. The racemate *RS* always melts at a higher temperature than the conglomerate [*R* + *S*]. It can be seen on the left-hand side that the $\varepsilon 2$ equilibrium ([*R* + *S*] → L) does not intersect the racemate-liquid equilibrium at positive pressure (compare eqs 6 and 9). These topological inferences indicate that the eutectic $\varepsilon 2$ is inherently unstable.

The question that remains is where the two sublimation curves (*RS*−V and [*R* + *S*]−V) intersect, because it will give rise to the invariant with *RS*, [*R* + *S*], and the vapor phase in equilibrium, and this invariant represents the transition between *RS* and [*R* + *S*] under ordinary conditions (i.e., at positive pressure). Using both expressions for the sublimation pressure by Perlovich et al.[9] (eqs 1 and 2), the intersection of the curves is found at *T* = 438 K and *P* = 5381 Pa. These coordinates are located in the domain where the liquid is stable and the (*RS*−[*R* + *S*]−V) invariant must therefore be metastable.

The slope of the *RS* to [*R* + *S*] equilibrium can be calculated at the invariant point (*RS*−[*R* + *S*]−V), however the enthalpy of transition needs to be known and the variation in the specific volumes. For the latter the curves measured by X-ray diffraction can be extrapolated, this results in a difference for the transition in the direction of *RS* → [*R* + *S*] of $\Delta v = +0.0223\ \mathrm{cm^3 g^{-1}}$. The enthalpy difference is given by the difference between the two melting enthalpies, one obtained at the melting point of the racemate and one at the melting point of the pure enantiomer. Ideally, these values should be corrected for the change in temperature by the heat capacities of the respective solids. Both Burger et al. and Xu et al. have determined the heat capacity of ibuprofen, and the values determined by Xu et al. appear to be more precise, as they have been determined by adiabatic calorimeter.[14,20] Unfortunately, Xu et al. have not determined the heat capacity of (*S*)-ibuprofen. Because the differences in heat capacity between Burger and Xu are rather large, it has been decided to assume that the heat capacities of both forms are similar and that simply the difference between the melting enthalpies between the two forms can be used. This leads to an enthalpy variation for the *RS* → [*R* + *S*] transition of $\Delta_{fus}H_{RS} - \Delta_{fus}H_{R\text{-}S} = 7.076\ \mathrm{kJ\ mol^{-1}}$. With the Clapeyron eq 7, this leads to a slope in the pressure − temperature diagram of 3.51 MPa $\mathrm{K^{-1}}$, which is less steep than the slope for the equilibrium between the racemate and the liquid at 3.75 MPa $\mathrm{K^{-1}}$. With the values for the invariant *RS*−[*R* + *S*]−V the approximate expression for the equilibrium in the *P*−*T* diagram can be obtained

$$\mathrm{RS} \rightarrow [\mathrm{R} + \mathrm{S}]:\ P(\mathrm{MPa}) = -1539 + 3.51T(\mathrm{K}) \qquad (10)$$

The fourth invariant, that between the racemate, the conglomerate, and the liquid, is drawn at the bottom of the *P*−*T* phase diagram in Figure 5. This is a schematic estimate because none of the involved equilibrium lines (eqs 6, 9, or 10) cross at positive absolute temperature. Because negative temperature has no physical meaning, the topologically obtained invariant point can be considered to be just above 0 K and around −1300 MPa; it has to be kept in mind that the extrapolations (eqs 6, 9, and 10) contain a significant uncertainty at the estimated intersection.

■ CONCLUDING REMARKS

Even though part of the conclusion must be that there is unfortunately no spontaneous separation of the ibuprofen racemate into pure enantiomers, the example demonstrates the strength of the topological method in combination with direct measurements of phase equilibria as a function of temperature and pressure. With the use of information about the temperature and pressure behavior of ibuprofen, the racemate - conglomerate transition has been irrefutably placed within the domain, where the liquid phase is stable; thus leading to the conclusion that there is no single pressure − temperature coordinate with a stable domain for the conglomerate.

There are several tools that can be used in the topological approach of which the simplest is the principle of Le Chatelier. Although not mentioned above, Le Chatelier's principle implies that the densest form will be stable at high pressure and the highest energy forms will be stable at high temperature. Considering the X-ray diffraction results in Table 1 this immediately leads to the conclusion that the conglomerate is not stable at high pressures, it is actually the low pressure form with the lowest density. Since the racemate is stable at ordinary pressure, any domain with a stable conglomerate should be found at the rims (high or very low temperature) of the phase diagram. The next step is to consider the melting enthalpies, and it can be seen that the enthalpy for the congruent melting of the racemate is higher than that for the melting for the pure enantiomer (and thus for the conglomerate). This implies that the phase change from the racemate to the conglomerate must be endothermic and that the conglomerate is essentially stable at higher temperatures than the racemate. Because the racemate is the highest melting form, it settles the fate of the

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conglomerate as a form that only becomes more stable than the racemate when the liquid is the most stable phase. The final blow to the chances of the conglomerate to have a stable domain is the crossing of the sublimation curves measured by Perlovich et al.[9] The intersection places the transition in the stable domain of the liquid phase and with the help of the Clapeyron equation, the slope of the racemate−conglomerate equilibrium can be calculated. This allows comparison with the slopes of the measured equilibria, such as the racemate's congruent fusion and that undeniably demonstrates that there is no stable domain for the conglomerate at positive pressures (cf. Figure 5).

As far as the invariant point is concerned of the equilibrium between racemate, conglomerate, and liquid, it is clear that it has to be close to 0 K and at very low negative pressures. This invariant point must exist, because the lines will have to cross somewhere if they are monotonously increasing, which is imposed by thermodynamics. Because the uncertainty of the position of the equilibrium curves is large far from the point where they have been measured or calculated, the triple point has simply been placed close to 0 K (i.e., at a temperature that still makes sense physically).

The ibuprofen system at 0.5 mol-fraction is a case of overall monotropy with the racemate as the only stable form. The system is comparable with the dimorphism of biclotymol, which also displays overall monotropy.[4] This example demonstrates that at the racemate composition, a system of optical antipodes from a thermodynamic point of view behaves like a single dimorphic compound, because the pure enantiomers, the two components of the binary system, melt at the same pressure and temperature. Previously, the $P-T$ phase diagram of the system of mandelic acid system has been published, which becomes enantiotropic at high pressure.[2] However, how monotropy and enantiotropy are distributed in racemic systems will remain an open question for some time to come.

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Notes

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