Journal of Pharmaceutical Science

An Examination of the Phase Transition Thermodynamics of (*S*)- and (*RS*)-Naproxen as a Basis for the Design of Enantioselective Crystallization Processes

Hannes Buchholz[a], Vladimir N. Emel'yanenko[b], Heike Lorenz[a] and Sergey P. Verevkin[b,c]

[a]*Max Planck Institute for Dynamics of Complex Technical Systems, Sandtorstraße 1, D-39106, Magdeburg, Germany*

[b]*Department of Physical Chemistry, Kazan Federal University, Kremlevskaya str. 18, 420008, Kazan, Russia*

[c]*Department of Physical Chemistry and Department „Science and Technology of Life, Light and Matter", University of Rostock, Dr-Lorenz-Weg 1, D-18059, Rostock, Germany*

Abstract

A detailed experimental analysis of the phase transition thermodynamics of (*S*)-naproxen and (*RS*)-naproxen is reported. Vapor pressures were determined experimentally via the transpiration method. Sublimation enthalpies were obtained from the vapor pressures and from independent TGA measurements. Thermodynamics of fusion which have been well-studied in the literature were systematically remeasured by DSC. Both sublimation and fusion enthalpies were adjusted to one reference temperature, T = 298 K, using measured heat capacities of the solid and the melt phase by DSC. Average values from the measurements and from literature data were suggested for the sublimation and fusion enthalpies. In order to prove consistency of the proposed values the vaporization enthalpies obtained by combination of both were compared to vaporization enthalpies obtained by the group-additivity method and the correlation-gas chromatography method. The importance of reliable and precise phase transition data for thermochemical calculations such as the prediction of solid/liquid phase behavior of chiral compounds is highlighted.

Introduction

The production of pure enantiomers is important for the food and drug industry and increasingly for the agrochemical sector. It has been reported that about 56% of the marked drugs are chiral.[1] Crystallization processes have been reported to be especially efficient for large scale enantioseparation.[2] Solubilities play an important role for process design as they

define feasibility and productivity of a crystallization process. Naproxen as well as about 90-95 % of the chiral systems[3] can form a stoichiometric 1:1 molecular racemic compound, (*RS*)-naproxen (see Figure 1, left).

Figure 1.

The eutectic composition, x_{eu}, defines the boundary between the areas where pure enantiomer or the racemic compound can be crystallized from solution (indicated as grey area in Figure 1, left). Hence, for process design of such systems the solubility of the enantiomers, $x_{(S)}$ and $x_{(R)}$, and of the molecular compound, $x_{(RS)}$, as well as the eutectic composition in solution are characteristic information. In earlier investigations we studied solubility behaviour and crystallization-based enantioseparation on several substances e.g. propranolol hydrochloride[4], 3-chloromandelic acid[5] and guaifenesin[6] on an experimental basis. However, especially in early stages of process design, the available amount of substance is often scarce for detailed experimental studies. Solubility prediction can support and complement experimental examinations.

To access solubility by computational methods the free energy change of the solution process, $\Delta_{cr}^{sol}G_{sol}^{\circ}$, has to be split up into accessible quantities by a thermodynamic cycle. The solution process can be thermodynamically described by either transferring the molecule from the solid crystal via (1) the subcooled melt or via (2) the gas phase into the solution (illustrated in Fig. 1, right).[7] The two thermodynamic cycles have been compared in a previous study[8] for chiral lactide where experimental melting properties and sublimation enthalpies are used to calculate solubilities and to estimate the eutectic composition in a solvent mixture. For a merely predictive method besides solvent interaction-based quantities the solid/liquid or solid/vapor phase change quantities have to be computed as well. State of the art methods to predict the melting temperature still give errors above 30 K.[9] Palmer et al.[10] proposed a method to calculate solubilities with information on the molecular structure only by using calculated lattice energies. Otero-de-la-Roza et. al.[11] successfully used differences in lattice energies to estimate the eutectic composition of several compounds in solution. However, recent benchmarks on the computation of lattice energies[12, 13] show that computations depend strongly on the computational method used and hence are related to relatively large errors. Precise experimental thermochemical data can help to improve computational methods by giving a basis to compare computations to experimental values.

In this contribution we report carefully measured thermochemical data for the naproxens, i.e. the (*S*)-enantiomer and the racemic molecular compound, (*RS*)-naproxen. Molar heat capacities of the solid and the liquid naproxens as well as their fusion enthalpies were measured by Differential Scanning Calorimetry (DSC). Absolute vapor pressures of the solid naproxens were measured with the transpiration method. Molar enthalpies of sublimation were derived from the temperature dependences of the vapor pressures as well as directly measured by means of the Thermogravimetric Analysis (TGA). In order to prove consistency of the experimental thermochemical results, the vaporization enthalpies of the naproxens were derived by combination of sublimation and fusion enthalpies and compared to vaporization enthalpies obtained by the group-additivity (GA) method and the correlation-gas chromatography (CGC) method.

Materials and methods

Materials

Samples of (*RS*)-naproxen, (*RS*)-(±)-2-(6-Methoxy-2-naphthyl)propionic acid, and (*S*)-naproxen, (*S*)-(+)-2-(6-Methoxy-2-naphthyl)propionic acid, were of commercial origin (TCI-Europe) with specified purities of 98 % and 99 %, respectively. They were further purified by recrystallization. No impurities > 0.01 mass fractions could be detected via HPLC-analysis* in samples used for the measurements.

Heat capacity measurements

Heat capacity measurements were carried out using a DSC 111 calorimeter (Setaram, France) which operates with a Tian-Calvet sensor.[14] Temperature calibration was conducted using indium, tin and lead as reference material. Since the Calvet detector was absolutely calibrated calorically by the Joule effect, the heat capacity was not measured against a reference material. The calorimetric resolution of the instrument is 0.4 μW, and the detection limit 5–15 μW. Two succeeding measurements were performed using the temperature step method while purging with highly pure helium (99.999 Vol %) at a constant flowrate of 20 ml·min^{-1}. In the first run the empty aluminum crucible was measured (150 μl, purchased from Setaram) which

*HPLC analysis conditions: Chiralpak AD-H column (Chiral Technologies) with mobile phase consisting of n-Hexane/IPA/TFA in a ratio of 80:20:0.1. The flow rate was 1 ml·min^{-1} and the temperature 25 °C.

was then filled with the sample and closed with the same aluminum lid for the second run. Sample masses were between 60 to 80 mg (±10μg).

The heat capacity measurements were performed in 10 K steps with a heating rate of 5 $K \cdot min^{-1}$ followed by isotherms of 600 s duration. Sapphire and benzoic acid were used as test substances. Average deviations to published data were 1.4 % for sapphire[15] and 2.6 % for benzoic acid[16]. Four series of measurements were carried out for both substances in the solid state. Heat capacities of the liquid samples were measured separately. In order to reduce the duration of thermal stress, the solid sample was heated to the melting temperature with high heating rate and then equilibrated at temperatures above the melting point. Subsequent heat capacity measurements were performed with the step-wise method, but we reduced steps to 5 K steps. The measurements have been repeated twice for (*RS*)-naproxen and four times for (*S*)-naproxen.

Vapor pressure measurements via the transpiration method

Vapor pressures of the naproxens were measured using the transpiration method which was described before in detail by the authors.[17,18] About 0.5 g of solid sample was dissolved in acetonitrile and mixed with small glass beads in a glass beaker. Under vigorous stirring with a spatula and gentle heating the solvent was removed from beaker producing glass beads covered uniformly with the sample. These covered glass beads were placed in a thermostated U-shaped saturator. A well-defined nitrogen stream was passed through the saturator at a constant temperature (± 0.1 K), and the transported material was collected in a cold trap. The amount of condensed sample was determined by weighing with microbalances of 0.0001 g resolution. The absolute vapor pressure p_i at each temperature T_i was calculated from the amount of the product collected within a definite period. Assuming validity of Dalton`s law applied to the nitrogen stream saturated with the substance *i*, values of p_i were calculated with eq. (1):

$$p_i = m_i \cdot R \cdot T_a / V \cdot M_i \; ; \qquad V = V_{N2} + V_i ; \qquad (V_{N2} \gg V_i) \qquad (1)$$

where R is the universal gas constant; m_i is the mass of the transported compound M_i is the molar mass of the compound, and V_i its volume contribution to the gaseous phase. V_{N2} is the volume of the carrier gas and T_a is the temperature of the soap bubble meter used for measurement of the gas flow. The volume of the carrier gas V_{N2} was determined from the flow rate and the measurement time. Uncertainties of absolute vapor pressures measured by

the transpiration method were estimated according to the procedure described in detail in the literature.[18] They are governed mostly by the reproducibility of the GC analysis as well as by the V_{N2} volume determination. The combined uncertainties $u(p)$ of vapor pressures derived from the transpiration method are generally in between 1 to 3 % and the corresponding deviations from the smoothed equations are adequate estimates of the uncertainty.[18] In order to confirm that the deposited naproxen on the glass beads is completely crystalline additional transpiration experiments for both naproxens have been performed as follows. In contrast to the previously described procedure using a solvent, an abundant amount of the crystalline sample of the naproxen was as uniformly dispersed as possible among the glass beads in the saturator. Transpiration measurements were performed at two different temperatures and the results were indistinguishable with those after crystallization from acetonitrile.

Sublimation enthalpy via TGA

Enthalpies of sublimation of the naproxens were additionally measured with a Perkin Elmer Pyris 6 TGA. A plane platinum crucible with vertical walls, diameter of 10 mm and height 3 mm with about 70 mg of the sample was heated with a ramp of 10 $K \cdot min^{-1}$ under nitrogen purge gas flow. In order to obtain a smoothed surface of the sample inside the crucible, the sample was gently melted and cooled down to room temperature before the TGA experiment. No decomposition of the sample was observed (according to the FT-IR spectra) after the pre-treatment of the sample. Isothermal TGA curves were measured in the temperature range 395-425 K at a nitrogen flow rate of 200 $ml \cdot min^{-1}$. Measurements of the mass loss rate *dm/dt* were performed in a few consequent series of steps of increasing and decreasing temperature. Every step consisted of 7 to 11 points of the mass loss rate determination at each temperature. Several runs have been performed to assess the reproducibility of the results. The detailed procedure was described elsewhere. [19]

Enthalpy of fusion via DSC

The thermal behavior of the naproxens including melting temperature and enthalpies of fusion was studied both in Rostock and Magdeburg. In Rostock a Mettler-Toledo DSC 822 was applied. The instrument was standardized using indium metal with a mass fraction of 0.9999. The samples were hermetically sealed in 50 µl pans supplied by Perkin Elmer. Measurements were performed in triplicate with a heating rate of 10 $K \cdot min^{-1}$. Thermodynamics of fusion of

naproxens was additionally studied at MPI in Magdeburg using a Setaram DSC 131. Temperature and enthalpy calibration was performed using indium, tin and lead reference material. Samples with typical masses of ~10 mg (± 10 µg) were weighed into 30 µl Al-pans which have been supplied by Setaram, closed with a lid and heated from 300 K to 573 K with a constant heating rate of 1 and 2 K/min while purging with highly pure helium (99.999 Vol. %) at a constant flow rate of 70 ml·min^{-1}. The measurements were repeated twice for both heating rates.

Results

Heat capacity measurements

DSC is conventionally used to study phase transitions and heat capacities of materials. The heat capacity measurements of naproxens were performed below and above the melting temperature. Results of the heat capacity measurements are shown in Figure 2. No significant heat capacity difference between the enantiomer and the racemic compound could be observed for the solid or the melt. The average difference between the heat capacities of the solid enantiomer and the racemic compound of 2.5 J·K^{-1}·mol^{-1} was below the experimental error (see Table 1). In contrast, for some other chiral species like mandelic acid and erythro-phenylglyceric acid significantly larger heat capacity differences between the enantiomer and the corresponding racemic molecular compound were observed.[21]

Figure 2.

Slightly different experimental heat capacities of an unspecified sample of naproxen have been reported in the literature.[20] In view of the poorly defined nature and purity of the studied sample the reported data are not further discussed in this work.

The standard molar heat capacities, $C^{\circ}_{p,m}$(298 K), are needed in order to adjust sublimation and fusion enthalpies measured in this work to the reference temperature, T = 298 K. As indicated by the experimental results (see Fig. 2) the temperature-dependent behavior of the molar heat capacities of the solid and the melt was assumed to be linear in between reference temperature and the melt and correlated by equation 2:

$$C^{0}_{p,m} = A + B \cdot T/K \qquad (2)$$

The resulting $C^{\circ}_{p,m}$-values at 298 K are given in Table 1. Coefficients of eq. 2 are summarized in Table S1 (supporting information) together with all primary experimental data of the heat capacities measured in this work.

In addition to the solid and liquid state heat capacities, the ideal gas heat capacities are required to adjust measured enthalpies of sublimation to the reference temperature. Differences between the molar heat capacities of the gaseous phase $C^{\circ}_{p,m}$(g, 298 K) and the crystalline phase $C^{\circ}_{p,m}$(cr, 298 K), $\Delta^{g}_{cr}C^{\circ}_{p,m}$, are summarized in Table 1. Hereby, the experimental values of $C^{\circ}_{p,m}$(cr, 298 K) were used for the solid phase whereas the values of $C^{\circ}_{p,m}$(g, 298 K) were determined computationally by density functional theory.

Table 1.

Vapor pressure and sublimation enthalpies from the transpiration method

Absolute vapor pressures p_i measured by the transpiration method were correlated with the following equation: [17]

$$\ln\left(p_i / p^0\right) = \frac{a}{R} + \frac{b}{R \cdot T} + \frac{\Delta^{g}_{cr}C^{\circ}_{p,m}}{R} \cdot \ln\left(\frac{T}{T_0}\right) \qquad (3)$$

where a and b are adjustable parameters. Absolute vapor pressures of the naproxens and the resulting correlation for $\ln(p_i/p^{\circ})$ are given in Table 2 (p° = 1 Pa). T_0 in eq. (3) is the reference temperature T = 298 K and R is the gas constant. The sublimation enthalpy was calculated from equation:

$$\Delta^{g}_{cr}H^{\circ}_{m}(T) = -b + \Delta^{g}_{cr}C^{\circ}_{p,m} \cdot T \qquad (4)$$

The heat capacity differences between the gaseous and the crystalline phase $\Delta^{g}_{cr}C^{\circ}_{p,m}$(298 K) were taken from Table 1 for the calculation. Sublimation entropies at temperature T were also derived from the temperature dependence of vapor pressures using eq. (5):

$$\Delta^{g}_{cr}S^{\circ}_{m}(T) = \Delta^{g}_{cr}H^{\circ}_{m} / T + R \cdot \ln(p_i / p^{\circ}) \qquad (5)$$

The resulting enthalpy of sublimation at the reference temperature $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K) as well as the values for $\Delta^{g}_{cr}H^{\circ}_{m}(T)$ and $\Delta^{g}_{cr}S^{\circ}_{m}(T)$ are summarized in Table 2.

Table 2.

Uncertainties in the temperature adjustments of the sublimation enthalpies to the reference temperature T = 298 K were calculated assuming a standard deviation of ±16 J·mol^{-1}·K^{-1} for the crystalline phase heat capacity, $C^{\circ}_{p,m}$(cr).[25] Uncertainties of the sublimation enthalpy include uncertainties of the transpiration experimental conditions, of the vapor pressure and of the temperature adjustment to 298 K. Details on this procedure can be found in Ref. 18.

Sublimation enthalpy from the TGA method

Enthalpies of sublimation of (*RS*)- and (*S*)-naproxen measured with the TGA are given in Table 3. The relationship between the mass loss $r = dm/dt$ and the sublimation enthalpy was derived according to the equation of Clausius-Clapeyron by using the rate of mass loss dm/dt measured by the TGA (instead of the absolute pressure): [19]

$$\ln\left(\frac{dm}{dt}\sqrt{T}\right) = A' - \frac{\Delta^{g}_{cr}H^{o}_{m}(T_0) - \Delta^{g}_{cr}C^{o}_{p,m}T_0}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right) + \frac{\Delta^{g}_{cr}C^{o}_{p,m}}{R}\ln\left(\frac{T}{T_0}\right)d \qquad (6)$$

With a constant A' which includes parameters that are specific for our setup but which is independent from the substance studied. T_0 is the reference temperature T = 298 K.

Table 3.

Thermodynamics of fusion

The melting temperatures and enthalpies of fusion of (*RS*)- and (*S*)-naproxen measured by DSC in Rostock and Magdeburg are given in Table 4 in comparison to literature data. Values of the fusion enthalpies measured are referred to the melting temperature T_{fus}. The experimental enthalpies of fusion have been adjusted to T = 298 K by:[23]

$$\Delta^{l}_{cr}H^{o}_{m}(T_{fus}/\mathrm{K}) - \Delta^{l}_{cr}H^{o}_{m}(298\,K) = \left(0.75 + 0.15\cdot C^{o}_{p,m}(\mathrm{cr})\right)\cdot\left[(T_{fus}/K) - 298\,K\right] - \left(10.58 + 0.26\cdot C^{o}_{p,m}(\mathrm{liq})\right)\cdot\left[(T_{fus}/K) - 298\,K\right] \qquad (7)$$

where $C^{\circ}_{p,m}$(cr) and $C^{\circ}_{p,m}$(liq) are the isobaric molar heat capacities of the solid and the liquid naproxens (given in Table 1). The adjusted molar enthalpies of fusion, $\Delta^{l}_{cr}H^{\circ}_{m}$(298 K), are summarized in Table 4. Uncertainties in the temperature adjustment of fusion enthalpies from T_{fus} to the reference temperature given in Table 4 are estimates and amount to 30 % of the total adjustment.[25] In addition Table 4 summarizes the determined enthalpies of fusion, sublimation and vaporization at 298 K.

Table 4.

Discussion

Absolute vapor pressures of naproxens

Measured vapor pressures of (*RS*)- and (*S*)-naproxen via the transpiration method are similar but still distinguishable especially at low temperatures (see Fig. 3) where vapor pressures of the enantiomer are slightly higher in comparison to the racemic compound. Literature data[26] are available for (*S*)-naproxen only and they surprisingly disagree dramatically with the results of this work.

Figure. 3.

Sublimation enthalpies of naproxens

Sublimation enthalpies $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K) of (*RS*)- and (*S*)-naproxen are collected in Table 3. The experimental result published for (*S*)-naproxen in Ref. 26 was adjusted to the reference temperature using equations (3) and (4) and is given in Table 3 for comparison. It shows that the sublimation enthalpy of the racemate is 6.2 ± 2.2 kJ·mol^{-1} larger compared to the enantiomer. The experimental $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K)-values for both naproxens derived from the two different measurement methods (transpiration and TGA) are in a good agreement within experimental uncertainties. A mean average $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K)-value for each chiral species is given in Table 3 which can be recommended for further thermochemical calculations. The uncertainty of the sublimation enthalpy was taken as the weighting factor.

Fusion enthalpies of naproxens

The DSC-measurements of enthalpies of fusion for the naproxens have been a popular endeavor in the past.[20,26,28-33] A collection of $\Delta^{l}_{cr}H^{\circ}_{m}(T_{fus})$ from literature results as well as from own measurements can be found in Table 4. Measurements performed in this study are hardly distinguishable from the literature values within the limits of experimental uncertainties. The available data on the fusion enthalpies of both naproxens are remarkably consistent and are close to the level of 32 kJ·mol^{-1} for both chiral species. A mean average value was calculated by taking the experimental uncertainty of the fusion enthalpy as the weighting factor and adjusted to the reference temperature using eq. (7) (see Table 4, column 3). The averaged $\Delta^{l}_{cr}H^{\circ}_{m}$(298 K)-values can be recommended for further thermochemical calculations.

Vaporization enthalpies and internal consistency of the phase change enthalpies of naproxens

Sublimation enthalpies $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K) and fusion enthalpies $\Delta^{l}_{cr}H^{\circ}_{m}$(298 K) evaluated in this work for both naproxens need to be tested for internal consistency before recommending for thermochemical calculations. Such checks can be performed according to the general relationship:

$$\Delta^{g}_{cr}H^{\circ}_{m} = \Delta^{g}_{l}H^{\circ}_{m} + \Delta^{l}_{cr}H^{\circ}_{m} \quad (8)$$

provided that all enthalpies in eq. (8) are referred to the same temperature. Resulting vaporization enthalpies can be found in Table 4 along with the sublimation and fusion enthalpies used for their calculation.

The sublimation enthalpy values are difficult for any kind of interpretation because they include two non-equal contributions from the vaporization and from fusion enthalpy as it can be seen in eq. (8). In contrast, the vaporization enthalpies willingly obey the additivity rules,[18] as well as it can be involved in different types of structure-property correlations.

In order to establish validity of the $\Delta^{g}_{cr}H^{\circ}_{m}$(298 K) results evaluated in this study eq. (8) was used in combination with the $\Delta^{l}_{cr}H^{\circ}_{m}$(298 K)-values to obtain vaporization enthalpies for the naproxens. The resulting vaporization enthalpies are then compared to different $\Delta^{g}_{l}H^{\circ}_{m}$(298

K)-values coming from two additional independent methods, the group-additivity method and the gas-correlation chromatography.[35]

4.4.1. Validation of vaporization enthalpy of naproxen using the group-additivity Method

The group-additivity (GA) method is admittedly an empirical tool to prove experimental results for consistency or estimate missing values with a reasonable accuracy.[36,37] The Benson`s methodology[36] was adjusted for the prediction of vaporization enthalpies in our previous work.[37,38] The group-additivity values (GAVs) required to calculate $\Delta_l^g H_m^\circ$(298 K) of the naproxens are collected in Table S3. In order to enhance quality of the $\Delta_l^g H_m^\circ$(298 K) prediction we decided not to collect the naproxen molecule from GAVs. It seemed to be more convenient to start with the similar shaped model compound 1-naphthaleneacetic acid (see Figure 4), where reliable data on sublimation[27] and fusion enthalpy[34] are available. The vaporization enthalpy $\Delta_l^g H_m^\circ$(298 K) = 96.3 ± 2.1 kJ·mol^{-1} was derived using eq. 8 (see Table 4, column 6).

Figure 4.

Starting from this molecule and GAVs given in Table S3 we estimated vaporization enthalpy of naproxen as the sum:

$\Delta_l^g H_m^\circ$(298 K, naproxen) = $\Delta_l^g H_m^\circ$(298 K, 1-naphthaleneacetic acid) - C-$(C)_2(H)_2$ + C-$(C)_3$(H) + C-(C)$(H)_3$ + ΔH(H → OCH_3) = 111.8 kJ·mol^{-1}

Admittedly, the GA-method is not able to differ between the enantiomer and the racemic compound. However, our estimate from GA $\Delta_l^g H_m^\circ$(298 K, naproxen) = 111.8 kJ·mol^{-1} is very close to the $\Delta_l^g H_m^\circ$(298 K, *RS*-naproxen) = 110.7 ± 2.8 kJ·mol^{-1} derived from the combination of experimental sublimation and fusion enthalpies. Such good agreement can be considered as an evidence of internal consistency of the experimental data measured in this work.

4.4.2. Validation of vaporization enthalpy of naproxen using the correlation-GC analysis.

The correlation-GC-method[35,38] (CGC) correlates the gas-chromatographical behaviour (retention time t_r) of a compound of interest with the retention times of some parent compounds with known enthalpies of vaporization. The retention times are used for calculation of enthalpies of transfer from solution to the gas phase, $\Delta^{g}_{sol}H^{\circ}_{m}$. The linear relationship between $\Delta^{g}_{sol}H^{\circ}_{m}$ and $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) for structurally related compounds provides a possibility for obtaining the vaporization enthalpy of the compound of interest, provided that all $\Delta^{g}_{sol}H^{\circ}_{m}$-values used were measured in the same conditions. The accuracy of the predictions depends mostly on the accuracy of the $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) of the reference compounds. Reliable results are usually derived when the reference compounds are structurally similar and from the same chemical family.

Experimental $\Delta^{g}_{sol}H^{\circ}_{m}$ -values for (*S*)-naproxen and the reference compounds benzoic acid, 4-ethylbenzoic acid, 4-ethoxybenzoic acid, and 1-naphthaleneacetic acid were reported by Maxwell and Chickos[33] and they are listed in Table S2. Vaporization enthalpies of the reference compounds have been evaluated in our recent work[39]. In this work we recalculated correlations developed by Maxwell and Chickos[33] using our new experimental results on $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) for benzoic acid, 4-ethylbenzoic acid, 4-ethoxybenzoic acid (see Table S2). The following equation for the estimation of vaporization enthalpy of (*S*)-naproxen was obtained:

$$\Delta^{g}_{l}H^{\circ}_{m}(298\ \mathrm{K}) = 1.1 \times \Delta^{g}_{sol}H^{\circ}_{m} + 35.0 \qquad R^2 = 0.830 \qquad (9)$$

Using $\Delta^{g}_{sol}H^{\circ}_{m}$ of (*S*)-naproxen from Ref. 33 (see Table S2), the enthalpy of vaporization of (*S*)-naproxen, $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) = 109.3 ± 5.0 kJ·mol^{-1}, was estimated. It should be mentioned that the reliability of the sublimation enthalpy of (*S*)-naproxen obtained from eq. 9 is not high for a comparison due to the low correlation factor, R^2 = 0.803. $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) is however still within the limits of experimental uncertainties of ± 5.0 kJ·mol^{-1} and in a reasonable agreement with the enthalpy of vaporization $\Delta^{g}_{l}H^{\circ}_{m}$(298 K) calculated via eq. 8 (see. Table 4). Thus, the sets of sublimation, fusion, and vaporization enthalpies for (*RS*)- and (*S*)-naproxen seem to possess an internal consistency.

Summary and conclusions

A detailed experimental analysis of the phase transition thermodynamics of the enantiopure (*S*)-naproxen and the racemic molecular compound (*RS*)-naproxen has been performed. Vapor pressures have been measured via the transpiration method. Enthalpies of sublimation have been derived from the vapor pressures and complemented for comparison by independent TGA measurements. Thermodynamics of fusion and heat capacities of the solid and the melt phase have been measured via DSC. The latter were used to adjust experimental enthalpies of sublimation and enthalpies of fusion to the reference temperature, T = 298 K. Only small differences between the enantiomer and the racemate have been observed for the measured vapor pressures with slightly higher results for the enantiomer. Measured enthalpies of sublimation from transpiration and TGA were in good agreement to earlier published transpiration results of (*S*)-naproxen. [26] Differences between the racemate and the enantiomer were found to be around 6 $kJ \cdot mol^{-1}$ after the adjustment to 298 K which is large in comparison to the very similar thermodynamics of fusion. Data sets on sublimation and fusion enthalpies have been successfully checked for internal consistency by using two independent methods, the group-additivity and the correlation-GC methods. Average values from own measurements and from literature were determined for the sublimation and fusion enthalpies of both naproxens and recommended for thermochemical calculations. This study complements available thermochemical data for (*S*)- and (*RS*)-naproxen. New accurate and consistent results of thermophysical data of both chiral species provide the basis for the computation of characteristic quantities in the ternary phase diagram (see Figure 1) which are necessary for the design of enantioselective crystallization processes.

Acknowledgements

This work has been partly supported by the Russian Government Program of Competitive Growth of Kazan Federal University.

Literature

1. Nguyen LA, He H, Pham-Huy C. 2006. Chiral Drugs: An Overview. Int J Biomed Sci 2:85-100.

2. Lorenz H and Seidel-Morgenstern A. 2014. Processes To Separate Enantiomers. Angew Chem Int Ed 53:1218-1250.

3. Collet A, Ziminski L, Garcia C and Vigne-Maeder F. 1995. Chiral discrimination in crystalline enantiomer systems: facts interpretations, and speculations. In Siegel, editor,

NATO ASI Series-Supramolecular Stereochemistry. Kluwer Academics: The Netherlands. p 91-110.

4. Polenske D, Lorenz H and Seidel-Morgenstern A. 2007. Separation of Propranolol Hydrochloride Enantiomers by Preferential Crystallization: Thermodynamic Basis and Experimental Verification. Cryst Growth Des 7:1628–1634.

5. Le Minh T, Langermann J, Lorenz H, Seidel-Morgenstern A. 2010. Enantiomeric 3-Chloromandelic Acid System: Binary Melting Point Phase Diagram, Ternary Solubility Phase Diagrams and Polymorphism. J Pharm Sci 99:4084-4095.

6. Fayzullin RR, Lorenz H, Bredikhina ZA, Bredikhin AA, Seidel-Morgenstern A. 2014. Solubility and Some Crystallization Properties of Conglomerate Forming Chiral Drug Guaifenesin in Water, J Pharm Sci 103:3176–3182.

7. Grant DJW, Higuchi T. 1990. Solubility Behavior of Organic Compounds. John Wiley and Sons: New York. p 373-378.

8. Buchholz H, Lorenz H, Seidel-Morgenstern A. 2015. Computation of solubilities for the design of enantioselective crystallization processes. Kim KJ and Lee K, editors. Proceedings BIWIC2015, 22nd International Workshop on Industrial Crystallization. Deajeon: Hanbat National University. p 196-220.

9. Tetko TV, Sushko Y, Novotarskyi S, Patiny L, Kondratov I, Petrenko AE, Charochkina L and Asiri AM. 2014. How Accurately Can We Predict the Melting Points of Drug-like Compounds? J Chem Inf Model 54:3320−3329.

10. Palmer DS, Llinàs A, Morao I, Day GM, Goodman JM, Glen RC, Mitchell JBO. 2007. Predicting Intrinsic Aqueous Solubility by a Thermodynamic Cycle. Mol Pharm 5:266-279.

11. Otero-de-la-Roza A, Huynh Cao B, Price IK, Hein JE, Johnson ER. 2014. Predicting the Relative Solubilities of Racemic and Enantiopure Crystals by Density-Functional Theory. Angew Chem Int Ed 53:7879-7882.

12. Otero-de-la-Roza A and Johnson ER. 2012. A benchmark for non-covalent interactions in solids. J Chem Phys 137:054103.

13. Reilly AM and Tkatchenko A. 2013. Understanding the role of vibrations, exact exchange, and many-body van der Waals interactions in the cohesive properties of molecular crystals. J Chem Phys 139:024705.

14. Parlouer P. 1987. Simultaneous TG-DSC: a new technique for thermal analysis. Thermochim Acta 121:307-322.

15. Ditmars DA, Ishihara S, Chang SS, Bernstein G. 1982. Measurement of the relative enthalpy of pure a-Al2O3 (NBS heat capacity and enthalpy Standard Reference Material No. 720) from 273 to 1173 K. J Res Nat Bur Stand 87:159-163.

16. Robie RA, Hemingway B. 1972. Calorimeters for Heat of Solution and Low-Temperature Heat Capacity Measurements. Geological Survey Professional Paper 755.

17. Verevkin SP, Emel'yanenko VN. 2008. Transpiration method: vapour pressures and enthalpies of vapourization of some low-boiling esters. Fluid Phase Equilibr 226:64-75.

18. Verevkin SP, Sazonova AY, Emel'yanenko VN, Zaitsau DH, Varfolomeev MA, Solomonov BN, Zherikova KV. 2015. Thermochemistry of halogen-substituted methylbenzenes. J Chem Eng Data 60:89-103.

19. Verevkin SP, Ralys RV, Zaitsau DH, Emel'yanenko VN, Schick C. 2012. Express thermo-gravimetric method for the vaporization enthalpies appraisal for very low volatile molecular and ionic compounds. Thermochim Acta 538:55-62.

20. Neau SH, Bhandarkar SV and Hellmuth EW. 1997. Differential Molar Heat Capactities to Test Ideal Solubility Estimations. Pharm Res 14:601-605.

21. Leclercq M, Collet A, Jacques J. 1976. Etude des melanges d'antipodes optiques—XII: Mesure de la stabilite des racemiques vrais. Tetrahedron 32:821-828.

22. Chickos JS, Hosseini S, Hesse DG, Liebman JF. 1993. Heat capacity corrections to a standard state: a comparison of new and some literature methods for organic liquids and solids. Struct Chem 4:271-277.

23. Chickos JS, Acree WE. 2002. Enthalpies of sublimation of organic and organometallic compounds. 1910-2001. J Phys Chem Ref Data 31:537–698.

24. Risch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery Jr. JA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. 2004. Gaussian 03, Revision C.02. Wallingford: Gaussian, Inc.

25. Gobble C, Chickos JS, Verevkin SP. 2014. Vapour pressures and vaporisation enthalpies of a series of dialkyl phthalates by correlation gas chromatography. J. Chem. Eng Data 59:1353-1365.

26. Perlovich GL, Kurkov SV, Kinchin AN, Bauer-Brandl A. 2004. Thermodynamics of solutions III: comparison of the solvation of (+)-naproxen with other NSAIDs. Euro J Pharm Biopharm 57:411-420.

27. Roux MV, Temprado M, Notario R, Verevkin SP, Emel'yanenko VN, Demasters DE, Liebman JF. 2004. The energetics of naphthalene derivatives, III: phenylacetic acid and the isomeric 1- and 2-naphthylacetic acids. Mol Phys 102:1909-1917.

28. Manimaran T, Stahly GP. 1993. Optical purification of profen drugs. Tetrahedron: Asymmetry 4:1949–1954.

29. Braun DE, Ardid-Candel M, D'Oria E, Karamertzanis PG, Arlin JB, Florence AJ, Jones AG and Price SL. 2011. Racemic naproxen: A Multidisciplinary Structural and Thermodynamic Comparison with the Enantiopure Form. Cryst Growth Des 11:5659-5669.

30. Claramonte MDC, Vialard APV, Vilchez FG. 1993. An application of regular solution theory in the study of the solubility of naproxen in some solvents used in topical preparations. Int J Pharm 94:23-30.

31. Wassvik CM, Holmén AG, Bergström CAS, Zamora I, Artursson P. 2006. Contribution of solid-state properties to the aqueous solubility of drugs. Euro J Pharm Sci 29:294-305.

32. Zhou CR, Shi XH, Wang HF, Jiang, DG. 2011. Thermal decomposition and the non-isothermal decomposition kinetics of DL-2-naproxen. Journal of Chemical Engineering of Chinese Universities 25:442-446.

33. Maxwell R, Chickos J. 2012. An examination of the thermodynamics of fusion, vaporization, and sublimation of ibuprofen and naproxen by correlation gas chromatography. J Pharm Sci 101:805-14.

34. Acree WE. 1991. Thermodynamic properties of organic compounds: enthalpy of fusion and melting point temperature compilation. Thermochim Acta 189:37-56.

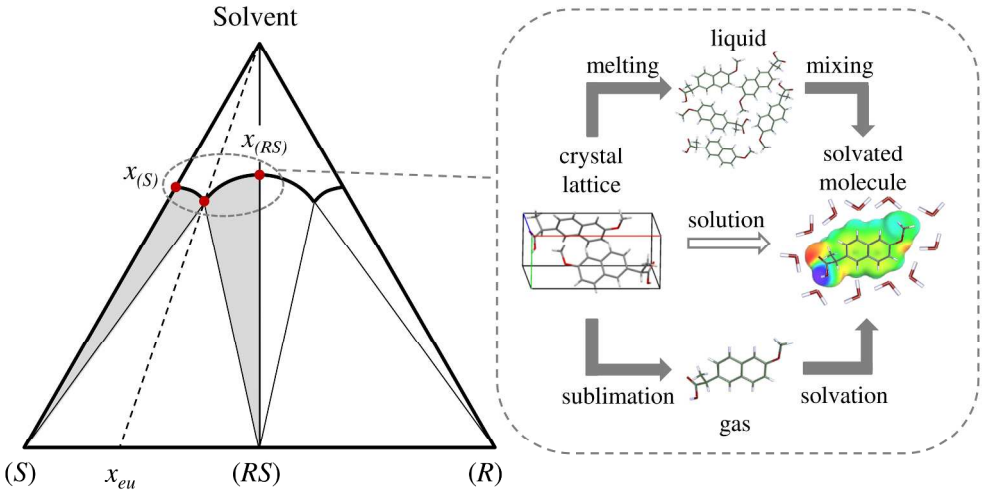
35. Verevkin SP, Heintz A. 1999. Determination of Vaporization Enthalpies of the Branched Esters from Correlation Gas Chromatography and Transpiration Methods. J Chem Eng Data 44:1240-1244.

36. Benson SW. 1976. Thermochemical Kinetics. New York: John Wiley & Sons. p 320.

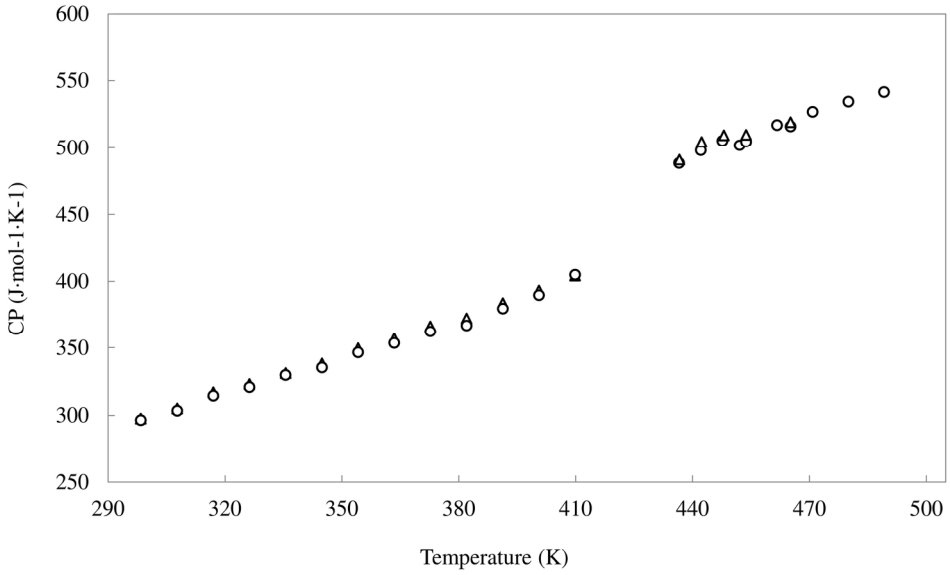
37. Verevkin SP, Emel'yanenko VN, Diky V, Muzny CD, Chirico RD and Frenkel M. 2013. New Group Contribution Approach to Thermochemical Properties of Organic Compounds: Hydrocarbons and Oxygen Containing Compounds. J Phys Chem Ref Data 42:033102.

38. Chickos JS, Hosseini S, Hesse DG. 1995. Determination of Vaporization Enthalpies of Simple Organic Molecules by Correlations of Changes in Gas Chromatographic Net Retention Times. Thermochim Acta 249:41-61.

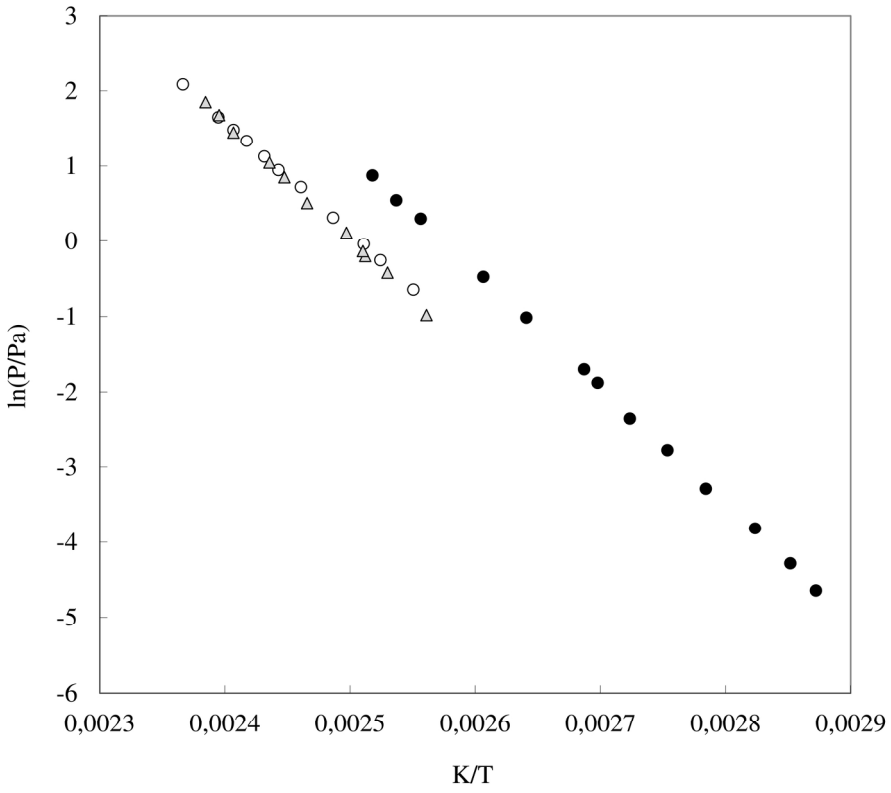
39. Jakubczyk M, Sporzyński A, Emel'yanenko VN, Varfolomeev MA, Verevkin SP. 2015. Thermodynamic properties of isomeric iso-butoxybenzoic acids: experimental and theoretical study. Thermochimica Acta 615:88–97.



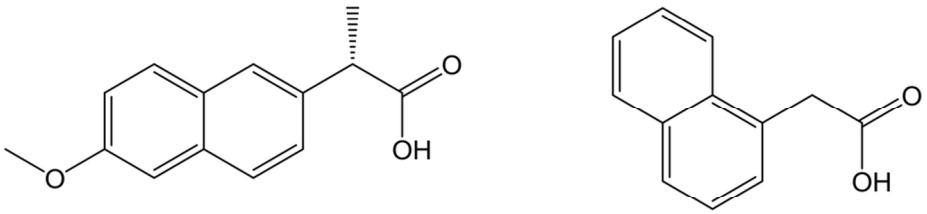
(left) Scheme of a ternary solubility phase diagram of a typical chiral substance. (right) Illustration of two thermodynamic approaches to describe solubilities.
254x147mm (300 x 300 DPI)



Heat capacities of (○) (*S*)-naproxen and (Δ) (*RS*)-naproxen measured in this work.
166x108mm (300 x 300 DPI)



Experimental vapor pressures as a function of the reciprocal temperature: (Δ) (*RS*)-naproxen transpiration, this work); (○) (*S*)-naproxen (transpiration, this work); (●) (*S*)-naproxen (transpiration Perlovich et. al. Ref. 26).
189x164mm (300 x 300 DPI)



Structures of (*S*)-naproxen and the similarly shaped 1-naphthaleneacetic acid.
90x32mm (300 x 300 DPI)

Table 1. Compilation of data on molar heat capacities $C^{\circ}_{p,m}$ (in J·K^{-1}·mol^{-1}) at 298 K as well as heat capacity differences between the solid and the gas phase (cr – crystalline solid state, liq – liquid (molten) state).

Compounds	$C^{\circ}_{p,m}$ (cr)	$C^{\circ}_{p,m}$ (liq)	$-\Delta^{g}_{cr}C^{\circ}_{p,m}$
naproxen	325.3[a]	-	49.5[b]
(*RS*)-naproxen	296.3 (1.9)[c]	373.6 (5.9)[c]	41.9[d]
(*S*)-naproxen	294.4 (5.3)[c]	351.8 (6.4)[c]	40.0[d]
1-naphthaleneacetic acid	229.2[a]	-	35.1[b]

[a]Calculated according to procedure developed by Chickos et al[22].
[b]Calculated according to procedure developed by Chickos and Acree[23].
[c]Measurements from this work along with the average standard deviations in J·K^{-1}·mol^{-1}.
[d]Calculated as the difference between $C^{\circ}_{p,m}$(g) = 254.5 J·K^{-1}·mol^{-1} and $C^{\circ}_{p,m}$(cr or liq) from this Table. $C^{\circ}_{p,m}$(g) was calculated from harmonic molecular vibrations determined by DFT. For calculations the 6-311++g(3df,3pd) basis set and b3lyp density functional has been used as implemented in Gaussian 09. [24]

Table 2. Absolute vapor pressures p, sublimation enthalpies, $\Delta^{g}_{cr}H^{\circ}_{m}$, and sublimation entropies, $\Delta^{g}_{cr}S^{\circ}_{m}$ for (*RS*)- and (*S*)-naproxen obtained by the transpiration method.

T^{a} (K)	m^{b} (mg)	$V(N_2)^{c}$ (dm^3)	$T_a{}^{d}$ (K)	Flow ($dm^3 \cdot h^{-1}$)	p^{e} (Pa)	$u(p)^{f}$ (Pa)	$\Delta^{g}_{cr}H^{\circ}_{m}$ ($kJ \cdot mol^{-1}$)	$\Delta^{g}_{cr}S^{\circ}_{m}$ ($J \cdot K^{-1} \cdot mol^{-1}$)
(*RS*)-naproxen; $\Delta^{g}_{cr}H^{\circ}_{m}$ (298 K) = 135.9 ± 1.8 $kJ \cdot mol^{-1}$								
$\ln(p/p^{\circ}) = \frac{383.38}{R} - \frac{148376.89}{R \cdot (T/\mathrm{K})} - \frac{41.9}{R} \ln\left(\frac{T/\mathrm{K}}{298.15}\right)$								
390.5	13.1	374.8	296.2	5.08	0.37	0.01	132.02	234.2
395.3	12.7	207.7	296.2	5.26	0.65	0.02	131.82	234.2
398.1	9.5	124.4	296.2	5.08	0.82	0.03	131.70	233.5
398.4	17.7	217.5	296.2	5.08	0.87	0.03	131.69	233.7
400.5	12.4	118.7	296.2	5.08	1.12	0.03	131.60	233.8
405.6	19.0	122.5	296.2	5.11	1.66	0.05	131.38	232.4
408.6	47.8	219.4	296.2	5.08	2.33	0.06	131.26	232.6
410.6	22.0	83.01	296.2	5.11	2.83	0.08	131.17	232.4
415.5	11.0	27.67	296.2	5.11	4.25	0.11	130.97	231.6
417.5	12.9	25.73	296.2	5.08	5.36	0.14	130.89	231.8
419.4	13.8	23.21	296.2	5.26	6.36	0.18	130.81	231.6
(*S*)-naproxen; $\Delta^{g}_{cr}H^{\circ}_{m}$ (298 K) = 127.3 ± 1.2 $kJ \cdot mol^{-1}$								
$\ln(p/p^{\circ}) = \frac{360.66}{R} - \frac{139192.08}{R \cdot (T/\mathrm{K})} - \frac{40.0}{R} \ln\left(\frac{T/\mathrm{K}}{298.15}\right)$								
392.1	12.5	253.0	293.2	5.50	0.52	0.02	123.51	213.9
396.2	9.5	131.2	295.9	5.40	0.77	0.02	123.35	213.5
398.3	11.5	127.0	293.2	5.61	0.96	0.03	123.26	213.4
402.2	31.0	239.9	293.2	5.61	1.37	0.04	123.11	213.0
406.4	9.8	50.65	293.2	5.43	2.05	0.06	122.94	212.8
409.4	18.8	77.52	293.2	5.43	2.57	0.07	122.82	212.1
411.3	11.2	38.94	295.9	4.81	3.07	0.08	122.74	212.1
413.7	53.8	149.8	293.2	5.50	3.80	0.10	122.65	211.9
415.5	11.4	27.64	295.9	4.81	4.41	0.12	122.57	211.6
417.6	8.7	17.70	293.2	5.47	5.20	0.14	122.49	211.3
422.6	16.8	22.26	295.9	5.47	8.06	0.23	122.29	211.0

[a]Saturation temperature with $u(T) = 0.1$ K.

[b]Mass of transferred sample condensed at $T = 273$ K.

[c]Volume of nitrogen ($u(V) = 0.005$ dm^3) used to transfer m ($u(m) = 0.0001$ g) of the sample.

[d]T_a is the temperature of the soap bubble meter used for measurement of the gas flow.

[e]Vapor pressure at temperature T calculated from the m and the residual vapor pressure at $T = 273$ K calculated by an iteration.

[f]Uncertainties were calculated with $u(p/\mathrm{Pa}) = 0.005 + 0.025(p/\mathrm{Pa})$ for pressures below 5 Pa and with $u(p/\mathrm{Pa}) = 0.025 + 0.025(p/\mathrm{Pa})$ above 5 Pa.

Table 3. Compilation of data on enthalpies of sublimation, $\Delta_{cr}^{g}H_{m}^{\circ}$ (in kJ·mol^{-1}), from own experiments and from literature.

Compounds	Method[a]	*T*-range (K)	$\Delta_{cr}^{g}H_{m}^{\circ}$ (T_{av})	$\Delta_{cr}^{g}H_{m}^{\circ}$ (298 K)	Ref
(*RS*)-naproxen	T	390.5-419.4	131.4±1.5	135.9±1.8[b]	this work
	TGA	395-425	129.8±1.7	134.5±2.0[b]	this work
				135.3±1.3[c]	
(*S*)-naproxen	T	341.2-397.2	128.3±1.2	131.0±1.6[b]	26
	T	392.1-422.6	122.9±1.5	127.3±1.2[b]	this work
	TGA	395-425	127.8±2.3	132.3±2.5[b]	this work
				129.1±0.9[c]	
1-naphthalene-acetic acid	T	-	-	**112.3±0.9**	27

[a]T = transpiration method; TGA = thermogravimetric analysis.

[b]Uncertainties of sublimation enthalpies are expressed as standard deviations. Vapor pressure available in the literature[26] were treated using eqs. 3 and 4 in order to evaluate enthalpy of sublimation at 298 K in the same way as for own results.

[c]Mean average values were calculated using the uncertainty of the experiment as a weighting factor.

Table 4. Compilation of enthalpies of phase transitions (in kJ·mol^{-1}) of (*S*)- and (*RS*)-naproxen determined in this work and from literature

Compounds	T_{fus} (K)	$\Delta^{l}_{cr}H^{\circ}_{m}$ at T_{fus}	$\Delta^{l}_{cr}H^{\circ}_{m}$ [a]	$\Delta^{g}_{cr}H^{\circ}_{m}$ [b]	$\Delta^{g}_{l}H^{\circ}_{m}$ [c]	Ref.
			298 K			
1	2	3	4	5	6	7
(*RS*)-naproxen	428.2	32.3±1.0				28
	429.0±0.3	33.2±0.3				29
	429.9±0.2	32.5±0.3[f]				this work
	429.0±0.4	32.3±0.8[g]				this work
	429.1±0.4	32.7±0.6[g]				this work
	429.0	**32.8±0.2**[d]	**24.6±2.5**	**135.3±1.3**	**110.7±2.8**	
(*S*)-naproxen	439.2	29.4±1.0				30
	428.5	31.5±0.7				20
	427.6	31.5±2.1				26
	428.8	34.2±0.9				31
	431.3±0.6	32.4±0.5				32
	429.2±0.1	31.7±0.1				29
	428.7	30.3±0.3				33
	429.1±0.1	29.9±0.5[f]				this work
	428.1±0.4	31.8±0.4[g]				this work
	429.2	**31.6±0.1**[d]	**24.1±2.3**	**129.1±0.9**	**105.0±2.5**	
1-naphthalene-acetic acid	**405.3**	**22.3±0.2**	**16.0±1.9**	**112.3±0.9**	**96.3±2.1**	34

[a]The experimental enthalpies of fusion $\Delta^{l}_{cr}H^{\circ}_{m}$ measured at T_{fus} and adjusted to 298 K according to procedure developed by Chickos and Acree.[23]

[b]Recommended values taken from Table 2.

[c]Calculated as the difference between column 5 and 4 in this Table.

[d]Mean average values were calculated using the uncertainty of the experiment as a weighting factor.

[f]Measured with a Setaram DSC 131

[g]Measured with a Mettler-Toledo 822.

Table S1. Results of the Heat Capacity Measurements for the naproxens (in $J \cdot K^{-1} \cdot mol^{-1}$) along with the resulting linear correlation using eq. 8.

(*RS*)-naproxen		(*S*)-naproxen	
T, K	C_p°	*T*, K	C_p°
Solid phase		Solid phase	
$C_p^\circ(cr) = 16.951 + 0.937 \cdot T/K$		$C_p^\circ(cr) = 18.342 + 0.926 \cdot T/K$	
298.42	297.43	298.43	296.33
307.77	304.91	307.76	303.20
317.05	316.83	317.04	314.28
326.30	322.91	326.30	320.73
335.59	330.99	335.59	329.67
344.91	338.13	344.91	335.24
354.21	349.46	354.2	346.43
363.48	356.82	363.47	353.45
372.75	366.18	372.74	362.13
382.04	372.16	382.03	366.75
391.34	383.53	391.34	379.51
400.62	393.04	400.62	389.56
409.91	404.16	409.90	404.90
Liquid phase		Liquid phase	
$C_p^\circ(liq) = 111.06 + 0.881 \cdot T/K$		$C_p^\circ(liq) = 53.995 + 0.999 \cdot T/K$	
436.65	490.78	436.59	488.28
442.36	504.36	442.15	497.91
448.06	509.32	447.71	505.21
453.79	509.75	452.13	501.74
465.20	519.09	453.79	504.55
		461.71	516.93
		465.20	515.98
		470.87	526.77
		480.03	534.39
		489.17	541.44

Table S2. Correlations between enthalpies of transfer $\Delta^{g}_{sol}H^{\circ}_{m}$ and experimental vaporization enthalpies $\Delta^{g}_{l}H^{\circ}_{m}$ of carboxylic acid derivatives (in kJ·mol^{-1}).

Compound	$\Delta^{g}_{sol}H^{\circ}_{m}$ (from Ref. 1)	$\Delta^{g}_{l}H^{\circ}_{m}$ (298 K)	Ref.
benzoic acid	39.7	75.8±0.8	2
4-ethylbenzoic acid	45.8	86.4±3.0	2
4-ethoxybenzoic acid	50.2	95.5±2.8	3
1-naphthaleneacetic acid	58.5	96.3±2.1	4
(*S*)-naproxen	67.5	-	1

Table S3. Parameters for the calculation of enthalpies of vaporization at 298 K using the group-additivity Method (in kJ·mol^{-1})[a]

Parameters	$\Delta_l^g H_m^\circ$
1-naphthaleneacetic acid[4]	96.3
$\Delta H($H→CH_3O)	12.5
C-(C)$(H)_3$	6.33
C-$(C)_2(H)_2$	4.52
C-$(C)_3$(H)	1.24

[a]Group contributions for methoxybenzoic acids were taken from Ref. 2. Increments for alkyl chains and ethers were taken from our previous study[5].

Literature

1. Maxwell R, Chickos J. 2012. An examination of the thermodynamics of fusion vaporization and sublimation of ibuprofen and naproxen by correlation gas chromatography. J Pharm Sci 101:805-14.

2. Verevkin SP, Zaitsau DH, Emel´yanenko VN, Stepurko EN, Zherikova KV. 2015. Benzoic acid derivatives: evaluation of thermochemical properties with complementary experimental and computational methods. Thermochim Acta doi:10.1016/j.tca.2015.03.026.

3. Jakubczyk M, Sporzyński A, Emel'yanenko VN, Varfolomeev MA, Verevkin SP. 2015. Thermodynamic properties of isomeric iso-butoxybenzoic acids: experimental and theoretical study. Thermochim Acta 615: 88–97.

4. Roux MV, Temprado M, Notario R, Verevkin SP, Emel'yanenko VN, Demasters DE, Liebman JF. 2004. The energetics of naphthalene derivatives. III: phenylacetic acid and the isomeric 1- and 2-naphthylacetic acids. Mol Phys 102:1909-1917.

5. Roganov GN, Pisarev PN, Emel'yanenko VN, Verevkin SP. 2005 Measurement and prediction of thermochemical properties. Improved benson-type increments for the estimation of enthalpies of vaporization and standard enthalpies of formation of aliphatic alcohols. J Chem Eng Data 50:1114-1124.