Solubility and Melting Properties of Salicylamide

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The solubility of salicylamide in methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate has been determined between (10 to 50) °C. The onset melting temperature and enthalpy of fusion has been determined by differential scanning calorimetry to 138.7 °C and 29.0 kJ·mol^{-1}, respectively. Only the monoclinic structure of salicylamide was observed at crystallization.

Introduction

The solubility of solids in solution is a vital process parameter and of interest for numerous applications. In this work, the solubility of salicylamide has been investigated in five organic solvents and water from (10 to 50) °C. The melting temperature and enthalpy of fusion of salicylamide have also been determined.

Salicylamide or 2-hydroxybenzamide is a mild analgesic with anti-inflammatory and antipyretic properties.[1] It has been used in protections against fungus in, for example, oils, soaps, and lotions.[2]

The crystal structure of salicylamide has been resolved[3−5] and only been found as a monoclinic form in which carboxy group dimerization is a key structural element, resembling the crystal structure of salicylic acid. The existence of polymorphic or solvated modifications of salicylamide has hitherto not been encountered. Limited solubility data of salicylamide are available in the literature. The molecular structure of salicylamide is presented in Figure 1.

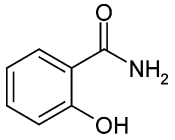

Figure 1. Salicylamide.

Experimental Section

Salicylamide was purchased from Sigma-Aldrich (purity > 99 %) and used as obtained. The solubility of salicylamide (CAS Registry No. 65-45-2) was determined gravimetrically in methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate between (10 and 50) °C. The solubility of salicylamide was determined through (2 to 9) measurements at each temperature for all solvents. The temperature was controlled by thermostat baths, and the true temperature was validated by a calibration mercury thermometer (Thermo-Schneider, Wertheim, Germany, uncertainty of ± 0.01 °C). Saturation was established from an undersaturated solution (dissolution) as well as from a supersaturated solution (crystallization through primary nucleation at a cooling rate of 1 K·min^{-1}). The solution concentration was recorded over time at constant temperature to evaluate the time needed for equilibrium to be established. Preheated syringes (10 mL) and needles were used to sample (3 to 6) mL of solution into preweighed glass vials. The mass of the saturated solution was recorded. The samples were dried in ventilated laboratory hoods at room temperature. The mass of the samples was recorded repeatedly throughout the drying process to establish the point at which no solvent remained. The samples were weighed a final time when all the solvent was evaporated. The balance used during the experimental work had an accuracy of ± 0.0001 g.

The melting temperature, t_m, and enthalpy of fusion at the melting temperature, $\Delta_{fus}H$, was determined by differential scanning calorimetry (TA Instruments, DSC 2920) at a heating rate of 2 K·min^{-1} from (10 to 170) °C. Samples were prepared in hermetic aluminum pans and purged with nitrogen at a rate of 50 mL·min^{-1}. The calorimeter was calibrated against the melting temperature and enthalpy of fusion of indium. The experimental procedure conducted for salicylamide is similar to the procedure described in previous contributions for *p*-hydroxybenzoic acid,[6] *m*-hydroxybenzoic acid,[7] and salicylic acid.[8]

Results and Discussion

The monoclinic phase of salicylamide was obtained from all solvents in the given temperature interval. Crystallization experiments with primary nucleation yielded no other modifications. The solubility of salicylamide with associated uncertainty is listed in Table 1 and presented in Figure 2.

The solubility data were fitted with a second order polynomial:

$$\ln x = A(\mathrm{K}/T)^2 + B(\mathrm{K}/T) + C \qquad (1)$$

where *A*, *B*, and *C* are solvent-specific constants. Table 2 lists the regression curve coefficients of salicylamide between (10 and 50) °C where R^2 exceeds 0.998 for all solvents.

Reproducible solubility data were obtained through dissolution and crystallization experiments from all solvents. The solubility data of salicylamide in water are similar to the data reported by Edwards et al.[9] ($x = 0.000404$ vs $x = 0.000391$ of the present work at 30 °C).

The $\Delta_{fus}H$, t_m, and entropy of fusion, $\Delta_{fus}S$, of salicylamide have been determined by DSC and are given in Table 3. The

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10.1021/je060178m CCC: $30.25
Published on Web 08/11/2006

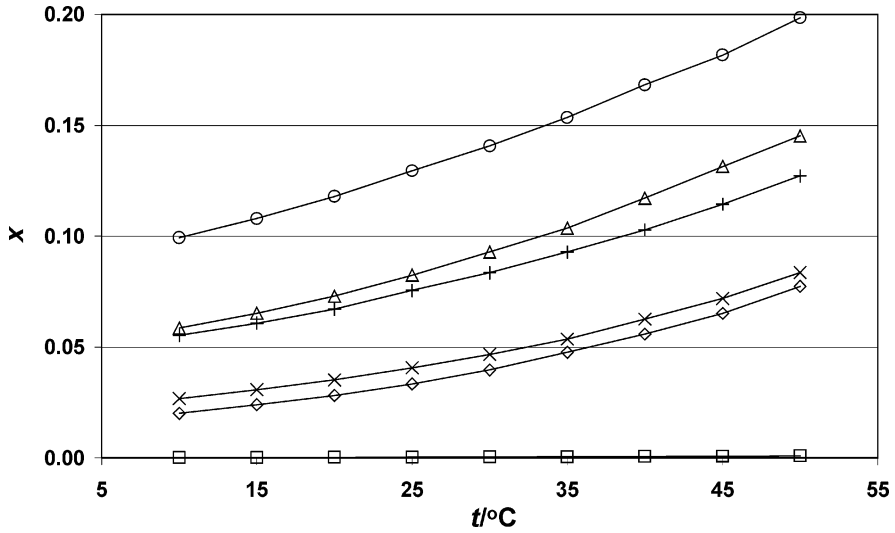

Figure 2. Mole fraction solubility, *x*, of monoclinic salicylamide in methanol; ×, acetonitrile; ◇, acetic acid; △, acetone; ○, water; □, ethyl acetate; +, between (10 and 50) °C.

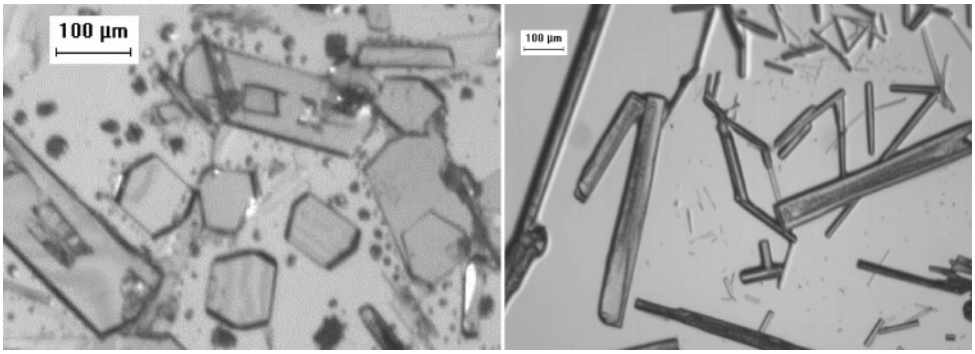

Figure 3. Left: Crystal morphology of salicylamide at 90× magnification, obtained through evaporation crystallization from ACN at room temperature. Right: Crystal morphology of salicylamide at 40× magnification, as obtained from water through evaporation crystallization at room temperature.

Table 1. Mole Fraction Solubility, *x*, of Salicylamide (1) in Six Solvents between (10 and 50) °C with 95 % Confidence Limits

t	$10^3(x_1 \pm 95\ \%$ confidence limits)					
°C	methanol	acetonitrile	acetic acid	acetone	water	ethyl acetate
10	26.72 ± 0.23	20.10 ± 0.10	58.54 ± 0.08	99.30 ± 0.41	0.160 ± 0.003	55.28 ± 0.39
15	30.69 ± 0.09	24.04 ± 0.13	65.25 ± 0.12	107.85 ± 0.23	0.205 ± 0.005	60.70 ± 0.18
20	35.12 ± 0.16	28.18 ± 0.12	72.95 ± 0.22	117.83 ± 0.24	0.261 ± 0.002	67.03 ± 0.45
25	40.60 ± 0.19	33.28 ± 0.16	82.39 ± 0.27	129.43 ± 0.31	0.317 ± 0.006	75.49 ± 1.04
30	46.66 ± 0.28	39.58 ± 0.22	92.78 ± 0.39	140.62 ± 0.33	0.391 ± 0.010	83.45 ± 0.41
35	53.58 ± 0.37	47.64 ± 0.46	103.59 ± 0.29	153.52 ± 0.38	0.485 ± 0.041	92.81 ± 0.61
40	62.51 ± 0.26	55.79 ± 0.47	117.15 ± 0.39	168.19 ± 0.43	0.594 ± 0.003	102.76 ± 0.38
45	71.91 ± 0.18	65.15 ± 0.72	131.38 ± 0.37	181.61 ± 0.48	0.757 ± 0.027	114.32 ± 0.48
50	83.59 ± 0.17	77.32 ± 0.94	145.16 ± 0.19	198.42 ± 0.74	0.974 ± 0.008	127.16 ± 0.53

Table 2. Solubility Regression Curve Coefficients of Equation 1

solvent	$10^{-5}A$	$10^{-3}B$	*C*
methanol	10.612	−9.6331	17.165
acetonitrile	7.7728	−8.2299	15.464
acetic acid	5.8647	−5.9911	11.001
acetone	3.8895	−4.1667	7.5517
water	12.693	−12.437	19.3719
ethyl acetate	6.6841	−6.3453	11.173

$\Delta_{fus}H$ determined in the present work to 29.0 kJ·mol^{-1} is higher than the value of 26.7 kJ·mol^{-1} previously reported.[10] The melting temperature of salicylamide has previously been reported to be in the range of (138 to 142) °C.[11]

Salicylamide crystallizes in the form of hexagonal plates. The crystal morphology of SA, as typically obtained from all solvents but water, is displayed in Figure 3 (left). The crystals obtained from water were found in the form of needles, as depicted in Figure 3 (right).

Table 3. Melting Properties of Salicylamide as Determined by 13 DSC Scans at 2 K/min with 95 % Confidence Limits

t_m(peak)/°C	140.0 ± 0.4
t_m(onset)/°C	138.7 ± 0.5
$\Delta_{fus}H$/kJ·mol^{-1}	29.0 ± 0.3
$\Delta_{fus}S$/J·mol^{-1}·K^{-1}	70.4 ± 0.7

Conclusions

The highest molar solubility of salicylamide was obtained in acetone, followed by acetic acid, ethyl acetate, methanol, acetonitrile, and finally water. The onset melting temperature and enthalpy of fusion were determined to be 138.7 °C and 29.0 kJ·mol^{-1}, respectively. Only the monoclinic structure was encountered in this study.

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Received for review April 27, 2006. Accepted July 11, 2006. The authors appreciate an acknowledge the Swedish Research Council for financial support.

JE060178M