Solubility and Melting Properties of Salicylic Acid

Fredrik L. Nordström[†] and Åke C. Rasmuson*

Department of Chemical Engineering and Technology, Royal Institute of Technology, SE-100 44 Stockholm, Sweden

The solubility of salicylic acid has been investigated in methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate from (10 to 50) °C. No new polymorphs or solvates of salicylic acid were found. The melting properties of salicylic acid were determined by differential scanning calorimetry. A correlation was observed between the solubility and the van't Hoff enthalpy of solution. A higher solubility was related to a lower van't Hoff enthalpy of solution. Water differed from the organic solvents in terms of solubility and its correlation to the van't Hoff enthalpy of solution. In addition, the morphology of salicylic acid crystals recrystallized from water differed from the other solvents.

Introduction

Salicylic acid, also known as ortho-hydroxybenzoic acid or 2-hydroxybenzoic acid, was used as early as 400 B.C. as an analgesic and is naturally prevalent in willow leaves, as well as in poplar and birch trees, through its glucosides.[1] The main part of the production of salicylic acid is currently used in the manufacture of aspirin.[2] The molecular structure of salicylic acid is given in Figure 1.

As opposed to its isomers, *p*- and *m*-hydroxybenzoic acid, no polymorphism of salicylic acid has been discovered, nor have solvated modifications been encountered. The crystal structure salicylic acid is monoclinic and has been resolved by Cochran,[3] Sundaralingam and Jensen,[4] and most recently by Bacon and Jude.[5] The basic synthon of the crystal structure of salicylic acid is centrosymmetric carboxylic acid dimers. The hydroxyl group is hydrogen bonded intramolecularly to the carbonyl oxygen. This leads to a less flexible molecule and dimer and a reduced intermolecular hydrogen bonding capacity, which likely explains why the overall tendency for polymorphism and solvation is reduced.

Limited data is available on the solubility and temperature dependence of the solubility of salicylic acid. The aim of this paper is to explore the melting properties and solubility of salicylic acid in six solvents, that is, methanol, acetonitrile, acetic acid, acetone, water, and ethyl acetate in the temperature range (10 to 50) °C.

Experimental Section

The solubility of salicylic acid in six different pure solvents has been determined gravimetrically in the temperature range (10 to 50) °C, and the melting temperature and enthalpy of fusion at the melting temperature have been determined by differential scanning calorimetry.

Materials. Salicylic acid (CAS Registry Number 69-72-7) was purchased from Sigma-Aldrich, purity >99 %, and was used as obtained. The five organic solvents were purchased from VWR/Merck: methanol (HiperSolv, >99.8 %), acetonitrile (LiChroSolv, Gradient grade, >99.8 %), acetic acid (Pro Analysi, 96 %), acetone (HiperSolv, >99.8 %), and ethyl acetate (HiperSolv, >99.8 %). The water was distilled, deionized, and filtered at 0.2 μm.

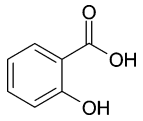

Figure 1. Salicylic acid.

Equipment and Procedures. Saturated solutions were prepared in test tubes and in 250 mL bottles. Solubilities were measured at temperatures ranging from (10 to 50) °C in 5 °C increments. 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).

Syringes (10 mL) and needles were used to sample (3 to 6) mL of solution into preweighed glass vials. Syringes and needles were preheated when necessary to prevent nucleation inside the syringes during sampling. Filters (PTFE, 0.2 μm) were utilized when the sedimentation rate was slow or when instant sampling was necessary. The filters were also preheated to exceed the solution temperature. Suspensions of water and salicylic acid were always filtered (nitrocellulose, 0.2 μm). The mass of the saturated (filtered) clear solution was recorded. Drying of samples was conducted primarily 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. Complete drying was determined as occurring when the mass of the sample remained constant over time.

Fourier transform infrared spectroscopy with attenuated total reflectance module, FTIR-ATR (Perkin-Elmer Instruments, Spectrum One), having a ZnSe window, was used for identification of the solid phase. A wavelength range of (4000 to 650) cm^{-1} and a scanning frequency of eight per sample was used for each analysis. Visual identification and imaging was carried out with a photo microscope, Olympus, SZX12, and at elevated temperatures with a hot stage microscope, Olympus BH-2. Differential scanning calorimetry (DSC), TA Instruments, DSC 2920, provided information of melting temperature and enthalpy of fusion at the melting temperature. The calorimeter was calibrated against the melting temperature and enthalpy of fusion

* Corresponding author. E-mail: Rasmuson@ket.kth.se. Fax: +46 8 105228.
[†] E-mail: Fredrik.nordstrom@ket.kth.se.

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Table 1. Mole Fraction Solubility of Salicylic Acid (1) in Six Solvents between (10 and 50) °C

	10^3x_1 (standard deviation) [number of samples]					
t/°C	methanol	acetonitrile	acetic acid	acetone	water	ethyl acetate
10	99.35 (0.40) [8]	19.17 (0.22) [6]	37.77 (0.31) [5]	146.25 (0.08) [4]	0.156 (0.010) [12]	109.08 (0.57) [3]
15	107.81 (0.12) [4]	22.29 (0.22) [8]	42.93 (0.22) [6]	156.85 (0.05) [4]	0.178 (0.010) [12]	116.47 (1.05) [9]
20	117.72 (0.18) [9]	25.49 (0.20) [7]	48.38 (0.84) [7]	168.04 (0.09) [4]	0.208 (0.012) [8]	125.14 (0.38) [8]
25	128.02 (0.26) [11]	29.44 (0.31) [5]	54.93 (0.60) [8]	179.24 (0.11) [4]	0.247 (0.020) [14]	135.71 (0.74) [10]
30	139.37 (0.43) [8]	34.43 (0.19) [5]	62.54 (0.69) [10]	191.85 (0.24) [6]	0.304 (0.025) [15]	145.17 (1.12) [10]
35	150.53 (0.25) [6]	38.96 (0.38) [4]	71.11 (0.05) [5]	202.38 (0.19) [5]	0.368 (0.018) [10]	156.56 (1.02) [12]
40	163.59 (0.46) [8]	45.30 (0.05) [2]	80.54 (0.66) [7]	215.04 (0.38) [4]	0.452 (0.018) [15]	167.52 (1.50) [10]
45	176.81 (0.36) [7]	52.42 (0.34) [6]	091.82 (0.45) [6]	228.01 (0.32) [6]	0.553 (0.015) [10]	179.88 (1.69) [9]
50	191.68 (0.35) [5]	59.37 (0.89) [11]	104.24 (0.36) [6]	241.28 (0.24) [4]	0.682 (0.018) [8]	192.15 (1.90) [9]

of indium. Samples, (1 to 10) mg, were heated at (1, 2, or 5) K/min from (10 to 180) °C in hermetic Al pans while being purged with nitrogen at a rate of 50 mL/min. The crystal structure was determined using a Bruker-Nonius KappaCCD single-crystal X-ray diffractometer.

Equilibrium was established by dissolution to saturation of solid material as well as by crystallization to saturation in a solution originally brought into a supersaturated state. The attainment of equilibrium was confirmed by repeated measurements over time and from different mother liquors. In all dissolution experiments, an excess amount of commercial salicylic acid was partly dissolved either in glass bottles or in glass test tubes. The bottles/tubes were placed in a water bath and magnetic stirring was used at 300 rpm and 600 rpm, respectively. In the crystallization experiments, supersaturation was generated by cooling at 1 K/min until the solution nucleated spontaneously. In some experiments, the concentration of the solution was recorded for up to 2 weeks to evaluate the time required for establishment of equilibrium. This also allowed for evaluation of solid-phase stability and possible chemical degradation. The solid phase in equilibrium with the solution was analyzed by sampling suspensions of crystals and solution. The suspension samples were collected in conjunction to extracting the first and last solubility samples of the experiment. The filtered crystals were analyzed with FTIR-ATR at room temperature. IR spectra from (4000 to 650) cm^{-1} were then collected throughout the drying of the crystals until no solvent remained. Complete dryness was determined as when the obtained IR pattern remained constant over time. The filtered and dried crystals obtained from the suspension were also examined by DSC at a heating rate of 2 K/min, ranging from (10 to 180) °C.

Results

The solubility of salicylic acid with associated standard deviation is listed in Table 1. In all experiments, salicylic acid emerged only in its unsolvated monoclinic modification, as determined through FTIR-ATR, DSC, and photomicroscopy. The monoclinic structure as characterized by Cochran,[3] Sundaralingam and Jensen,[4] and Bacon and Jude[5] was confirmed identical to the phase in this study by single-crystal X-ray diffraction crystallography. The solubilities of salicylic acid in the solvents methanol, acetonitrile (ACN), acetic acid, acetone, and ethyl acetate are presented in Figure 2.

The solubility of salicylic acid was found to be very sensitive to trace amounts of water in some organic solvents. Small quantities of water gave rise to considerable solubility increases in the solvents acetonitrile, acetone, and ethyl acetate. Experimental variations observed between experiments are thus likely due to the effect of water contamination. The changing solubility of the binary solvent system of water and ACN has been investigated by Gomaa et al.[6] The mole fraction solubility of salicylic acid, *x*, in ethyl acetate at 25 °C in the present study is lower than the solubility given by De Fina et al.[7] ($x = 0.1357$ vs $x = 0.1425$).

Salicylic acid crystallized from water differed from the organic solvents by a significantly lower solubility and altered crystal morphology. The solubility of salicylic acid in water is listed in Table 1 and depicted in Figure 3 together with data of Apelblat and Manzurola.[8]

Salicylic acid crystallizes as needles in all solvent but form peculiar hollow tubes with square cross-sectional areas from water, as illustrated in Figure 4. In addition, these crystals exhibited the unusual quality of being able to adsorb water either inside the tubes or on the surface of the crystals (due to this property of the crystals, the gravimetrically conducted solubility analysis suffered from difficulties). Thus, the primary source of error of the solubility study in water stems from water adsorbed on salicylic acid crystals.

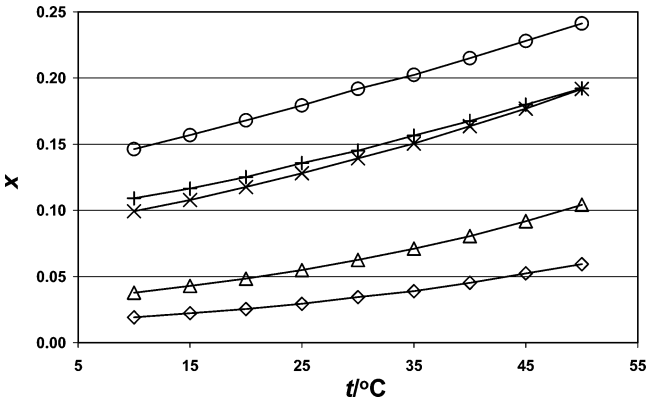

Figure 2. Mole fraction solubility, *x*, of salicylic acid in methanol, ×; acetonitrile, ◇; acetic acid, △; acetone, ○; and ethyl acetate, +, between (10 and 50) °C.

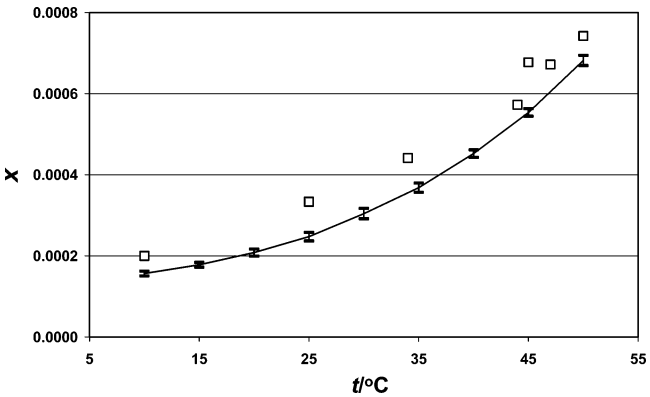

Figure 3. Mole fraction solubility, *x*, of salicylic acid in water at (10 to 50) °C with 95 % confidence limits. Solubility data of Apelblat et al.[8] is included, □.

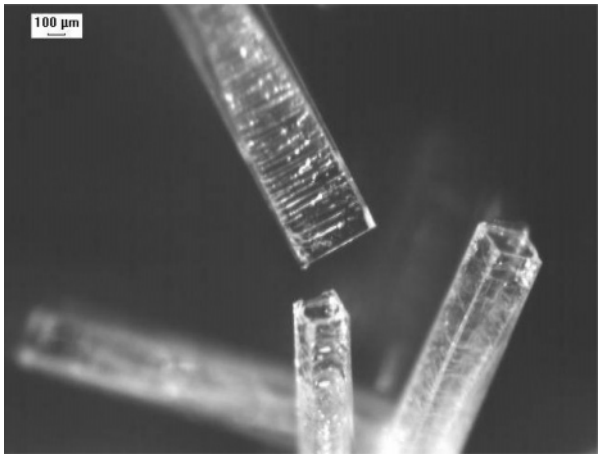

Figure 4. Microscope photo of salicylic acid (32 times magnification) recrystallized from water through evaporation crystallization at room temperature.

Table 2. Enthalpy of Fusion at the Melting Temperature and the (peak and onset) Melting Temperature of Salicylic Acid as Determined by DSC at (1, 2, and 5) K/min

	average $\Delta_{fus}H$	average peak t_m	average onset t_m
	kJ·mol^{-1}	°C	°C
	27.09	159.5	158.2
standard deviation	0.22	0.3	0.6
scans	9	14	14

Table 3. Regression Curves of Salicylic Acid in Six Solvents between (10 and 50) °C

	regression curve $\ln x = A(K/T)^2 + B(K/T) + C$		
solvent	$10^{-5}A$	$10^{-3}B$	C
methanol	2.8005	−3.3598	6.0623
acetonitrile	6.1837	−6.6941	11.975
acetic acid	8.1088	−7.6933	13.781
acetone	−0.16214	−1.0345	1.9335
water	27.341	−21.529	33.157
ethyl acetate	2.9967	−3.2949	5.6791

The enthalpy of fusion at the melting temperature, $\Delta_{fus}H$, and the melting temperature, t_m, have been determined by DSC at (1, 2, and 5) K/min. The outcome of the study is summarized in Table 2. The $\Delta_{fus}H$ value has also been determined by Pinto et al.[9] to 26.1 kJ/mol with a melting temperature of 159.3 °C and 158.7 °C (onset), respectively, Sabbah and Le[10] to 18.2 kJ/mol (at the triple point), and by Mayer et al.[11] to 14.2 kJ/mol.

Discussion

Figure 5 depicts the solubility of salicylic acid as obtained in a van't Hoff plot. The curves displayed in Figure 5 are nonlinear and well correlated with 2nd degree polynomials for their respective solvent. The regression curve coefficients are listed in Table 3. Fits of R^2 exceeding 0.9997 were obtained in all solvents.

The slope of a van't Hoff curve corresponds to the so-called van't Hoff enthalpy of solution (sometimes referred to as the apparent enthalpy of solution), $\Delta^{vH}_{soln}H$, through

$$\Delta^{vH}_{soln}H = -R\cdot\text{slope} \qquad (1)$$

The $\Delta^{vH}_{soln}H$ value reflects the temperature dependence of solubility and is different from the (calorimetric) enthalpy of solution.[12] The relation between solubility and $\Delta^{vH}_{soln}H$ of salicylic acid at 30 °C is given in Figure 6.

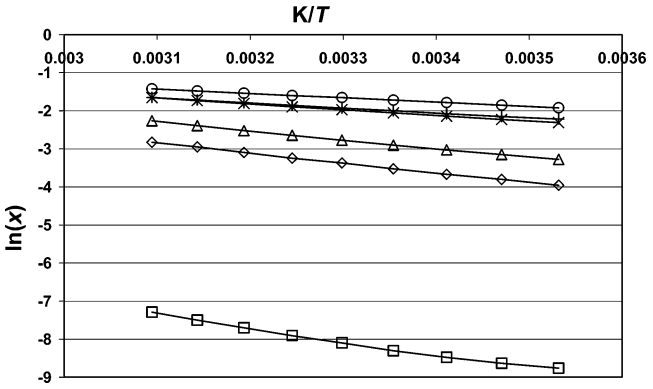

Figure 5. van't Hoff plot of salicylic acid in methanol, ×; acetonitrile, ◇; acetic acid, △; acetone, ○; water, □; and ethyl acetate, +, from (10 to 50) °C.

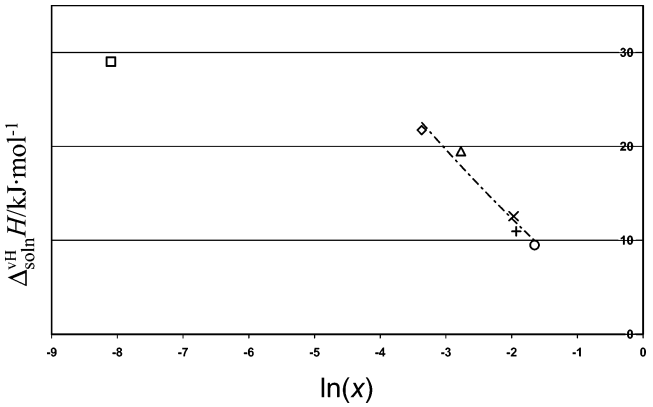

Figure 6. Mole fraction solubility and van't Hoff enthalpy of solution of salicylic acid at 30 °C, in methanol, ×; acetonitrile, ◇; acetic acid, △; acetone, ○; water, □; and ethyl acetate, +.

Table 4. Regression Curves Coefficients of eq 2 of Salicylic Acid between (10 and 50) °C

t/°C	α	β
10	0.0651	−4.67
15	0.136	−4.82
20	0.195	−5.03
25	0.270	−5.24
30	0.383	−5.40
35	0.466	−5.66
40	0.617	−5.83
45	0.787	−6.04
50	0.912	−6.38

A marked correlation between solubility and $\Delta^{vH}_{soln}H$ was found between all solvents except water. It has been shown in previous work with *p*-hydroxybenzoic acid[12] and *m*-hydroxybenzoic acid[13] that these correlations (excluding water) at each temperature can be well fitted with 2nd degree polynomial regression curves (dot−dashed curve in Figure 6)

$$\Delta^{vH}_{soln}H = \alpha \ln x^2 + \beta \ln x \qquad (2)$$

where α and β denote regression curve coefficients. The regression curve coefficients and associated fits are listed in Table 4.

Overall, fits are obtained where R^2 exceeds 0.906. Fits of higher R^2 are obtained at lower temperatures. The trend is attributed to solution properties solely as solid-state properties are constant at constant temperature.

The behavior of salicylic acid in water deviates from the organic solvents in Figure 6. The lower solubility is not

compensated sufficiently by a higher van't Hoff enthalpy of solution to allow salicylic acid to follow the observed trend. A behavior consistent with the observed correlation between the organic solvents implies a 60 times higher solubility in water at 30 °C. However, the data of the salicylic acid−water system is outside the range of the observed correlation.

The lowest solubility of salicylic acid at 30 °C was obtained in water giving $x = 3 \times 10^{-4}$, whereas the highest solubility at 30 °C amounted to $x = 0.19$ in acetone. Thus, the ratio between the highest and lowest solubility exceeds 630. The molar solubility decreases in the order of acetone, ethyl acetate, methanol, acetic acid, acetonitrile, and water. The high solubility in acetone, ethyl acetate, and methanol may relate to a fairly low cohesive energy of the solvent itself. Methanol is also capable of hydrogen bond donation and acceptance simultaneously, as well as being able to accommodate the aromatic ring of the solute. Acetic acid appears as the most ideal solvent as suggested by the predominant carboxylic acid groups of both salicylic acid and acetic acid. In acetonitrile, the affinity for salicylic acid is reduced. Acetonitrile cannot provide hydrogen bond donation but is only capable of hydrogen bond acceptance. Consequently, the solute−solvent affinity is not fully developed.

Salicylic acid exhibits a very low solubility in water as compared with the organic solvents. The aromatic ring of the solute induces an increased structuring of the surrounding water, which leads to an unfavorable decrease of entropy. Moreover, the cohesive energy of water itself is high as substantiated through the high boiling point and density. In addition, salicylic acid in water deviated from the organic solvents in terms of the correlation between solubility and the temperature dependence of solubility (i.e., the van't Hoff enthalpy of solution).

Conclusions

No new polymorphs or solvates were found of salicylic acid as investigated in six solvents between 10 °C and 50 °C. The solubility of salicylic acid varied considerably with solvent, indicative of nonideal behavior. A correlation between different solvents at constant temperature was observed by plotting the van't Hoff enthalpy of solution vs ln x. Higher solubility was related to a lower van't Hoff enthalpy of solution at all temperatures. Salicylic acid in water differed significantly from the organic solvents in terms of solubility, van't Hoff enthalpy of solution, and through the crystal morphology.

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