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Solubility of Paracetamol in Pure Solvents

Roger A. Granberg and Åke C. Rasmuson*

Department of Chemical Engineering and Technology, Royal Institute of Technology, SE-10044 Stockholm, Sweden

The solubility of paracetamol (4-hydroxyacetanilide) in 26 solvents in the temperature range from −5 to +30 °C is reported. Paracetamol has a very low solubility in nonpolar and chlorinated hydrocarbons such as toluene and carbon tetrachloride whereas the solubility is very high in solvents of medium polarity such as *N*,*N*-dimethylformamide, dimethyl sulfoxide, and diethylamine. Paracetamol is soluble in alcohols, but the solubility decreases with an increase in the length of the carbon chain in the *n*-alcohol homologous series (methanol to 1-octanol). The solubility of paracetamol in water is much lower than in other polar solvents such as the alcohols. The ideal solubility of paracetamol is calculated, and the activity coefficient in the saturated solutions is estimated.

Introduction

Solubility data of bioactive compounds have a broad application and importance in the pharmaceutical industry. A variety of pure solvents, including water, and solvent mixtures (e.g., binary and ternary mixtures) can usually be employed in a particular crystallization process during the manufacturing of pharmaceuticals (Grant and Higuchi, 1990).

Paracetamol (PA) is an important analgesic and antipyretic agent. It is also used as an intermediate in the manufacture of azodyes and photographic chemicals.

Solubility studies on paracetamol in organic solvents have been carried out by, e.g., Romero et al. (1996) (in water, ethanol, and ethyl acetate) and Subramanyam et al. (1992) (in methanol, ethanol, propanol, and butanol) at 25 °C. Grant et al. (1984) determined the solubility of PA in water in the range from 5 to 70 °C.

In the present work, solubility data for paracetamol in 26 different pure solvents, spanning a wide range of polarity, are reported in the temperature range −5 to +30 °C.

Experimental Section

The 25 solvents listed in Table 1 and paracetamol (Astra Production Chemicals AB, fine powder of pharmaceutical grade, 100.3% on dry basis determined as specified by the European Pharmacopé) were used without further purification. The water used was distilled, deionized, and filtered (0.2 μm).

The experimental setup consists of a thermostatic water bath standing on a serial magnetic stirrer. Erlenmeyer flasks (250 cm^3) with a Teflon-coated magnetic stirrer were filled with an excess of PA in a solvent (Table 1). The flasks were placed in the thermostat bath and agitated for at least 72 h at each temperature. The temperature was kept within ±0.02 °C of the desired temperature and was checked with a Pt-100 resistance thermometer. The Pt-100 thermometer used was calibrated against a calibrated mercury precision thermometer (Thermo-Schneider, Wertheim, Germany) having an uncertainty of ±0.01 °C. After the equilibration, excess PA was allowed to settle for at least 4 h with no agitation. A sample of the clear saturated solution (approximately 10 cm^3) was transferred with a preheated syringe into a previously weighed sample vial with mass m_v. The vials had Teflon septums to prevent solvent evaporation during the weighing procedure. The mass of the sample vial with the saturated solution, m_{vs}, was measured. (m_v and m_{vs} both denote masses without the Teflon septum.) Then, the septums are removed and the solvent was allowed to evaporate in an air oven at 40 °C for approximately 1 week for solvents where the boiling point is below 120 °C. The drying of solvents having a boiling point >120 °C was performed at 40 °C in a vacuum oven. With only the solid residue remaining in the sample vials, the temperature is raised to 105 °C, and after 3 days the vials were placed in a desiccator to attain room temperature. Then the constant "dry residue" mass, m_{vdr}, was determined. The solubility, expressed in g of solute/kg of solvent, was calculated by eq 1.

$$C_S = 10^3(m_{vdr} - m_v)/(m_{vs} - m_{vdr}) \quad (1)$$

The state of saturation was approached from both supersaturation and undersaturation; i.e., equilibrium was reached by cooling (supersaturated case) or heating (undersaturated case) the solution to the desired temperature in the presence of excess solid phase.

The reproducibility/repeatability was determined in three different solvents (water, 2-propanol, and dimethyl sulfoxide with solubilites of 17, 135, and 1133 g of PA/kg of solvent, respectively) by cooling a solution to 30 °C in the presence of excess solid phase and taking three solubility samples. The solution was then cooled to 20 °C before it was heated to 30 °C, and three new samples were withdrawn. As can be seen in Table 3, the solubility was not affected by whether equilibrium was approached from an undersaturated or from a supersaturated solution. The uncertainty due to temperature measurements, water bath stability, and weighing is estimated to be 0.15%. Samples from the clear solution were taken at the bottom, in the middle, and near the top of the flask. No differences were found, showing that that the solutions were homogeneous. Filtered (0.2 μm) samples were also taken, showing that that there were no particles remaining in the clear solution.

* To whom correspondence should be addressed. E-mail: rasmuson@ket.kth.se.

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Table 1. Solubility, C_S, Given in g of Paracetamol/kg of Solvent, of Paracetamol in Different Solvents at 30 °C with the Corresponding Standard Deviation (s.d.) and the Number of Samples (n)[a]

solvent	C_S	s.d.	n	γ_S
water	17.39	0.02	7	43.23
methanol (Merck, p.a.)	371.61	0.73	5	1.23
ethanol (Kemetyl AB, >99.5%)	232.75	0.31	4	1.35
1,2-ethanediol (Merck, purum)	144.30	4.10	2	1.60
1-propanol (Merck, p.a.)	132.77	0.21	4	1.78
2-propanol (Merck, p.a.)	135.01	0.31	5	1.75
1-butanol (Merck, p.a.)	93.64	0.31	2	2.04
1-pentanol (Merck, p.a.)	67.82	0.22	2	2.35
1-hexanol (Merck, p.a.)	49.71	0.96	4	2.75
1-heptanol (Sigma, p.a.)	37.43	0.24	4	3.20
1-octanol (Merck, p.a.)	27.47	0.30	3	3.87
acetone (Merck, p.a.)	111.65	0.37	7	2.17
2-butanone (Merck, p.a.)	69.99	0.39	4	2.77
4-methyl-2-pentanone (Merck, p.a.)	17.81	0.54	3	7.66
tetrahydrofuran (JT Baker, p.a.)	155.37	3.95	4	1.30
1,4-dioxane (Merck, p.a.)	17.08	0.44	3	9.06
ethyl acetate (Merck, p.a.)	10.73	0.10	5	14.39
acetonitrile (Merck, p.a.)	32.83	0.13	5	10.13
diethylamine (Sigma, 98%)	1316.90	5.05	2	0.23
N,*N*-dimethylformamide (Merck, purum)	1012.02	10.43	3	0.27
dimethyl sulfoxide (Riedel-De Haën, p.a.)	1132.56	38.18	5	0.24
acetic acid (Merck, p.a.)	82.72	3.34	3	2.81
dichloromethane (Merck, p.a.)	0.32		1	503.58
chloroform (Riedel-De Haën, p.a.)	1.54		1	73.71
carbon tetrachloride (Merck, p.a.)	0.89		1	99.26
toluene (Merck, p.a.)	0.34	0.00	2	431.62

[a] Activity coefficients, γ_S, at 30 °C are calculated from eq 3. The supplier and the grade (purity) of the solvent are also given.

Table 2. Solubility, C_S, Given in g of Paracetamol/kg of Solvent, of Paracetamol in Different Solvents at Temperatures between −5 and +25 °C (Solubilities at 30 °C Are Given in Table 1) with the Corresponding Standard Deviation (s.d.) and the Number of Samples (n)

	−5 °C			0 °C			5 °C			10 °C			15 °C			20 °C			25 °C		
solvent	C_S	s.d.	n	C_S	s.d.	n	C_S	s.d.	n	C_S	s.d.	n	C_S	s.d.	n	C_S	s.d.	n	C_S	s.d.	n
water				7.21	0.06	6	8.21	0.12	2	9.44	0.07	3	10.97	0.09	2	12.78	0.05	5	14.90	0.03	4
methanol	174.48	2.35	2	191.48	4.63	3	215.09		1	239.60	0.92	2	265.43		1	297.81	1.28	4	332.11		1
ethanol	118.56		1	129.65	1.40	5	141.82		1	156.14	0.60	2	171.40		1	190.61	0.41	3	209.91		1
1-propanol	65.88		1	72.30	0.24	4	79.62		1	88.22	0.69	2	96.77		1	108.09	0.45	3	119.32		1
2-propanol	64.41	0.03	2	71.19	0.16	4	79.02		1	87.67	0.05	2	97.38		1	108.78	0.30	3	121.15		1
1-butanol	47.55		1	51.96	0.12	3	57.21		1	63.31		1	69.29		1	77.07	0.42	2	83.27		1
acetone	50.39	0.75	2	55.61	0.34	6	62.32	0.22	2	69.63	0.41	3	78.48	0.51	2	88.09	0.34	7	99.83	0.71	3
ethylacetate	4.46		1	5.27	0.20	4	5.78		1	6.42	0.06	2	7.37		1	8.52	0.05	3	9.45		1
acetonitrile	9.44		1	11.18	0.10	4	13.44		1	15.98	0.11	2	19.34		1	23.10	0.08	3	27.54		1
toluene				0.22	0.03	2	0.27		1	0.32		1	0.36		1	0.37	0.01	2	0.37	0.00	2

Table 3. Reproducibility/Repeatability Experiments of the Solubility Determinations

solvent	samples taken when cooled to 30 °C			samples taken when heated to 30 °C			C_S [g/kg]	s.d. [g/kg]	n
2-propanol	135.30	134.57	135.00	135.11	135.26	134.83	135.01	0.31	6
water	17.35	17.41	17.38	17.38	17.39	17.41	17.39	0.02	6
dimethyl sulfoxide		1070	1157	1165	1145	1126	1133	38	5

Table 4. Error Analysis of the Drying Procedure (Loss on Drying/Residue after Evaporation)

	added amounts [g] before the drying procedure			weight [g] after the drying procedure	
no.	$m_{paracetamol}$	$m_{1-octanol}$	$m_{dimethyl\ sulfoxide}$	$m_{paracetamol}$	loss/residue* [%]
1	0.5066	0	0	0.5063	0.06
2	2.4161	0	6.9635	2.4149	0.05
3	2.5329	0	3.4893	2.5309	0.08
4	0	5.4613	0		0.00*
5	0	0	6.6749		0.00*

A saturated solution of paracetamol in acetone was cooled from 30 to 20 °C, with an excess of paracetamol, and the approach to equilibrium at 20 °C was evaluated by taking samples after 2, 5, 24, 48, and 72 h. The results show that the solutions had reached equilibrium after about 5 h. Five samples were prepared where known amounts of PA and/or some selected solvents with high boiling points (1-octanol and dimethyl sulfoxide) were added (Table 4). These samples went through the same drying procedure as the solubility samples with 1 week at 40 °C, 3 days at 105 °C, and slow cooling in a desiccator. As can be seen in Table 4, the loss of paracetamol during the drying procedure is <0.08% in sample nos. 1−3. No detectable residue was found on evaporation of these pure solvents (sample nos. 4 and 5). The water content of the paracetamol used in this work, according to specifications (Astra Production Chemicals AB), is <0.1% (loss on drying at 105 °C). This value is in agreement with sample no. 1 in Table 4. On the basis of this error analysis, the overall uncertainty of the solubility measurements is estimated to be less than 1%.

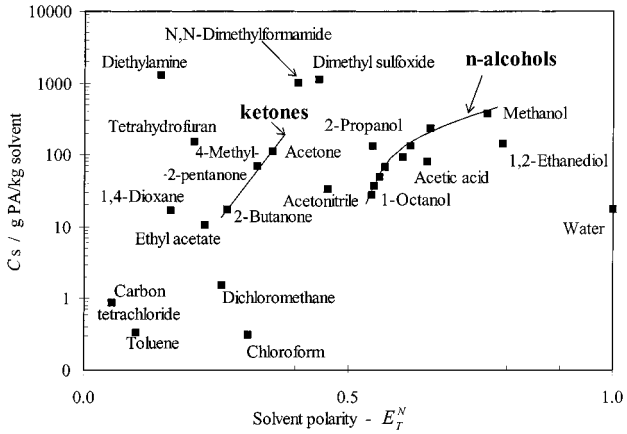

Figure 1. Solubility, C_S, of paracetamol at 30 °C versus solvent polarity (E_T^N-values, Reichardt, 1990).

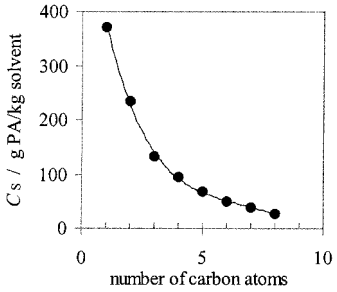

Figure 2. Solubility, C_S, of paracetamol at 30 °C in *n*-alcohols versus the number of carbon atoms.

Results and Discussion

Tables 1 and 2 list experimental results over the solubility of paracetamol in the 26 pure solvents studied. The solubility, C_S, is given as g of PA/kg of solvent (solute-free basis) and represents the average of *n* samples from the same solution. The corresponding standard deviation, s.d., for each mean value is also reported.

In Figure 1 the solubility at 30 °C (Table 1) is plotted versus solvent polarity, i.e., E_T^N-values (Reichardt, 1990). The E_T^N-value is derived from the transition energy for the longest wavelength in UV/vis spectra solvatochromic absorption band using the pyridinium-*N*-phenoxide betaine dye (Dimroth and Reichardt, 1968).

The figure shows that PA has a very low solubility (<1 g of paracetamol/kg of solvent) in nonpolar hydrocarbons (toluene) and chlorinated hydrocarbons (carbon tetrachloride), whereas in dimethyl sulfoxide, diethylamine, and *N*,*N*-dimethylformamide, the solubility is >1000 g of paracetamol/kg of solvent. The solubility of paracetamol in *n*-alcohols decreases monotonically with a decrease in polarity or, as shown in Figure 2, with an increase in the length of the carbon chain, from 370 g in methanol down to 28 g/kg of solvent in 1-octanol. In fact, if the vertical axis in Figure 1 is made linear instead of logarithmic, the solubility versus the polarity parameter becomes a straight line for the homologous *n*-alcohols. The solubility of PA in the isomers 1-propanol and 2-propanol differs only slightly. Paracetamol is more soluble in ethanol than in ethanediol. The solubility also decreases with an increase in the length of the carbon chain for the ketones (acetone, 2-butanone, and 4-methyl-2-pentanone). The solubility of PA in water is much lower than that in other polar solvents such as the alcohols. Figure 3 shows how the solubility increases with increasing temperature.

The results on the solubility in water (0−30 °C) are in good agreement with data reported by Grant et al. (1984)

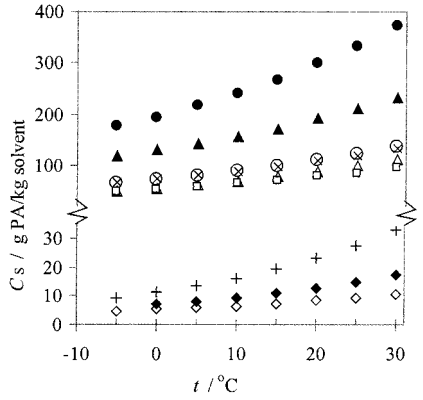

Figure 3. Solubility, C_S, of paracetamol versus temperature in ●, methanol; ▲, ethanol; ×, 1-propanol; ○, 2-propanol; △, acetone; □, 1-butanol; +, acetonitrile; ◆, water; ◇, ethyl acetate.

and Romero et al. (1996). The results in the present work on the solubility in alcohols, e.g., in ethanol at 25 °C (C_S = 209.9), are higher than the values reported by Romero et al. (1996) (C_S = 187.9) or Subramanyam et al. (1992) (C_S = 166.4), whereas the solubility in ethyl acetate (C_S = 9.4) is lower than the value reported by Romero et al. (1996) (C_S = 12.6). These differences may be due to the purity of the paracetamol and/or the solvents used, where, e.g., small amounts of water in ethanol significantly increase the solubility (Prakongpan and Nagai, 1984).

Two polymorphic forms of paracetamol are generally mentioned in the literature: a monoclinic form, which is the usual pharmaceutical material (with melting points about 170 °C), and an orthorhombic form (with melting points about 157 °C) (Di Martino et al., 1996). The orthorhombic undergoes an endothermic transition to the monoclinic form at about 87 °C (Grant et al., 1984), which is above the range of temperatures used in the present work, implying that it is unlikely that paracetamol is undergoing any polymorphic transitions during the solubility determinations. Furthermore, equilibrated crystals (from the solubility determinations) and the original crystals (the pharmaceutical material) were found to give identical X-ray powder diffraction patterns and identical behavior under DSC (i.e., melting points and enthalpies of fusion), showing no polymorphic changes.

Activity Coefficients

In a saturated solution, the chemical potential of the solute in the solution is equal to that of the solute in the pure solid state, and hence the fugacity in the two phases is equal. A suitable standard state for our purposes is the solute as a pure supercooled liquid at the same temperature (T) as the solution in question, i.e., a Raoult's law type of standard state. Based on rigorous thermodynamics, the activity of the pure solute in the solid state (a_S^{solid}) can be expressed as (Walas, 1985)

$$\mathrm{d}\ln a_S^{solid} = \frac{\Delta H_{tp}^f + \int_{T_{tp}}^{T}(C_{p,l} - C_{p,s})\,\mathrm{d}T}{RT^2}\,\mathrm{d}T - \frac{V_l - V_s}{RT}\,\mathrm{d}P \qquad (2)$$

where ΔH_{tp}^f is the enthalpy of fusion at the triple point T_{tp} and R is the gas constant. The difference ($C_{p,l} - C_{p,s} = \Delta C_p$), between the heat capacity of the hypothetical supercooled liquid form $C_{p,l}$ and the heat capacity of the crystalline form $C_{p,s}$, is often assumed to be relatively insensitive to temperature (Walas, 1985; Grant and Higuchi, 1990). Usually the last term on the right-hand side, in which P is pressure

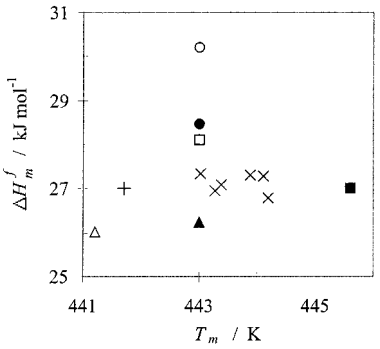

Figure 4. Enthalpy of fusion (ΔH^f_m) at the melting point (T_m) of solid paracetamol determined by differential scanning calorimetry (×, present work; ○, Grant et al. (1984); ●, Fairbrother (1974); □, Burger (1982); +, Neau et al. (1997); ▲, Romero et al. (1996); △, Manzo and Ahamuda (1990); ■, Ohm and Lippold (1982)).

Table 5. Ideal Solubility, x^i_S, of Paracetamol between −5 and +30 °C Calculated from Eq 3 (with $\gamma_S = 1$)

t [°C]	x^i_S [mole fraction]	t [°C]	x^i_S [mole fraction]
−5	0.0497	15	0.0690
0	0.0538	20	0.0751
5	0.0584	25	0.0818
10	0.0635	30	0.0891

and $V_l - V_s$ is the difference in specific volumes of the condensed phases, is negligible, and often the triple point is very close to the atmospheric melting point (Walas, 1985). The solubility (x_S) expressed as the mole fraction of PA is related to the activity of the solute in the saturated solution by the corresponding activity coefficient (γ_S), and with the approximations described above, we derive:

$$x_S\gamma_S = a_S^{solid} = \exp\left[\frac{\Delta H^f_m}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_m}{T} - \frac{T_m}{T} + 1\right)\right] \quad (3)$$

where the subscript m designates the atmospheric melting point.

The enthalpy of fusion was determined by a Perkin-Elmer DSC-7 differential scanning calorimeter, using indium as the calorimetric standard. The mean value and the standard deviation of six measurements are (27.1 ± 0.2) kJ mol^{-1} at the melting point (T_m): (443.6 ± 0.5) K of solid PA. As shown in Figure 4, the enthalpy of fusion varies (e.g., depending on the purity of the paracetamol) in the literature from about 26 kJ mol^{-1} (Manzo and Ahamuda, 1990; Romero et al., 1996) to 30.2 kJ mol^{-1} (Grant et al., 1984). Neau et al. (1997) determined experimentally ΔC_p at the melting point for paracetamol to be (99.8 ± 2.8) J mol^{-1} K^{-1}.

By insertion of our measured enthalpy of fusion and melting point temperature and the heat capacity difference value of Neau et al. (1997) in eq 3, we may estimate the ideal solubility (x^i_S) of PA (i.e., $\gamma_S = 1$). The ideal solubility of paracetamol, between −5 and +30 °C, is given in Table 5. The experimental solubility is lower than the ideal solubility in all solvents except for dimethyl sulfoxide, diethylamine, and *N*,*N*-dimethylformamide. If the ideal solubility is compared with our measured solubilities, we may estimate the activity coefficient of the solute in the saturated solutions. Results are given in Table 1 at 30 °C and at various temperatures in Figure 5.

Because the ideal solubility only depends on temperature, the estimated activity coefficient becomes inversely proportional to the measured solubility when different solvents are compared at equal temperatures. A high activity coefficient value relates to a low solubility, as in water, and reflects that as a whole the paracetamol molecule is not very comfortable in the water environment. The alcohol group and the amide group are polar and may form hydrogen bonds to water, but the aromatic ring and the methyl group influence the structure of the surrounding water molecules to such an extent that the net result becomes a low solubility. The low activity coefficient in methanol, for example, relates to the high solubility and reflects that the entropy effects are much weaker in methanol. The activity coefficient decreases with increasing temperature in all solvents.

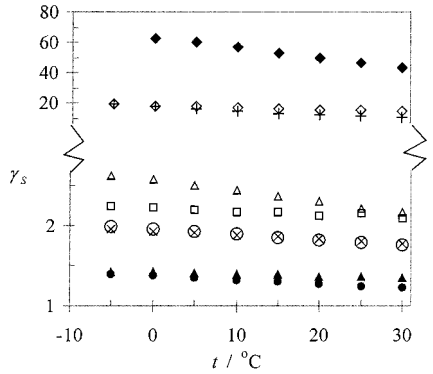

Figure 5. Activity coefficients, γ_S, of paracetamol versus temperature in ●, methanol; ▲, ethanol; ×, 1-propanol; ○, 2-propanol; △, acetone; □, 1-butanol; +, acetonitrile; ◆, water; ◇, ethyl acetate.

The contribution from the heat capacity term in eq 3 is often assumed to be minor and is neglected (Walas, 1985) even though it has been reported that this can lead to significant errors (Snow et al., 1986; Grant and Higuchi, 1990; Neau et al. 1997). Hildebrand et al. (1970) suggested that ΔC_p could be approximated with the entropy of fusion ($\Delta S^f_m = \Delta H^f_m/T_m \approx \Delta C_p$), which becomes 61.1 J mol^{-1} K^{-1} for PA using our own data. For PA these two approximations are not justified in the temperature range of the present study. At 30 °C, for example, the ideal solubility becomes lower by a factor of 2.7 if the heat capacity term is completely neglected and becomes lower by a factor of 1.5 if the Hildebrand approximation is used. This explains the much lower ideal solubilities that are reported by Barra et al. (1997), Romero et al. (1996), Subrahmanyam et al. (1992), and Manzo et al. (1990).

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