J. Chem. Eng. Data **2000,** *45,* 478−483

Solubility of Paracetamol in Binary and Ternary Mixtures of Water + Acetone + Toluene

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The solubility of paracetamol (4-hydroxyacetanilide) in binary mixtures of acetone + water and acetone + toluene and in ternary mixtures of water + acetone + toluene is reported. The temperature range is −5 to +30 °C. In acetone + water the solubility increases to a maximum at approximately 25 mass % water before decreasing to a much lower value in pure water as compared to pure acetone. In acetone + toluene the solubility decreases monotonically with increasing toluene concentration. The water content has a strong influence also in ternary mixtures. Activity coefficients in the saturated solutions are estimated.

Introduction

In the industrial crystallization of inorganic substances, water is almost exclusively used as the solvent because a large number of chemicals dissolve in it; water is readily available, cheap, and innocuous (Mullin, 1993). The manufacture of organic fine chemicals, specialty chemicals, and pharmaceuticals, however, often involves crystallization from organic solvents or mixtures of solvents. Solubility data of organic compounds in solvent mixtures are therefore of importance and have a broad application, for example, in the manufacture of pharmaceuticals (Grant and Higuchi, 1990). In addition, there is a close relation between the solubility and the crystallization (nucleation and growth) kinetics of the compound (Davey, 1982), as has been shown in the case of paracetamol (Granberg et al., 1999). Paracetamol (PA) is an important over-the-counter analgesic, and it is also used in the manufacture of azo-dyes and photographic chemicals.

The solubility of paracetamol in solvent mixtures has been measured in dioxane + water at 25 °C (Paruta and Irani, 1965), ethanol + water at 30 °C (Prakongpan and Nagai, 1984), and sucrose solutions at 25 °C (Sheth et al., 1966). Manzo and Aumada (1990) report solubility measurements in ethanol + water and in ethanol + cyclohexane between 15 °C and 50 °C.

In the present work, solubility data are reported for paracetamol in binary and ternary mixtures of water + acetone + toluene (shown in Figure 1), in the temperature range (−5 to 30) °C. This solvent system spans a large range of polarity where water, of course, is very polar, acetone is mildly polar, and toluene is nonpolar. Furthermore, the solvents are of industrial relevance. Acetone + toluene and acetone + water mixtures are miscible at all concentrations, and there is also a one-phase region of water + acetone + toluene at these temperatures. As can be seen in Figure 1, the mutual miscibility boundary (i.e. the curve that divides the single- and the two-phase regions) in water + acetone + toluene changes only slightly between 0 °C and 30 °C (Walton and Jenkins, 1923). The addition of a fourth compound to the water + acetone + toluene system can suppress or depress this curve (Hashim et al., 1989). The solubility measurements in the present study were carried out in the one-phase region, and in none of the experiments has a liquid-phase separation been observed. In a previous paper (Granberg and Rasmuson, 1999) the solubility of paracetamol in pure solvents was reported.

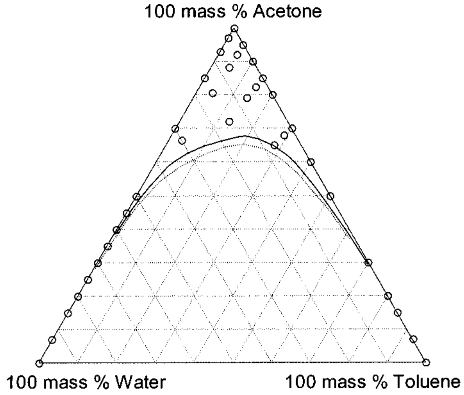

Figure 1. Investigated mixtures in the system water + acetone + toluene (○) and the mutual miscibility curves at 0 °C (solid line) and at 30 °C (dotted line) redrawn from Walton and Jenkins (1923).

Experimental Section

Acetone (Merck, p.a.), toluene (Merck, p.a.), 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, and the water was deionized, distilled, and filtered (0.2 μm).

Table 1 lists the 36 water + acetone + toluene mixtures studied, given in mass % for each solvent on a solute-free basis. There are 13 acetone + water, 11 acetone + toluene, and 9 ternary acetone + toluene + water mixtures.

The solubility was determined gravimetrically using a procedure described previously (Granberg and Rasmuson, 1999). A solution with an excess of PA was allowed to reach

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10.1021/je990272l CCC: $19.00

Table 1. Solubility (C_S)[a] of Paracetamol in the System Water + Acetone + Toluene at Temperatures between −5 °C and +30 °C with the Corresponding Standard Deviation (s.d.)[a] and the Number of Samples (*n*)

mass %			−5 °C			0 °C			5 °C			10 °C			15 °C			16 °C			20 °C			23 °C			25 °C			30 °C		
H_2O	acetone	toluene	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*	C_S	s.d.	*n*	C_S	s.d.	*n*	C_S	s.d.	*n*
100	0	0				7.21	0.06	6	8.21	0.12	2	9.44	0.07	3	10.97	0.09	2	11.32	0.07	3	12.78	0.05	5	13.98		1	14.90	0.03	4	17.39	0.02	7
93	7	0				12.68	0.04	2	14.48		1	16.92		1	20.02		1	20.78	0.14	3	23.79	0.01	2	26.31		1	28.18	0.06	2	33.35	0.02	3
85	15	0				22.15	0.03	3	25.97		1	30.98		1	37.18		1	38.46	0.65	3	44.37	0.32	2	50.6		1	53.0	0.3	2	63.8	1.2	3
80	20	0																57.7		1				73.8		1				94.7		1
75	25	0																82.2		1				103.9		1				131.8		1
70	30	0				67.3	0.0	3	77.7		1	91.2		1	107.8		1	111.9	0.9	3	127.5	0.1	2	140.8		1	150.0	0.1	2	175.8	0.1	3
65	35	0																148.0		1				181.5		1				223.8		1
60	40	0																186.8		1				225.5		1				271.9		1
55	45	0																227.5		1				270.7		1				322.5		1
50	50	0				182.6	0.6	2	204.6		1	230.3		1	259.3		1	267.9	0.6	3	290.8	1.2	2	313.4		1	327.0	0.3	2	367.4	1.8	3
30	70	0				305.9	0.6	2	328.3		1	354.6		1	384.2		1	393.2	1.4	4	417.4	0.5	3	441.0		1	454.6	1.0	3	494.6	1.2	3
15	85	0				305.8	1.1	2	323.1		1	343.6		1	366.5		1	371.5	0.9	4	392.3	0.6	4	405.3		1	420.3	1.0	2	448.3	1.2	3
7	93	0				216.2	0.7	2	228.4		1	243.4		1	260.7		1	264.4	0.7	3	280.6	1.0	3	291.0		1	302.2	0.3	3	324.4	0.8	4
3	97	0				131.4	0.6	6	141.5	0.7	2	152.6	0.6	2	165.3	1.0	2	169.8	2.5	3	180.7	1.2	4	187.9		1	197.1	1.9	3	213.8	0.6	7
0	100	0	50.39	0.75	2	55.6	0.3	6	62.3	0.2	2	69.6	0.4	3	78.5	0.5	2	80.6	1.0	3	88.1	0.3	7	94.5	1.1	2	99.8	0.7	3	111.7	0.4	7
0	95	5	45.95	0.16	2	51.3	0.5	7	57.6	0.2	2	64.2	0.5	3	72.4	0.6	2	75.1	0.9	2	81.2	0.6	7	87.7		1	91.7	0.6	3	103.0	0.4	6
0	90	10				46.45		1	51.6		1	57.7		1	64.9		1				73.1		1				82.4		1	92.6		1
0	85	15				42.50	0.47	2	47.19		1	53.0		1	60.7		1	63.3	0.4	2	67.2	0.6	3				75.7	0.5	3	84.2	0.2	2
0	80	20				37.81		1	41.85		1	46.73		1	52.5		1				59.0		1				66.4		1	74.7		1
0	70	30	26.54	0.03	2	30.06	0.82	6	33.48	0.42	2	37.28	0.66	3	41.74	0.61	2	43.79	0.69	2	47.07	0.92	7				52.8	0.8	3	58.5	0.7	6
0	60	40				21.41		1	23.64		1	26.33		1	29.46		1				33.05		1				37.08		1	41.57		1
0	50	50				15.41	0.02	2	17.02		1	18.96		1	21.20		1	21.92	0.28	3	23.82	0.09	2	25.00		1	26.56	0.09	2	29.81	0.01	2
0	30	70				4.97	0.03	2	5.51		1	6.12		1	6.83		1	6.89		1	7.66	0.04	2				8.55	0.03	2	9.52	0.01	2
0	20	80				1.74		1	1.99		1	2.28		1	2.61		1				2.98		1				3.39		1	3.84		1
0	15	85				1.18	0.00	2	1.34		1	1.50		1	1.69		1	1.64		1	1.93	0.06	2				2.12	0.04	2	2.30	0.04	2
0	7	93				0.39	0.00	2	0.42		1	0.47		1	0.55		1	0.53		1	0.68	0.03	2				0.78	0.00	2	0.93	0.01	2
0	0	100				0.22	0.03	2	0.27		1	0.32		1	0.36		1	0.29		1	0.37	0.01	2				0.37	0.00	2	0.34	0.00	2
3	92.15	4.85				128.0	0.8	2	137.1	0.5	2	147.7	0.6	2	159.6	0.6	2	164.0	0.5	4	173.4	0.5	4				189.1	1.0	3	205.2	0.6	6
3	82.45	14.55				118.1	1.0	2	125.4		1	134.7		1	145.4		1	147.8	0.4	2	157.3	0.3	3				171.6	1.0	2	185.8	0.3	2
3	67.9	29.1				98.0	0.1	2	103.8		1	110.8		1	118.9		1	120.7	0.5	2	128.3	0.1	2				138.6	0.0	2	150.1	0.1	2
7	88.35	4.65				209.5	0.7	2	222.8		1	237.5		1	253.9		1	257.5	0.7	2	272.6	0.4	3				292.6	0.6	2	314.5	0.7	2
7	79.05	13.95				199.0	0.3	2	210.4		1	223.5		1	238.0		1	241.5	0.5	2	254.1	1.0	3				272.5	1.3	2	290.3	0.4	2
7	65.1	27.9				178.0	0.4	2	182.3		1	191.2		1	204.4		1	206.0	0.0	2	217.3	0.6	3				244.2	1.1	2	264.9	0.2	2
15	80.75	4.25				299.7	0.2	2	317.5		1	337.6		1	359.6		1	364.6	0.2	2	384.3	0.9	4				410.1	0.4	2	437.8	0.3	3
15	72.25	12.75				281.4	0.3	2	298.5		1	317.7		1	338.9		1	343.7	0.4	2	362.7	0.9	4				387.8	1.1	2	415.0	0.9	3
30	66.5	3.5				300.6	0.7	2	324.5		1	350.9		1	380.4		1	386.8	1.0	3	412.1	0.8	3				448.0	0.9	3	487.6	0.3	2

[a] Units: g of paracetamol/kg of solvent.

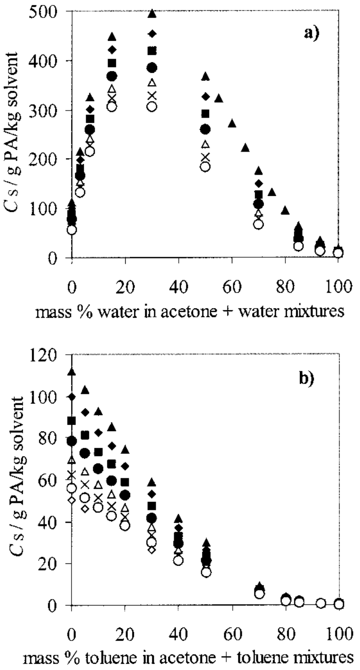

Figure 2. Solubility, C_S, of paracetamol in binary mixtures: (a) acetone + water mixtures and (b) acetone + toluene mixtures at ▲, 30; ◆, 25; ■, 20; ●, 15; △, 10; ×, 5; ○, 0; and ◇, −5 °C.

Table 2. Repeatability Experiment on the Solubility Determinations for the (0 + 95 + 5) Mixture

samples taken when cooled to 30 °C			samples taken when heated to 30 °C			C_S/ g kg^{-1}	s.d./ g kg^{-1}	*n*
102.7	102.9	103.4	102.5	103.1	103.4	103.01	0.36	6

equilibrium isothermally under agitation. Samples of clear solution were evaporated in a vacuum oven to dryness, and the constant (dry residue) mass was determined. The uncertainty in the solubility values due to uncertainties in temperature measurements, weighing procedure, and instabilities of the water bath is estimated to be 0.15%.

The repeatability was determined, in the (0 + 95 + 5) mixture, 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. Table 2 shows that there is no affect of the solution concentration whether saturation was approached from an undersaturated or from a supersaturated solution. Four reference samples were prepared where known amounts of PA and the various solvents were mixed (Table 3). These samples went through the same drying procedure as that for the solubility samples (Granberg and Rasmuson, 1999). Table 3 shows that the drying procedure works properly and that the loss of paracetamol during the drying procedure is <0.08% in all the samples.

As Figures 2 and 3 show, water has a very strong influence on the solubility of PA in acetone. The water content in the compounds used is given in Table 4. The water content in the PA used is <0.06% (sample no. 1 in Table 3). Solubility measurements in acetone pretreated with a molecular sieve (3 Å, cylindrical pellets with a diameter of 1.6 mm, Union Carbide) did not differ from solubility measurements performed in acetone as obtained from the supplier. Therefore, the acetone was used as purchased. The overall uncertainty of the solubility measurements is estimated to be <1%.

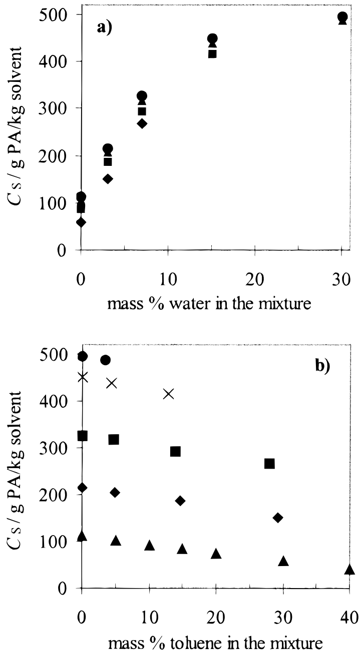

Figure 3. Solubility, C_S, of paracetamol at 30 °C in ternary mixtures: (a) influence of water content in mixtures with an acetone/toluene ratio of ●, 100/0; ▲, 95/5; ■, 85/15; and ◆, 70/30 and (b) influence of toluene content in mixtures with ●, 30; ×, 15; ■, 7; ◆, 3; and ▲, 0 mass % water. Given in mass % of each solvent, respectively, on a solute-free basis.

Results and Discussion

Table 1 lists experimental paracetamol solubilities, C_S, in the 36 water + acetone + toluene mixtures studied (the solvent composition is given in mass % water + acetone + toluene, on a solute-free basis). The solubility is given in grams of PA per kilogram 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.

The influence of solvent composition on the solubility of paracetamol in binary mixtures can be seen in Figure 2. Figure 2a shows that in acetone + water the solubility first increases strongly with increasing water concentration, passes through a maximum, and then decays to a low value in pure water. For example, at 30 °C, the solubility increases from 112 g in pure acetone up to a maximum of 500 g at approximately 25 mass % water before decreasing to 17 g per kg of solvent in pure water. Similar solubility maxima of paracetamol can be found in other aqueous mixtures, for example, ethanol + water (Prakongpan and Nagai, 1984; Romero et al., 1996), PEG400 + water (Prakongpan and Nagai, 1984), and dioxane + water (Paruta and Irani, 1965; Romero et al., 1996). The occurrence of these maxima has a complex thermodynamic basis, since they are a consequence of the influence of both enthalpy and entropy effects, and no definite explanation has been achieved (Grant and Higuchi, 1990). Binary aqueous mixtures can be classified on the basis of their thermodynamic properties, particularly their molar excess functions (Gibbs free energy (G^E), enthalpy (H^E), and entropy (S^E)). In aqueous mixtures of acetone, dioxane, and ethanol, the Gibbs excess free energy is positive and $|TS^E| > |H^E|$. It has been proposed that acetone (as well as ethanol and dioxane) acts as an overall water-structure-breaker (i.e. disrupts the three-dimensional hydrogen-bonded network) with a maximal effect at approximately 40 mass % water (Blandamer and Burgess,

Table 3. Error Analysis of the Drying Procedure (Loss on Drying)

	added amounts before the drying procedure				mass after the drying procedure	
no.	$m_{paracetamol}$/g	m_{water}/g	$m_{acetone}$/g	$m_{toluene}$/g	$m_{paracetamol}$/g	"loss"/%
1	0.5066	0	0	0	0.5063	0.06
2	0.9290	3.4598	2.9776	0	0.9287	0.03
3	0.2667	6.5022	1.1485	0	0.2665	0.07
4	0.1256	1.0233	5.2871	2.0385	0.1255	0.08

Table 4. Water Content in the Chemicals Used and the Residue after Evaporation/Drying

compound	water content	residue after evaporating	reference
paracetamol	<0.1%[a]		Astra Production Chemicals, Sweden
acetone	0.03%	<0.001%	Merck, Germany
toluene	0.01%	<0.001%	Merck, Germany

[a] The value is the loss of drying at 105 °C, which includes all volatile compounds.

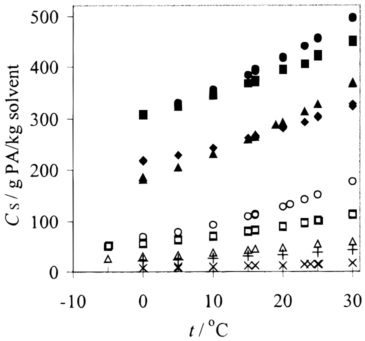

Figure 4. Solubility, C_S, of paracetamol versus temperature (●, (30 + 0 + 70); ■, (15 + 85 + 0); ▲, (50 + 50 + 0); ◆, (7 + 93 + 0); ○, (70 + 30 + 0); □, (0 + 100 + 0); △, (0 + 70 + 30); +, (0 + 60 + 40); and ×, (100 + 0 + 0), given in mass % of each of the solvents, respectively, on a solute-free basis).

Table 5. Activity Coefficients, γ_S, of Paracetamol in the System Water + Acetone + Toluene at 0 °C and 30 °C

mass %			γ_S	
water	acetone	toluene	0 °C	30 °C
100	0	0	62.7	43.2
93	7	0	33.9	21.4
85	15	0	18.3	10.6
80	20	0		6.89
75	25	0		4.78
70	30	0	5.37	3.46
65	35	0		2.62
60	40	0		2.08
55	45	0		1.69
50	50	0	1.67	1.42
30	70	0	0.82	0.87
15	85	0	0.66	0.78
7	93	0	0.80	0.91
3	97	0	1.19	1.25
0	100	0	2.57	2.11
0	95	5	2.73	2.30
0	90	10	2.96	2.50
0	85	15	3.17	2.69
0	80	20	3.48	2.96
0	70	30	4.20	3.61
0	60	40	5.63	4.84
0	50	50	7.46	6.43
0	30	70	20.9	18.1
0	20	80	56.7	42.6
0	15	85	81.4	69.2
0	7	93	236	164
0	0	100	401	432
3	92.15	4.85	1.20	1.27
3	82.45	14.55	1.26	1.35
3	67.9	29.1	1.42	1.57
7	88.35	4.65	0.81	0.93
7	79.05	13.95	0.83	0.97
7	65.1	27.9	0.88	1.01
15	80.75	4.25	0.67	0.79
15	72.25	12.75	0.69	0.81
30	66.5	3.5	0.82	0.88

1975). Investigations of the structure in acetone + water mixtures show that the ketone group in acetone tends to be partly hydrated, meaning that the dihydroxy structure $(CH_3)_2C(OH)_2$ is favored (Neto and Villaverde, 1996; Khanna et al., 1978).

In acetone + toluene mixtures, the solubility decreases monotonically with increasing toluene concentration at the temperatures studied, as shown in Figure 2b. The solubility decreases linearly with increasing toluene concentration up to approximately 50 mass % toluene in the mixture, indicating weak solute−solvent interactions (Li and Yalkowsky, 1994).

Other physical properties measured in binary acetone + toluene and acetone + water mixtures also indicate weak interactions (linear behavior with solvent composition) in acetone + toluene and strong interactions (nonlinear dependence) in acetone + water. Baldauf and Knapp (1983) measured the refractive index, the dynamic viscosity, the density, and the diffusion coefficients and found an almost linear dependence in acetone + toluene mixtures whereas in acetone + water mixtures maxima, inflection points, and minima were observed. Similar behavior is found for the surface tension (Khossravi and Connors, 1993; Onken and Hanns-Ingolf, 1990) and the solvent polarity (ET(30)-values) (Novaki and El Seoud, 1997; Mancini et al., 1995) in these mixtures.

Water also exerts a strong influence in ternary mixtures containing both acetone and toluene, as can be seen in Figure 3.

The temperature dependence of the paracetamol solubility is illustrated in Figure 4. The temperature dependence is stronger in water + acetone mixtures containing >25 mass % water. The (50 + 50 + 0) mass % mixture, for example, has a stronger temperature dependence than the (7 + 93 + 0) mass % mixture.

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 activity in both phases is equal ($a_S^{sat} = a_S^{solid}$). For our purposes, a suitable standard state is the solute as a pure supercooled liquid at the same temperature (T) as that of the saturated solution (i.e. a Raoult's law type of standard state (Walas, 1985)). The activity of the solute in the saturated solution is proportional to the solubility (x_S) expressed as mole fraction of PA, and the activity coefficient (γ_S) accounts for nonidealities:

$$a_S^{sat} = x_S \gamma_S \qquad (1)$$

Accordingly, an ideal solution is one in which the activity coefficient equals unity ($\gamma_S = 1$) and the ideal solubility x_S^i becomes $x_S^i = a_S^{sat} = a_S^{solid}$ and depends on solid-phase properties only. The estimated ideal solubility of paraceta-

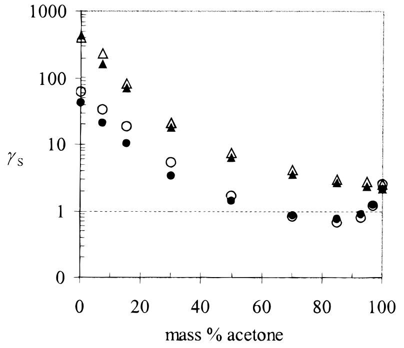

Figure 5. Activity coefficients, γ_S, of paracetamol in binary mixtures of acetone + water (at ●, 30 °C; and ○, 0 °C) and acetone + toluene (at ▲, 30 °C; and △, 0 °C).

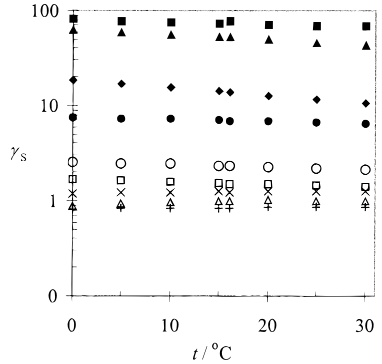

Figure 6. Activity coefficients, γ_S, of paracetamol versus temperature (■, (0 + 15 + 85); ▲, (100 + 0 + 0); ◆, (85 + 15 + 0); ●, (0 + 50 + 50); ○, (0 + 100 + 0); □, (50 + 50 + 0); ×, (3 + 92.15 + 4.85); △, (7 + 65.1 + 27.9); and +, (30 + 66.5 + 3.5), given in mass % of each of the solvents, respectively, on a solute-free basis).

mol between (−5 and 30) °C is given by Granberg and Rasmuson (1999), where the heat capacity term is also accounted for. In the present study, these ideal solubilities are used to estimate the activity coefficients for paracetamol. The calculated activity coefficients of paracetamol at 0 °C and 30 °C in various water + acetone + toluene solvent mixtures are given in Table 5.

The influence of solvent composition on the activity coefficients of paracetamol at (0 and 30) °C in acetone + water mixtures and in acetone + toluene mixtures can be seen in Figure 5. The activity coefficient is high in, for example, pure water (100 + 0 + 0) and the (0 + 15 + 85) mixture, because of the low solubility, and low in, for example, the (30 + 66.5 + 3.5) and the (7 + 65.1 + 27.9) mixtures due to the high solubility. In acetone + water mixtures there is a minimum at approximately 25 mass % water whereas in acetone + toluene mixtures the activity coefficient increases monotonically with increasing toluene concentration. The calculated activity coefficients are larger than unity in all mixtures except in mixtures containing (7, 15, and 30) mass % water.

Figure 6 shows the temperature dependence of the activity coefficient in various water + acetone + toluene solvent mixtures. The activity coefficient decreases with temperature in all solvent mixtures except for mixtures containing (3, 7, 15, and 30) mass % water. This is clearly shown in Figure 7. The activity coefficients in the (7 + 93 + 0) mixture increase with temperature, but all values are below unity. In the (50 + 50 + 0) mixture the activity coefficients decrease with increasing temperature and all values are larger than unity. This is also apparent in Figure 5, where the activity coefficient has a higher value at 0 °C than at 30 °C. An exception is acetone + water mixtures with <30 mass % water, where the opposite holds.

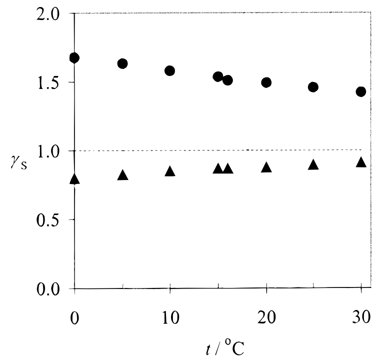

Figure 7. Activity coefficients, γ_S, of paracetamol versus temperature in the (50 + 50 + 0) mixture (●) and the (7 + 93 + 0) mixture (▲), given in mass % of each of the solvents, respectively, on a solute-free basis.

Acknowledgment

Astra Production Chemicals AB is acknowledged for providing the paracetamol used.

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Received for review October 5, 1999. Accepted January 31, 2000. The authors gratefully acknowledge the financial support of The Industrial Association for Crystallization Research and Technology (IKF) and The Swedish National Board for Industrial and Technical Development (NUTEK).

JE990272L