Solubilities of 6-Aminopenicillanic Acid and Phenoxyacetic Acid in Hydrotrope Solutions

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The solubilities of 6-aminopenicillanic acid and phenoxyacetic acid were determined at 25 °C in aqueous solutions of several hydrotropes by the weight disappearance method at different hydrotrope concentrations. Commercially available aqueous hydrotrope solutions employed were 50 mass % sodium butyl monoglycol sulfate, 40 mass % sodium cumenesulfonate, 40 mass % sodium xylenesulfonate, and 40 mass % potassium−sodium xylenesulfonate, all the hydrotrope concentration mass percentages being expressed on a mass/mass basis. At high concentrations, above the threshold hydrotrope concentration, hydrotropes enhance the solubilities of these components differently. The ternary solid−liquid phase equilibrium diagram for the 6-aminopenicillanic acid−phenoxyacetic acid−water system with sodium butyl monoglycol sulfate as a hydrotrope was constructed. Solubilities of 6-aminopenicillanic acid were also determined in the reaction product mixture with or without the 30 mass % sodium butyl monoglycol sulfate hydrotropic medium. A medium of aqueous sodium butyl monoglycol sulfate solution can be used for the better separation of 6-aminipenicillanic acid.

1. Introduction

Hydrotropes are freely water-soluble organic compounds that are capable of increasing significantly the water solubility of otherwise sparingly soluble substances at their relatively high concentrations above the threshold or critical hydrotrope concentration. They are effective at high hydrotrope concentrations in enhancing the aqueous solubility of other substances, normally otherwise sparingly soluble in water, because of the possibility of molecular solution structures probably in the form of stack-type aggregates. Most hydrotrope molecules appear to self-aggregate in aqueous solution to form organized assemblies in a stacklike fashion and solubilize the solute by a similar associative mechanism above a minimum hydrotrope concentration. Above the minimum hydrotrope concentration the solubilization rises markedly and levels off to a plateau, resulting in a sigmoidal solubility−hydrotrope concentration curve (see for example: Balasubramanian et al., 1989; Balasubramanian and Friberg, 1993; Tavare and Gaikar, 1991). The solubilizate (or solute) will therefore precipitate out on dilution with water (i.e., the original solvent) from most hydrotropic solutions. This process may be used to recover the solute in crystalline form at an improved purity, and the remaining mother liquor could be used to concentrate the hydrotrope for recycling. Such a technique will avoid the use of highly inflammable and expensive solvents as normally used in dilution crystallization and/or temperature changes and multistage operations often required in melt crystallization. The specificity in solubilization has been successfully employed for the separation of close-boiling isomeric components from binary mixtures forming simple eutectics, in some cases even at the eutectic compositions (Geetha et al., 1991; Raynaud-Lacroze and Tavare, 1993; Phatak and Gaikar, 1993; Colonia et al., 1993; Colonia and Tavare, 1994; Jadhav et al., 1995).

The present work aims at a fundamental study of the global role of hydrotropes in the selective and better separation of a component from mixtures via the solubilization and precipitation technique with particular emphasis on both the theoretical understanding of the mechanistic behavior and experimental studies to demonstrate the utility of these hydrotropes in the separation of commercially important mixtures. The separation system, a mixture of 6-aminopenicillanic acid (6-APA) and phenoxyacetic acid (PAA), was chosen to demonstrate the efficacy of commercially available hydrotropes in the separation of crystalline 6-APA from an industrial reaction mixture in a hydrotropic environment at an improved purity and quality.

6-APA, an important intermediate in the production of semisynthetic antibiotics, is basically the nucleus of the original *penicillin* molecule. 6-APA is a member of both the penicillin and β-lactum antibiotic families but surprisingly it possesses little antibiotic activity and is therefore of no direct medical use. The enzymatic hydrolysis reaction of potassium penicillin V yields 6-APA and PAA in stoichiometric amounts at near neutral pH. Conventionally, 6-APA is separated from the product reaction mixture by crystallizing it with a controlled addition of aqueous nitric acid solution up to pH $\sim$ 3.7. Frequently, the purity specification of 6-APA is rather difficult to attain in such a crystallization process, as PAA may cocrystallize as an impurity. The purpose of this study is to propose a novel technique of crystallizing 6-APA in high quality and pure crystalline form from a product reaction mixture in a hydrotropic environment. The remaining mother liquor may be used to recover crystalline PAA by dilution with water and subsequently to concentrate the hydrotrope solution for recycle. The scope of this paper is restricted to experimentally establishing thermodynamic solubility and phase relations for this separation system.

2. Solubilities of 6-APA and PAA in Hydrotropes

Initially, solubility data of 6-APA and PAA were determined in aqueous solutions of several hydrotropes by the mass disappearance method at different hydrotrope concentrations and temperatures. The mass of the disappeared material in the solution during the equilibration step was evaluated as the difference between masses of the initial solids charged and the final undissolved dry residue on filtration in order to determine the solubility. In the equilibration step, a known and excess amount of solubi-

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Table 1. Solubility Data for 6-Aminopenicillanic Acid (6-APA) and Phenoxyacetic Acid (PAA) at 25 °C

	solubility of 6-APA and PAA, g/g of water[a]							
	NaBMGS 50 (M = 220) (c_{Nc} ~ 0.2 g/g of water) (pH_{neat} = 7) (Jadhav et al., 1995)		NaCS 40 (M = 222) (c_{Nc} ~ 0.02 g/g of water) (pH_{neat} ~ 6.5−7.5)		NaXS 40 (M = 208) (c_{Nc} ~ 0.08 g/g of water) (pH_{neat} ~ 8.0−8.5)		KNaXS 40 (M = 216) (c_{Nc} ~ 0.08 g/g of water) (pH_{neat} ~ 6.5−7.5)	
hydrotrope concn, g/g of water	6-APA	PAA	6-APA	PAA	6-APA	PAA	6-APA	PAA
1.0 (neat)	0.0036	0.3890						
0.70	0.0042	0.2660						
0.667 (neat)			0.0030	0.2829	0.0020	0.1845	0.0021	0.3238
0.50	0.0037	0.2025	0.0026	0.2400	0.0018	0.1481	0.0027	0.2315
0.40	0.0041	0.1328	0.0030	0.1618	0.0016	0.1507	0.0029	0.1877
0.30	0.0037	0.0904	0.0031	0.1300	0.0025	0.0802	0.0028	0.1346
0.20	0.0031	0.0427	0.0028	0.0699	0.0027	0.0356	0.0030	0.0808
0.10	0.0033	0.0184	0.0030	0.030	0.0027	0.0191	0.0032	0.0330
0.0	0.0026	0.0111	0.0026	0.0111	0.0026	0.0111	0.0026	0.0111

[a] c_{Nc} = critical hydrotrope concentration, g/g of water. M = molecular weight.

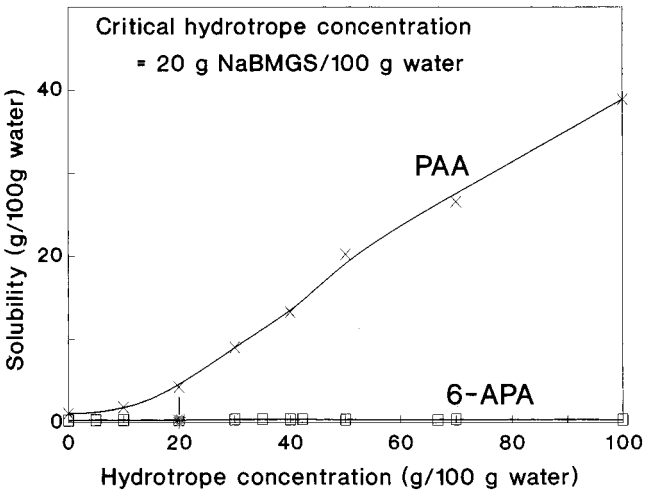

Figure 1. Typical hydrotropic solubilization curves for NaBMGS at 25 °C.

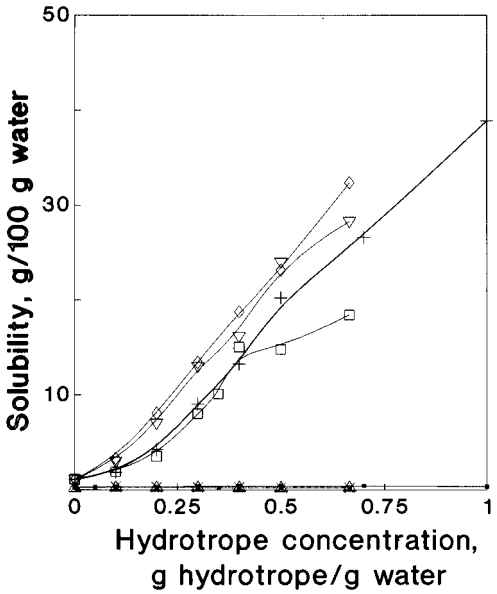

Figure 2. Solubilization curves of 6-APA and PAA for several hydrotropes. For 6-APA: (•) NaBMGS 50; (·) NaXS 40; (×) KNaCS 40; (△) NaCS 40. For PAA: (+) NaBMGS 50; (□) NaXS 40; (◊) KNaCS 40; (▽) NaCS 40.

lizate was equilibrated with the hydrotrope solution (usually about 20 mL) of known concentration for about 2 h in a magnetically stirred and jacketed vessel (about 100 mL capacity) maintained at a constant temperature of (25 ± 0.1) °C by circulating water from a constant temperature water bath. The slurry was then filtered through filter paper (Whatman No. 1), the residue on the filter paper was dried and weighed, and the differences in masses between the initial charge and the final residue were determined. The solubility data for pure components (viz. 6-APA and PAA) were empirically determined by this method in several commercially available hydrotropes [NaBMGS 50, NaCS 40, KNaCS 40, NaXS 40] at different solution hydrotrope concentrations. All hydrotrope concentration percentages were expressed in a mass/mass basis. Commercial aqueous solutions of sodium butyl monoglycol sulfate (NaBMGS 50) were supplied by Hüls (U.K.) Ltd., Milton Keynes, while all the other remaining solutions were obtained from Hickson Manro Ltd., Stalybridge. The other hydrotrope concentrations were prepared by diluting commercially available neat solutions with water. All the results are shown in Table 1 and also in Figures 1 and 2. The curves in these and subsequent figures are drawn using polynomial interpolations from the Harvard Graphics program. The estimated accuracy of the solubility values, based on error analysis and repeated observations, was within ±2%. This technique therefore yields reproducible results. In a few experiments during the development stage, a closure on component mass balance was checked and found to be satisfactory within the range of experimental errors.

Solubilities of 6-APA and PAA in water are low (~0.0025 and ~0.011 g/g of water, respectively). The solubility of PAA is considerably augmented in most hydrotropes, while that of 6-APA is not changed at all. Most hydrotrope molecules appear to self-aggregate in aqueous solution to form organized assemblies in stacklike fashion and may solubilize the solute by a similar associative mechanism above a minimum or critical hydrotrope concentration. As shown in Figure 1, the solubilization rises markedly and levels off to a plateau, resulting in a sigmoidal solubility−hydrotrope concentration curve for PAA in NaBMGS solution above the critical hydrotrope concentratio (~20 kg of NaBMGS/100 kg of water for this hydrotrope). Surface tension decreases gradually from 72 mN/m to a limiting value of ~37 mN/m at and above the critical hydrotrope concentration (Balasubramanian et al., 1989). Only the solubility of PAA is augmented rapidly with hydrotrope concentration (to ~0.39 g/g of water in neat sodium butyl monoglycol sulfate solution (NaBMGS 50 mass %) while that of 6-APA remains practically constant (~0.003−0.004 g/g of water). The hydrotrope augments the aqueous solubility of PAA by 35-fold and the relative enhancement in solubility, as defined by the ratio of solubility in neat hydrotrope to that at the critical hydrotrope concentration, is about 9. Clearly, this will have a beneficial effect in the

precipitation of 6-APA, as PAA being the most common impurity will remain in the solution. The other solubility data for PAA in Table 1 and Figure 2 show the sigmoidal curves with hydrotrope concentration with a definite critical or minimum hydrotrope concentration for each hydrotrope. These may indiate that the solubilization due to hydrotropy may be a cooperative multimolecular process.

In general, high concentrations of hydrotrope and solute are the characteristics of hydrotropic solubilization. From Figure 2, NaBMGS 50 appears promising from separation and recovery considerations and was employed in further studies. The solubility trends for the other hydrotropes confirm the previous hypothesis (Jadhav et al., 1995) that the bulkier hydrophobic and hydrophilic parts are useful in enhancement of the solubilization and are given by

$$\text{KNaCS 40} > \text{NaCS 40} > \text{NaXS 40}$$

Similar trends in the magnitude of solubilities for *m*- and *p*-aminoacetophenones with hydrotrope concentrations were observed (Jadhav et al., 1995). Thus, the size of the hydrotrope molecule appears to influence the relative solubilization of the solute. Similar studies, namely, the efficacies of a series of hydrotropes toward the same solute and the emphasis on looking at the structural features, have also been reported by Yamamoto et al. (1955) for riboflavin (vitamin B2).

The sigmoidal character in solubility−hydrotrope concentration curve may indicate that cooperative intermolecular interactions are involved in the solubilization process. The mechanistic action of hydrotropes may vary, and perhaps processes such as micellar solubilization, complexation, salting-in, dielectric constant effects, and hydrophobic interactions may be considered for possible contributions to the overall solubilization. Hydrotropy appears different from salting-in or cosolvency behavior but has some similarity with micellar solubilization. Both hydrotrope and surfactant micelles appear to form organized assemblies by self-aggregation above the minimum concentration level, the cooperation of association being stronger in the surfactant micelles. The idea of molecular aggregation is indicative of a multimolecular process rather than either a specific complexation event or a process dominated by medium effect (cosolvancy or salting in). The tensiometric behavior of most hydrotropes in aqueous solutions tends to indicate that surface tension decreases from 72 mN/m for water to a limiting value of about (35−55) mN/m for various hydrotropes. The concentration-dependent reduction in surface tension is gradual for hydrotropes as compared to the sharp drops encountered with micellar surfactants. As compared to most ionic micelles, most hydrotrope aggregates seem to provide a microenvironment that is slightly less polar and has comparable microviscosity. Although there appears to be a common assertion in the literature that hydrotropes themselves are not surface active, Balasubramanian et al. (1989) pointed out that most hydrotropes seem to attribute characteristics of micellar surfactant with a notable difference in solubilization as regards magnitude and selectivity.

6-APA is an ampholyte possessing a carboxyl group of $pK_{a1} = 2.29$ and amine group of $pK_{a2} = 4.9$ (Batchelor et al., 1961), while recently, Tewari and Goldberg (1988) reported different values ($pK_{a1} = 2.6$ and $pK_{a2} = 5.4$). In solution 6-APA behaves chemically as a base toward strong acids and as an acid toward strong bases. In solution an ampholyte of this type can exist as a combination of the three ionic species (namely, cation ($^+$HAPA), zwitterion ($^+$HAPA$^-$), and anion (APA$^-$)). The observed solubility under a given set of physical conditions (i.e., pH, ionic strength, hydrotropic environment, and temperature) is the sum of the concentrations of these ionic species. The actual concentrations of individual species are governed by the associated ionic equilibria and vary with pH and temperature. At low pH, 6-APA exists predominantly as the cation ($^+$HAPA) and as the anion (APA$^-$) at high pH. At the isoelectric point ($pH \sim pI = 0.5(pK_{a1} + pK_{a2}) = \sim 3.6$) 6-APA exists primarily as the zwitterion ($^+$HAPA$^-$) and the concentrations of the cation and anion are small but equal. Ampholytes, such as 6-APA, typically have a minimum solubility at the isoelectric point and may exist in aqueous solution as the zwitterionic form. In aqueous hydrotrope solutions there appears no possibility of self-association of these zwitterionic species and of attachment with hydrotrope solution structure. Consequently, the solubility of 6-APA is not affected by the presence of a hydrotropic environment.

3. Solubilities of 6-APA in Reaction Product Mixtures with or without a Hydrotropic Environment

In order to obtain solubility data that are pertinent to the semibatch precipitation process used in the plant and laboratory, the solubility was experimentally determined by approaching the equilibration from supersaturated conditions which simulate the precipitation process in stages. In this way the influence of time-varying solution ionic strength as a result of the semibatch nature of the precipitations is inherently accounted for. The solubilities of 6-APA in an aqueous standard reaction product solution (containing 250 mM 6-APA and 250 mM PAA buffered at pH = 7.5) used in the precipitation studies were evaluated at 20 °C with or without a hydrotropic environment. For a hydrotropic environment the initial standard solution was prepared in such a way that the final hydrotrope concentration in the solution was 30% NaBMGS hydrotrope on mass basis. Solubility variations were determined as a function of the added acid concentration and pH of the equilibrated solution.

Two liters of a 250 mM 6-APA plus 250 mM PAA standard precipitation solution was prepared by dissolving 108.15 g of 6-APA (commercial grade) and 76.08 g of PAA in 4 M ammonium hydroxide and distilled water at room temperature. The solution was then made up to 2 L and adjusted to pH = 7.4 before being filtered twice through 0.2 μm cellulose nitrate membrane filters (WCN, Whatman). While the solution was stirred in a jacketed vessel, the temperature was adjusted to 20 °C before the solution pH was adjusted to pH = 7.5 using a few drops of ammonium hydroxide.

Predetermined amounts of 2 M nitric acid, at 20 °C, were weighed into four 250 mL capacity jacketed glass vessels. The acid and standard solution densities were determined by weighing five 25 mL volume samples dispensed from a 25 mL pipet, from which the average density was determined. To each of the vessels, containing differing amounts of acid, approximately 200 mL of accurately weighed standard solution was charged. Each of the solutions was then charged with a 1 g excess of 6-APA powder and placed upon magnetic stirrers. The vessels were connected in parallel to a thermostated water bath using a peristaltic pump to circulate water through the jackets in order to control the temperature to (20 ± 0.1) °C. Vigorous stirring was established using the magnetic stirrers, and the solutions were left to reach equilibrium for 1 h. Initial screening experiments over 3 h had indicated that a period of 1 h was sufficient to attain relative equilibrium for these

Table 2. Solubility Data for 6-Aminopenicillanic Acid (6-APA) in Reaction Product Mixtures

t = 20 °C without hydrotrope			t = 10 °C without hydrotrope			t = 20 °C with hydrotrope (0.3 g of NaBMGS/g of water)		
added acid concn, mmol/kg of water	6-APA solubility, g/kg of water	pH of equilibrated soln	added acid concn mmol/kg of water	6-APA solubility, g/kg of water	pH of equilibrated soln	added acid concn mmol/kg of water	6-APA solubility, g/kg of water	pH of equilibrated soln
0.00	59.09	6.465	0.00	53.77	6.456	0.00	71.72	7.5
19.99	54.60	6.383	0.00	54.12	6.633	0.00	80.29	6.549
39.61	50.6	6.335	9.68	49.67	6.383	88.48	52.37	6.377
59.26	45.22	6.278	19.17	45.52	6.335	145.35	34.86	6.221
78.25	40.74	6.211	26.66	41.11	6.278	167.93	33.88	5.937
115.66	31.44	6.022	37.84	37.03	6.211	252.30	15.35	5.462
150.27	22.82	6.022	38.33	36.75	6.388	271.93	12.40	5.347
184.62	14.66	6.022	55.89	28.56	6.022	309.70	6.36	4.875
217.47	7.23	6.022	72.58	20.72	6.022	309.70	7.25	4.875
233.88	5.16	4.488	73.15	20.94	6.061	311.14	7.21	4.806
249.42	3.93	4.022	89.13	13.30	6.022	343.03	5.32	4.471
265.95	4.00	3.736	104.93	6.56	6.022	343.03	5.71	4.471
265.95	3.23	3.735	105.72	6.32	5.241	348.23	5.41	4.383
280.63	3.28	3.562	112.82	4.68	5.488	434.88	3.00	3.661
280.63	4.23	3.562	120.29	3.56	5.022	434.88	5.73	3.661
311.24	3.54	3.221	120.92	3.43	4.037			
311.24	5.04	3.221	128.23	2.93	3.736			
339.49	3.28	2.965	135.28	2.97	3.562			
339.49	5.09	2.965	136.39	3.43	3.496			
			149.96	3.21	3.221			
			163.51	2.97	2.965			

mixtures. Periods longer than 1 h resulted in the significant degradation of 6-APA in solution, especially at high equilibrium pH levels.

After 1 h a pH reading was taken for each solution before a 20 mL sample was taken using a syringe. This sample was filtered initially through a coarse filter of nonadsorbent cotton wool and then a 0.1 μm cellulose nitrate membrane syringe filter (Whatman SFA3). The 6-APA concentration within the sample was analyzed using a Varian 5000 HPLC with a 250 mm long and 4.6 mm diameter Supelcolsil LC-8 column. The mobile phase was a mixture of 96 vol % phosphate buffer (25.6 mM at pH 6.5) and 4 vol % methanol and set at 1.1 mL/min. A 20 μL sample loop was satisfactory and took 20 min for detection at 25 °C. The detector was programmed to operate at 215 nm for the first 6 min of analysis to detect the low sensitivity nitrate, 6-APA OIN, 8-HPA, and parahydroxy PAA components. The remainder of the analysis was carried out at 228 nm to detect 6-APA, 6-APA dimer, and PAA components. In order to provide three calibration standards ranging in the concentration from (1 to 2) mg/g of solution, 75 mg of doubly recrystallized 6-APA (99.9% purity) was dissolved in (25 to 75) g of 25.6 mM phosphate buffer. Although HPLC analysis was time-consuming, requiring elaborate sample preparation and around 1 h for complete analysis of a single sample, all samples were immediately diluted by three times on a mass basis to avoid the occurrence of further nucleation during refrigerated storage. The diluted samples were stored at 4 °C to minimize the extent of 6-APA degradation over the total analysis period, which is typically up to 12 h. All the analyses were performed on the same day without an overnight storage. Each sample was again repeatedly diluted until the concentration lay within the calibration range of (1 to 2) mg/g of solution. In the duration of the saturation period the pH probe was not placed within the vessels, as it was found that the leakage of the electrolyte significantly influenced the observed solubility. All 6-APA concentrations were evaluated on the basis of the total inert solvent, i.e. water, so as to be consistent with the time-varying solvent capacity in the subsequent semibatch precipitation experiments. This involved performing a water mass balance that accounted for both the water in the standard solution and that present in the added

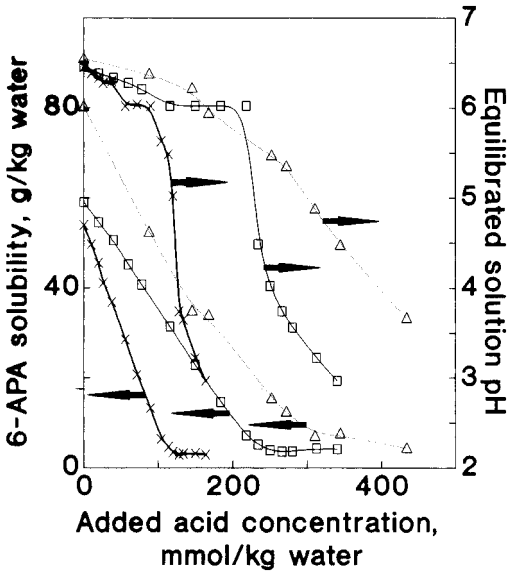

Figure 3. Variations of 6-APA solubility and solution pH with added acid concentration required in precipitation experiments with standard industrial reaction product solutions with or without hydrotrope: (□) t = 20 °C; (△) t = 20 °C with hydrotrope; (×) t = 10 °C.

diluent, i.e. dilute acid. Similar solubility measuremetns were repeated and also performed without a hydrotrope medium at 10 °C.

All the solubility data are presented in Table 2 and plotted in Figures 3 and 4 as functions of the added acid concentration and pH of the equilibrated solution, respectively. Clearly, the 6-APA solubilities in the standard reaction product solution are much higher than those in water and neat hydrotrope solutions. Also included in Figure 3 is the variation of the equilibrated solution pH. 6-APA solubility decreases rapidly first and remains practically constant both with increasing added acid concentration and with decreaing pH. Over the majority of the added acid concentration range of interest the decrease in solubility is approximately proportional to the added acid concentration, indicating that an equivalent reduction in the equilibrium concentration of 6-APA in solution is

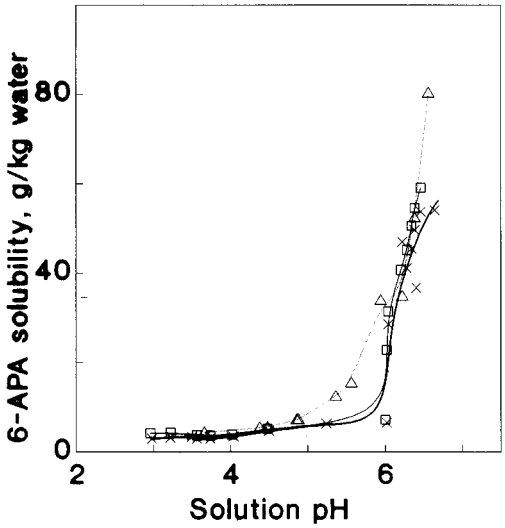

Figure 4. Variation of 6-APA solubility with solution pH for precipitation experiments with standard industrial reaction product solutions: (□) t = 20 °C; (△) t = 20 °C with hydrotrope; (×) t = 10 °C.

produced due to reaction. In both Figures 3 and 4 the solubility profiles are observed to attain a constant minimum plateau near the isoelectric point. This probably indicates that further acid added reacts with PAA instead of reacting with 6-APA. A slight increase in 6-APA solubility may be due to further dissolution. Typically, the equilibrated solution pH initially decreases slightly, remains constant around 6, and then decreases rapidly with added concentration. Some influence of temperature and hydrotrope environment of 6-APA solubility is apparent in Figure 3 but not so apparent in Figure 4. Clearly, 6-APA solubility in the reaction product solution is strongly influenced with pH over the pH range (up to ~4) used in the precipitation process. The solubility profiles attain a constant minimum plateau near the isoelectric point (pH ~ 3.6) and only a slight increase is observed with increasing added acid concentration. This probably indicates that further acid added beyond this point reacts with PAA instead of reacting with 6-APA to result in further dissolution.

6-APA displays a minimum solubility at isoelectric pH (~3.6) and increasing solubility with lower or higher pH levels. The zwitterionic species is the most stable and least soluble in water. The equilibrium concentration of the zwitterion depends weakly on temperature. At a fixed temperature, the observed variation in solubility with pH is due to the equilibrium concentration of the cation and anion. Equilibrated solution in solubility measurements is saturated with respect to the zwitterion. In the presence of H^+ in acid solution or OH^- in alkaline solutions the sparingly soluble zwitterion is converted into the more soluble anion or cation, respectively. The extent of conversion depends on the total amount of added acid/alkali and the resulting equilibrium free hydrogen ion concentration (i.e., pH). In the present study the solubility measurements and subsequent precipitation of 6-APA at pH greater than the isoelectric point is relevant. In this pH range the solubility of 6-APA is mainly contributed by the anion and zwitterion species and 6-APA acts as a weak acid. The added acid appears to react with 6-APA anions in solution to produce a relatively insoluble product in the form of the zwitterion on an equimolar basis. The amount of acid added therefore controls the residual anion concentration and hence the equilibrium hydrogen ion concentration (i.e., pH).

The influence of temperature as shown in the solubility–pH diagram (Figure 4) is relatively small. Changes in temperature may induce changes in the equilibrium ionization constant for the formation of zwitterion from the anion, but such changes appear to change only slightly the hydrogen ion concentration. The temperature does not significantly influence the zwitterion concentration. The minimum solubility is in large part indicative of the intrinsic solubility of the zwitterion. This appears generally independent of pH. The presence of hydrotrope in the standard reaction product solution increases the solubility of 6-APA, and consequently, the amount of acid that would be required to attain the minimum solubility and the corresponding pH range is more than that required without hydrotrope. The approach toward the isoelectric point is slightly slower than that without hydrotrope with the same amount of acid added.

4. Ternary Diagram

The phase diagram for the 6-APA, PAA, and water system with NaBMGS as a hydrotrope can be conveniently depicted by a terary diagram with each side of a right angle represented by one of the two components, viz. 6-APA and PAA. In addition to solubility data of the pure components (Figure 2, Table 1), solubility data for a component in the presence of the other component and hydrotrope at different concentration levels were used to construct several hydrotrope isoplethal (i.e., the same hydrotrope concentration) solubility curves. In order to cover the whole range of the composition triangle for a given aqueous NaBMGS hydrotrope solution, the three-component solutions were prepared by adding an accurately weighed excess amount of a pure component in a known undersaturated solution with respect to the other component. These solutions were equilibrated at 25 °C for 2 h in a small (~100 mL) magnetically stirred and jacketed vessel maintained at a constant temperature by circulating water from the thermostated water bath. The slurry was then filtered, and

Table 3. Solubility Data (Equilibrium Composition, % mol/mol) of Solutes in Different Aqueous Hydrotropic Solutions of Sodium Butyl Monoglycol Sulfate (NaBMGS) at 25 °C

Hydrotrope concn, g/g of water													
0.1		0.2		0.3		0.4		0.5		0.7		1.0	
6-APA	PAA	6-APA	PAA	6-APA	PAA	6-APA	PAA	6-APA	PAA	6-APA	PAA	6-APA	PAA
0.0	0.23	0.0	0.50	0.0	1.06	0.0	1.55	0.0	2.34	0.0	3.05	0.0	4.40
0.007	0.27	0.012	0.64	0.012	1.13	0.009	1.76	0.010	2.59	0.012	3.34	0.012	3.89
0.010	0.28	0.021	0.65	0.020	1.24	0.018	1.87	0.017	2.49	0.023	0.44	0.018	0.57
0.014	0.29	0.026	0.0	0.031	0.0	0.028	0.36	0.022	0.23	0.025	3.34	0.020	4.2
0.026	0.18	0.026	0.12	0.035	0.35	0.034	0.75	0.031	0.0	0.034	1.24	0.021	3.78
0.028	0.0	0.031	0.21	0.043	0.58	0.035	0.0	0.036	0.83	0.035	0.0	0.030	0.0
0.033	0.27	0.037	0.34	0.054	0.78	0.048	1.04	0.041	1.46	0.046	2.10	0.034	1.40
0.04	0.0	0.038	0.54	0.059	1.03	0.056	1.40	0.056	2.05	0.057	2.96	0.053	2.10
		0.041	0.45	0.063	1.51	0.06	2.01	0.056	2.68	0.069	3.11	0.087	3.17
												0.094	4.87

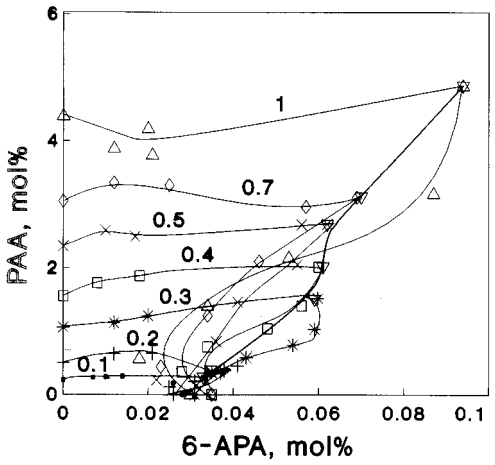

Figure 5. Ternary diagram on right-angled triangle: water−6-APA−PAA system with NaBMGS as a hydrotrope. Hydrotrope concentration, kg NaBMGS/kg of water: (•) 0,1; (+) 0.2; (∗) 0.3; (□) 0.4; (×) 0.5; (◊) 0.7; (△) 1.0; (▽) saturation with 6-APA and PAA.

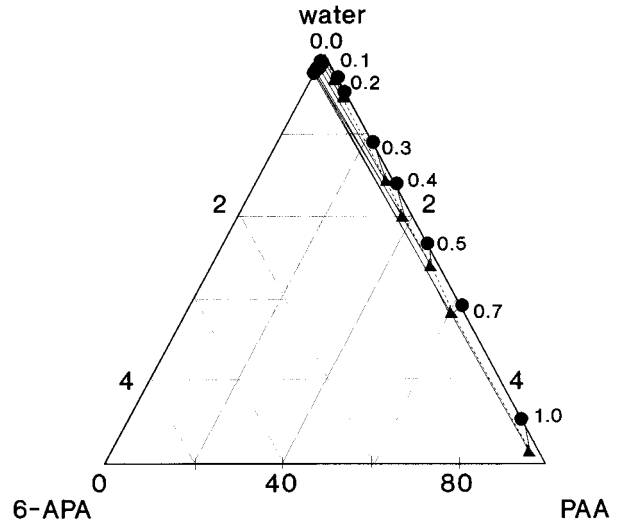

Figure 6. Ternary diagram on equilateral triangle: water−6-APA−PAA system. Saturation point: (●) single component; (▲) two component. Concentration: hydrotrope, kg NaBMGS/kg water; component, mol %.

the residue on the filter paper was dried and weighed. The filtrate and solid phase were analyzed on a Varian 5000 HPLC in order to determine the solubility and confirm the material balance constraint. The saturation concentrations were initially determined on a mass basis, and these data then converted into mole percent for the construction of the ternary diagrams. For the determination of composition of the solution which was saturated with respect to both these components in a given aqueous NaBMGS hydrotrope solution excess amounts of both solid components were added for the equilibration. Both the filtrate and solids were analyzed by the HPLC technique. It was always made sure for all the saturation experiments that the undissolved solids were well in excess of (at least 25−30%) dissolved solids. For the case of the two-component saturation experiments both components were detected in the solid residues. All the experimental results required for the construction of ternary diagrams are reported in Table 3. For the sake of clarity only the enlarged right angle apex of the ternary diagram with different scales is shown in Figure 5, the triangular section depicting seven hydrotrope isoplethal solubility curves. The two-component saturation curve was drawn through all data points at different hydrotrope concentrations using Harvard Graphics polynomial interpolations. This two-component saturation curve divides the hydrotrope *isopleths* into two sections, the left hand side curves represent the solubility of PAA as a function of 6-APA concentration in an aqueous hydrotrope undersaturated solution with respect to 6-APA, while the 6-APA solubility curves on the right are a function of PAA concentration in aqueous hydrotrope undersaturated solution with respect to PAA. As the concentration of hydrotrope increases, PAA solubilization increases without any significant influence of the presence of 6-APA, while PAA appears to change 6-APA solubilization. The same solubilization results of the water−6-APA−PAA system can be represented on an equilateral triangle. Figure 6 shows an enlarged section at the water apex of the ternary diagram depicting the same hydrotrope isoplethal solubility curves. For the sake of clarity the actual data points except single- and two-component saturation points are omitted. The two-component saturation tie line can be obtained by joining the water apex with the datapoints representing the solutions saturated with respect to both solubilizates for different hydrotrope concentrations. Clearly, with an increase in hydrotrope concentration the undersaturation regions for the components increase, more toward the PAA apex than the 6-APA apex.

5. Conclusions

The solubilities of 6-APA and PAA were determined in aqueous solutions of several hydrotropes by the weight disappearance method at different hydrotrope concentrations at 25 °C. Commercially available aqueous hydrotrope solutions employed with the concentrations expressed on a mass/mass basis were 50 mass % sodium butyl monoglycol sulfate (NaBMGS 50), 40 mass % sodium cumenesulfonate (NaCS 40), 40 mass % sodium xylenesulfonate (NaXS 40), and 40 mass % potassium−sodium xylenesulfonate (KNaXS 40). At high concentrations, above the critical hydrotrope concentration, hydrotropes enhance the solubilities of these components much differently. The ternary solid−liquid phase equilibrium diagrams for the 6-APA−PAA−water system with NaBMGS 50 as a hydrotrope were constructed. Solubilities of 6-APA were experimentally determined in the reaction product mixture with or without 30 mass % NaBMGS hydrotropic medium at various added acid concentrations over the precipitation pH range (7.5−4.2). These data points can directly be used for the evaluation of supersaturation profiles in subsequent precipitation studies. A medium of aqueous NaBMGS solution can be used for the better separation of 6-APA.

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