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Solubilities of *m*- and *p*-Aminoacetophenones in Hydrotrope Solutions

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The solubilities of *m*- and *p*-aminoacetophenones were determined in aqueous solutions of several hydrotropes by the weight disappearance method at different hydrotrope concentrations and temperatures. Commercially available aqueous hydrotrope solutions employed were 50% sodium butyl monoglycol sulfate, 40% sodium cumenesulfonate, 40% sodium xylenesulfonate, 40% sodium toluenesulfonate, and 40% ammonium xylenesulfonate, all the hydrotrope concentrations being expressed in mass/mass. At high concentrations, above the threshold hydrotrope concentration, hydrotropes enhance the solubilities of these components differently. The differences in solubilities with hydrotrope concentration and temperature can be exploited for the separation of these isomers.

Introduction

A variety of industrial mixtures having close boiling point isomeric or nonisomeric components present a challenging separation problem, as in most cases conventional separation methods cannot be successfully applied. These components usually have similar chemical properties and molecular sizes and comparable volatilities. In order to effect a physical separation of these mixtures, it is necessary to invoke some property which depends on molecular structure rather than on molecular size. Methods based on solvent extraction, dissociation extractive crystallization, selective reactions, fractional crystallization, and extractive or adductive crystallization have been reported. The use of commercial hydrotropes in difficult separations of commercially important close boiling mixtures, even at eutectic compositions in some simple eutectic systems, has been suggested (Geetha et al., 1991; Raynaud-Lacroze and Tavare, 1993; Phatak and Gaikar, 1993; Colonia et al., 1993; Colonia and Tavare, 1994).

Hydrotropic substances are a class of chemical compounds that are freely soluble organic compounds and 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. 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 may be used to concentrate the hydrotrope for recycle. Such a technique would avoid the use of highly inflammable and expensive solvents normally used in dilution crystallization and/or temperature changes and multistage operations often required in melt crystallization. Most hydrotrope molecules appear to self-aggregate in aqueous solution to form organized assemblies in a stack-like fashion and solubilize the solute by a similar associative mechanism above a minimum hydrotrope concentration. Above this threshold, 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), Tavare and Gaikar (1991), Balasubramanian and Friberg (1993), and Phatak and Gaikar (1993)).

The present work was initiated for the fundamental study of the global role of hydrotropes in the selective separation of a component from mixtures via solubilization and precipitation techniques with particular emphasis on both the theoretical understanding of the mechanistic behavior and the experimental studies to demonstrate the utility of these hydrotropes in the separation of commercially important mixtures. The system *m*- and *p*-aminoacetophenones (molecular weight $M = 135.16$) was chosen, and the solubility determined in several commercially available hydrotropes. The separation of *m*- and *p*-aminoacetophenones through solubilization and selective precipitation is important as both these isomers have not only close boiling points but also close melting points. The melting points of *m*- and *p*-aminoacetophenones are 99 and 106 °C, while the boiling points are 290 and 294 °C, respectively.

Experimental Section

The solubilities of *m*- and *p*-aminoacetophenones (Analar grade supplied by Aldrich Chemical Co. with purity ~99%) were determined in aqueous solutions of several hydrotropes by the mass disappearance method at different hydrotrope concentrations and temperatures. In order to determine the solubility, the mass of the material which disappeared in the solution during the equilibration step, normally at 25 °C, was evaluated as the difference between the masses of the initial charge and the final residue. In the equilibration step, a known and excess amount of solubilizate was equilibrated with the hydrotrope solution (usually about 20 cm^3) of known concentration for about 6 h in a magnetically stirred and jacketed vessel (about 100 cm^3 capacity) maintained at a constant temperature of 25 °C by circulating water from a constant temperature water bath. The temperature was controlled within ±0.1 °C. The slurry was then filtered through filter paper (Whatman No. 1), the residue on the filter paper was dried for 16 h in an oven at 60 °C and weighed and the difference in mass between the initial charge and final residue estimated to determine the solubility.

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Table 1. Solubility Data for *p*- and *m*-Aminoacetophenones[a]

hydrotrope concentration, g/g of water	solubility of *p*- and *m*-aminoacetophenones, g/g of water									
	NaBMGS 50 (M = 220) ($c_{Nc} \approx 0.2$ g/g of water)		NaTS 40 (M = 194) ($c_{Nc} \approx 0.07$ g/g of water)		NaCS 40 (M = 222) ($c_{Nc} \approx 0.02$ g/g of water)		NaXS 40 (M = 208) ($c_{Nc} \approx 0.08$ g/g of water)		AXS 40 (M = 203) ($c_{Nc} \approx 0.1$ g/g of water)	
	p	*m*	*p*	*m*	*p*	*m*	*p*	*m*	*p*	*m*
1.0 (neat)	0.1432	0.0921								
0.70	0.1149	0.0760								
0.667 (neat)			0.0709	0.0401	0.1184	0.0856	0.1152	0.0748	0.1550	0.0901
0.50	0.0872	0.0612	0.0473	0.0291	0.0985	0.0695	0.0956	0.0568	0.1118	0.0650
0.40	0.0593	0.0463	0.0341	0.0225	0.0809	0.0573	0.0730	0.0455	0.0862	0.0519
0.30	0.0399	0.0336	0.0234	0.0166	0.0625	0.0452	0.0523	0.0328	0.0598	0.0374
0.20	0.0209	0.0242	0.0150	0.0123	0.0424	0.0304	0.0307	0.0210	0.0349	0.0228
0.10	0.0105	0.0176	0.0093	0.0087	0.0196	0.0157	0.0141	0.0121	0.0156	0.0125
0.0	0.0065	0.0063	0.0065	0.0063	0.0065	0.0063	0.0065	0.0063	0.0065	0.0063
neat (50 °C)	0.3563	0.1889			0.3859	0.1916				

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

Results and Discussion

The solubilities for the pure components at 25 °C (namely, *m*- and *p*-aminoacetophenones) were empirically determined by this method in several commercially available hydrotropes [50% sodium butyl monoglycol sulfate (NaBMGS 50), 40% sodium cumenesulfonate (NaCS 40), 40% sodium xylenesulfonate (NaXS 40), 40% sodium toluenesulfonate (NaTS 40), and 40% ammonium xylenesulfonate (AXS 40) with all the percentages expressed on a mass/mass basis] at different solution phase hydrotrope concentrations. 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. Also included in Table 1 are the solubilities of these pure components in some commercially available neat hydrotrope solutions (namely, NaBMGS 50 and NaCS 40) at 50 °C. 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 satisfactory within the range of experimental errors.

The solubilities of pure components, namely, *m*- and *p*-aminoacetophenones, are shown as a function of NaBMGS concentration in Figure 1. The curves are drawn using polynomial interpolations from the Harvard graphics program. Above the minimum hydrotrope concentration, the solubilization rises markedly and may level off to a plateau, resulting in a sigmoidal solubility–hydrotrope concentration curve. The critical hydrotrope concentration appears to be a characteristic of a hydrotrope, as it is the same for many solubilizates. For NaBMGS, for example, it is about 0.20 g/g of water. The solubilities of *m*- and *p*-aminoacetophenones in water are practically the same (i.e., 0.0063 and 0.0065 g/g of water, respectively). All the hydrotropes augment the aqueous solubilities of both these components, the *p*-isomer being more soluble than the *m*-isomer in all cases (see Table 1). The trend in the magnitude of solubilities for both these components can be written for the commercially available neat hydrotropes investigated as

AXS 40 > NaBMGS 50 > NaCS 40 > NaXS 40 > NaTS 40

Thus, the size of the hydrophobic and hydrophilic parts appears to influence the solubilities, bulkier parts being useful in enhancing the solubilization. Solubility measurements of these pure components at 50 °C in NaCS 40 and NaBMGS 50 indicated a substantial rise (by a factor of 2–3) in their values. All these measurements suggest a possibility of separation. Preliminary precipitation experiments indicated that the *p*-isomer could be separated through solubilization and precipitation using both dilution and cooling effects at a reasonable recovery (~70%).

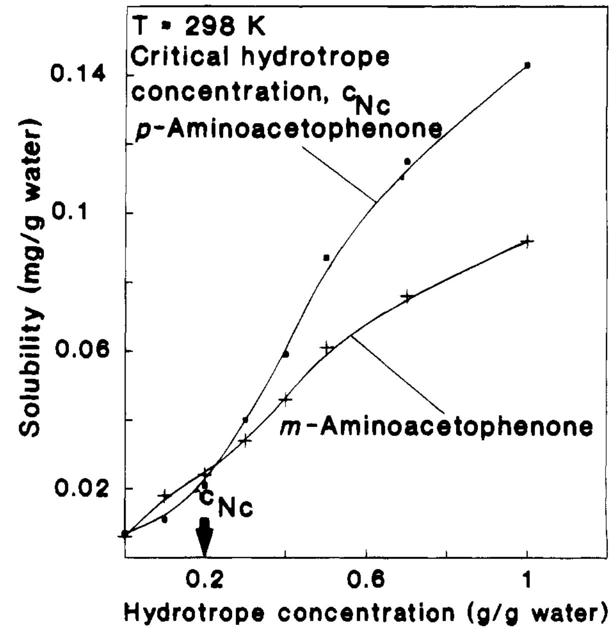

Figure 1. Typical hydrotropic solubilization curve for NaBMGS.

The solubility values of *m*- and *p*-aminoacetophenones in Table 1 show sigmoidal curves with hydrotrope concentration, when plotted, with a definite critical or minimum hydrotrope concentration for each hydrotrope. These may indicate 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. Since only above the critical or minimum hydrotrope concentration is the solubilization effective, the normalized solubility data for *p*- and *m*-aminoacetophenones are reported in Figures 2 and 3, respectively. Again the smooth curves are drawn through the data points using the graphics program. Both the solubility and hydrotrope concentrations are normalized in such way that they equal zero at the critical hydrotrope concentration and unity in a neat hydrotrope. The normalized solubility is defined as the ratio of the difference between the solubilities at any and critical hydrotrope concentration to that at neat and critical hydrotrope concentrations, while the normalized hydrotrope concen-

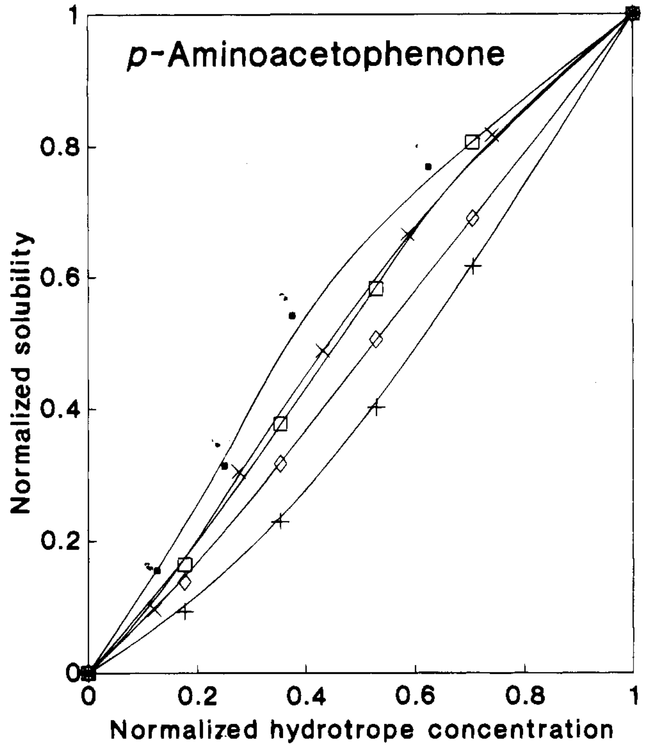

Figure 2. Normalized solubilization curves for several hydrotropes for *p*-aminoacetophenone: (■) NaBMGS 50; (+) NaTS 40; (×) NaCS 40; (□) NaXS 40; (◇) AXS 40.

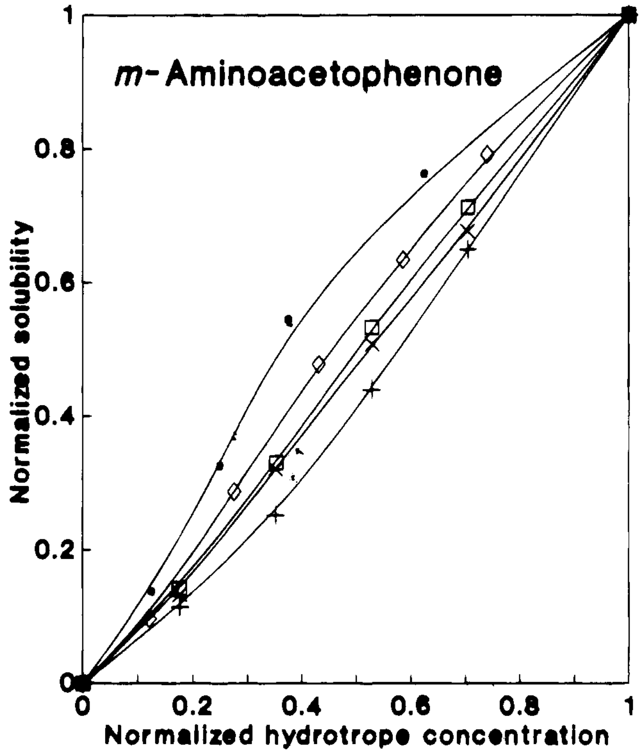

Figure 3. Normalized solubilization curves for several hydrotropes for *m*-aminoacetophenone: (■) NaBMGS 50; (+) NaTS 40; (◇) NaCS 40; (□) NaXS 40; (×) AXS 40.

tration is the ratio of the difference between any and critical concentration to that between neat and critical hydrotrope concentrations. Thus, normalized solubility is equal to $(c^* - c^*_c)/(c^*_{neat} - c^*_c)$, and normalized hydrotrope concentration is equal to $(c_N - c_{Nc})/(c_{Nneat} - c_{Nc})$. On such normalized plots, both components have similar solubilization patterns for a given hydrotrope. These curves have

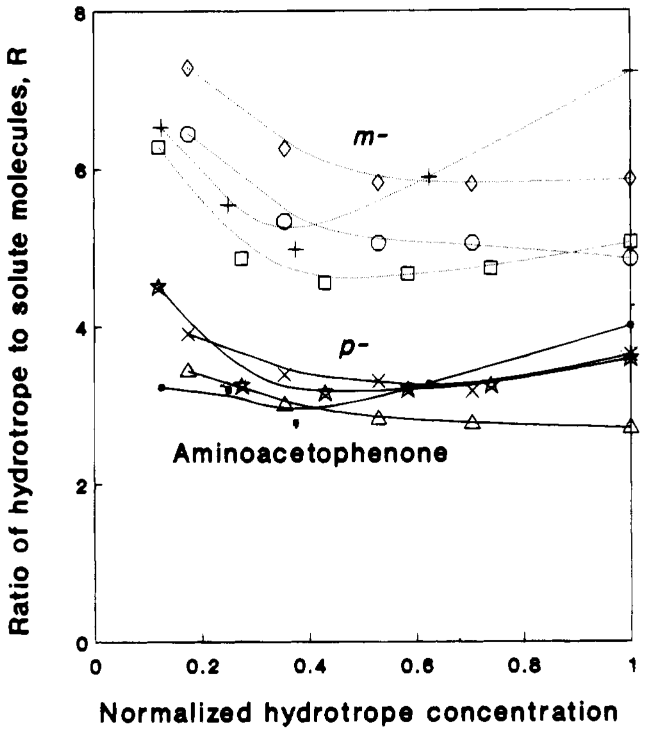

Figure 4. Variation of the number of hydrotrope molecules for a molecule of solute required with normalized hydrotrope concentration for aminoacetophenones with several hydrotropes. For *p*-aminoacetophenone: (■) NaBMGS 50; (×) NaXS 40; (☆) NaCS 40; (△) AXS 40. For *p*-aminoacetophenone: (+) NaBMGS 50; (◇) NaXS 40; (□) NaCS 40; (○) AXS 40.

less pronounced sigmoidal character than the corresponding absolute solubility curves. In general, except for NaTS, the normalized solubility of the *p*-isomer is slightly higher than that of the *m*-isomer. The trend in the magnitude of normalized solubilities for both these components with the normalized hydrotrope concentration can be written at about 0.5 as

NaBMGS 50 > NaCS 40 > NaXS 40 > AXS 40 > NaTS 40

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 been reported by Yamamata et al. (1955) for riboflavin (vitamin B_2). Sodium benzoate, hydroxybenzoic acid salts, and related compounds were very effective in solubilizing riboflavin in aqueous solution. The introduction of polar groups to sodium benzoate did not dramatically change hydrotropic solubilization, while changing from the benzene ring to the more hydrophobic naphthalene moiety caused a 10-fold improvement.

The sigmoidal character in the 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, and salting-in and 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

Table 2. Solubility Data of Solutes in Aqueous Hydrotropic Solutions of Sodium Butyl Monoglycol Sulfate at 25 °C[a]

hydrotrope concentration, g/g of water [NaBMGS 50 (M = 220) ($c_{Nc} \approx$ 0.2 g/g of water)]	solubility, g/g of water							
	aminoacetophenone (M = 135.16)		6-aminopenicilanic acid (6-APA) (M = 216)–phenoxyacetic acid (PAA)(M = 152)		nitrobenzoic acid (M = 167)		chlorobenzoic acid (M = 157)	
	p	*m*	6-APA	PAA	*o*	*p*	*o*	*p*
1.0 (neat)	0.1432	0.0921	0.0036	0.389	0.181	0.012	0.107	0.012
0.80					0.080	0.0072		
0.70	0.1149	0.0760	0.0042	0.266			0.065	0.008
0.60					0.053	0.005		
0.50	0.0872	0.0612	0.0037	0.203	0.039	0.003	0.041	0.005
0.40	0.0593	0.0463	0.0041	0.133	0.025		0.031	0.0034
0.30	0.0399	0.0336	0.0037	0.090	0.012		0.019	0.002
0.20	0.0209	0.0242	0.0031	0.043			0.009	0.0012
0.10	0.0105	0.0176	0.0033	0.018	0.0098		0.005	0.0008
0.0	0.0065	0.0063	0.0026	0.011	0.0078	0.0008	0.003	0.0001

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

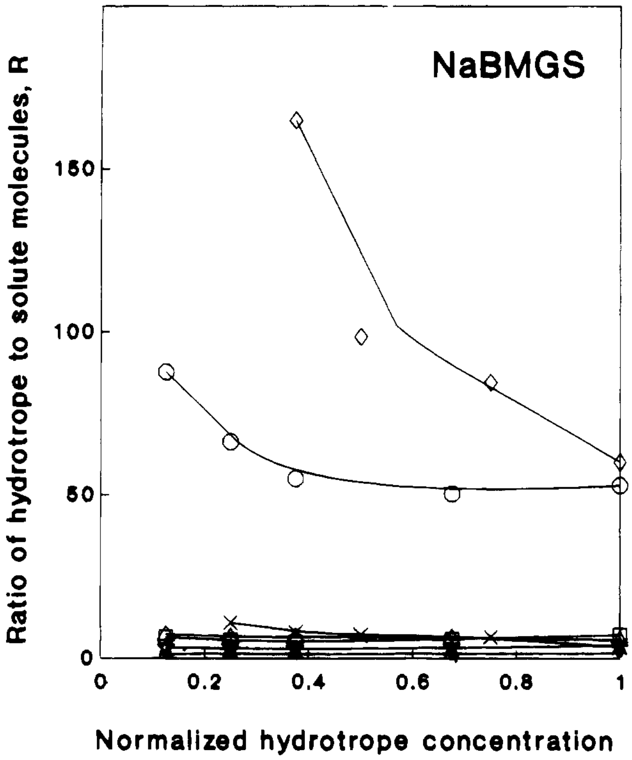

Figure 5. Variation of the number of hydrotrope molecules for a molecule of solute required with normalized hydrotrope concentration: several solutes with NaBMGS (■) Phenoxyacetic acid (PAA); (☆) *p*-Aminoacetophenone; (□) *m*-Aminoacetophenone; (×) *o*-Nitrobenzoic acid; (◇) *p*-Nitrobenzoic acid; (△) *o*-Chlorobenzoic acid; (○) *p*-Chlorobenzoic acid.

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 a 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, the majority of 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 a micellar surfactant with a notable difference in solubilization with regard to magnitude and selectivity. The ratio R can be defined as the number of hydrotrope molecules required to solubilize one molecule of solute and be used as a measure similar to the aggregation number defining the number of surfactant molecules in a micelle. These ratios for both *p*- and *m*-aminoacetophenones are plotted against the normalized hydrotrope concentration in Figure 4 for four hydrotropes, while Figure 5, constructed from the solubility data given in Table 2, depicts these plots for several solutes solubilized in NaBMGS. Although a slight curvature is apparent in all these curves, for practical purposes these ratios appear independent of dimensionless hydrotrope concentration. As *p*-aminoacetophenone is more soluble than its *m*-isomer, except for NaTS, the ratio for most hydrotropes is around 4 for the *p*-isomer and 6 for its *m*-isomer. For NaTS (not shown in Figure 4), these ratios have high values and show a downward curvature. In most solutes, the ratio appears to be independent of normalized concentration. For sparingly-soluble solutes like *p*-nitrobenzoic acid and *p*-chlorobenzoic acids, the ratios are high and, at low normalized concentrations, the level of uncertainty is high. The planar hydrophobic moiety in a hydrotrope molecule is thought essential for the stack-type aggregation, while the hydrophilic ionic part solubilizes the molecules in water. The ratio is independent of the normalized concentration in most cases, thus indicating that a fixed number of hydrotrope molecules are being used for solubilizing the solute over the entire range of concentration.

Conclusions

The solubilities of *m*- and *p*-aminoacetophenones were determined in aqueous solutions of several hydrotropes by the weight disappearance method at different hydrotrope concentrations and temperatures. Commercially available aqueous hydrotrope solutions employed with their concentrations expressed on a mass/mass basis were 50% sodium butyl monoglycol sulfate (NaBMGS 50), 40% sodium cumenesulfonate (NaCS 40), 40% sodium xylenesulfonate (NaXS 40), 40% sodium toluenesulfonate (NaTS 40), and 40% ammonium xylenesulfonate (AXS 40). At relatively high concentrations, i.e., above the threshold hydrotrope concentration, hydrotropes augment the solubilities of these components differently. These sigmoidal-type solubility variations are influenced by molecular structures. The differences in solubilities with hydrotrope concentration and temperature can be employed for the separation of closely related compounds.

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