Solubility of *o*-/*p*-Hydroxyacetophenones in Aqueous Solutions of Sodium Alkyl Benzene Sulfonate Hydrotropes

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Hydrotropes enhance solubility of water-insoluble or sparingly soluble solutes such as *o*- and *p*-hydroxyacetophenones (HAPs) in aqueous solutions. The solubility of HAPs is experimentally determined in aqueous solutions of sodium cumene sulfonate (NaCS), sodium *p*-xylene sulfonate (NaXS), and sodium *p*-toluene sulfonate (NaPTS). The solubility of phenols increases almost by an order of magnitude at higher concentrations of the hydrotropes in the order NaPTS, NaXS, and NaCS, at a given temperature. The solubility *o*-HAP was twice that of *p*-HAP in the NaCS solutions, and a similar trend was observed in other hydrotrope solutions. The solubility data was fitted in the Association model of hydrotropy to estimate the hydrotrope−hydrotrope and hydrotrope−solute interaction parameters. NaCS, the more hydrophobic hydrotrope, shows stronger interaction with the phenols and a higher association constant.

Introduction

Hydrotropes are highly soluble organic salts which, when present at sufficiently high concentrations, induce enhancement of solubility of other sparingly water-soluble or water-insoluble organic substances in water.[1,2] This increase is presumably through a self-aggregation process of the hydrotrope molecules because of their amphiphilic nature and varies with the nature of the organic compound.[3,4] Typical hydrotropes are alkali and alkaline metal salts of organic acids such as alkyl benzene sulfonic acid, alkyl monoglycol phosphoric or sulfonic acids, aromatic carboxylates, phenols, etc.

Hydrotropes have been used to solubilize organic compounds, drugs, and biochemicals.[5−7] Hydrotropes have been tested in the development of extractive separation processes and in distillation as an extractive solvent for separation of close boiling-point phenolic mixtures.[8−11] Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions.[12,13] The use of hydrotrope solutions in such industrial applications is attractive because of their easy availability, ready recovery of the dissolved solutes by simple dilution with water or by solvent extraction, and absence of any fire risk because of no volatility.

The isomers of hydroxyacetophenones (HAPs) are usually obtained as mixtures by acylation of phenol followed by a Fries rearrangement and are usually separated by steam distillation and/or crystallization.[14] The steam distillation process is an energy-intensive operation, and the steam condensate also gets contaminated by the dissolved phenolics. Since hydrotropes can distinguish between ortho and para isomers, as a part of our ongoing program of development of separation processes for the mixtures of ortho and para isomers, we decided to measure the solubilities of *o*- and *p*-HAPs in aqueous hydrotrope solutions.

Materials and Experimental Methods

Materials and Reagents. Hydrotropes, sodium *p*-toluene sulfonate (NaPTS), sodium *p*-xylene sulfonate (NaXS), and sodium cumene sulfonate (NaCS), of purity 98% each, were purchased from Navdeep Chemicals, Mumbai. Hydrotropes were dissolved in methanol to remove insoluble impurities and then recrystallized and dried in oven to ensure complete removal of methanol before use. The HAPs were purchased from HIMEDIA having the purity of 98%. Toluene was supplied by s.d. Fine Chemicals, Mumbai.

Solubility Studies. The solubility of *p*-HAP was measured by a mass-loss method. The solubilization experiments were conducted using stoppered glass flasks containing 10 cm^3 hydrotrope solutions of concentration in the range 0.10−2.0 mol·dm^{-3}. *p*-HAP, in powdered form, was added in excess to the solution to ensure saturation of the hydrotrope solution. The mixture was stirred with the help of a magnetic stirrer for 6−8 h to attain equilibrium although saturation was reached in the first 30 min of stirring. The temperature of the suspension was maintained by keeping the flasks in a constant-temperature water bath with temperature accuracy of ±1.0 K. To determine the mass of the dissolved material in the solution, the slurry was filtered using a standard filter paper. The filtration of slurry, for higher-temperature experiments, was conducted at the same temperature. The residue on the filter paper was thoroughly washed with water at 303 K. Since the solubility of *p*-HAP is negligible in water, its loss because of the water washing is negligible, while the hydrotrope is highly water soluble and the solid can be obtained completely free from the hydrotrope or any trace of the mother liquor. After the water washing, the solid residue was dried in a vacuum oven at 338 K for several hours to ensure its complete drying. *p*-HAP is a stable solid with a melting point of 381 K and is obtained after drying as a free-flowing crystalline solid. No melting or decomposition of the solid was detected in the drying process. The difference of the initial charge and the weight of the final residue was measured using an electronic balance of accuracy $\pm 1.0 \times 10^{-4}$ g, which gives the amount of *p*-HAP dissolved in the hydrotrope solutions. The repeated experiments of solubilization at higher hydrotrope concentrations, i.e., 1.0 mol·dm^{-3} and above where the

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hydrotropic solubilization effect was more pronounced, gave 0.1−0.4% variation in the solubility with NaXS and NaCS solutions and about 3.7% with NaPTS solutions. At lower concentrations of hydrotropes, below 0.5 mol·dm^{-3}, however, the variation was more as the solubility increase was not large. With NaXS and NaCS aqueous solutions, the variation in experimentally measured solubility of repeated experiments was 2−4.8%. But NaPTS showed a wide variation in solubility, from 3.7% at the lowest hydrotrope concentration of 0.2 mol·dm^{-3} to 8% at intermediate concentration.

A similar experimental procedure was used for the solubilization of *o*-HAP. However, *o*-HAP is liquid at 303 K, and the mass-loss method cannot be applied in the same manner as that for *p*-HAP. After giving sufficient time for equilibration, the hydrotropic solution was separated from the excess liquid phase of *o*-HAP. A known volume of the aqueous hydrotropic solution, now saturated with *o*-HAP, was then contacted with toluene to extract *o*-HAP into the organic phase. A minimum of three extractions, with fresh solvent each time of equal volume as the aqueous solution, were required for the complete transfer of *o*-HAP from the hydrotropic solutions to the organic phase. Separate studies on the partitioning of *o*-HAP between hydrotrope solutions and toluene showed the partition coefficient of *o*-HAP to be in the range 5 to 80 toward the toluene phase depending upon the concentration of hydrotrope. The concentrated hydrotrope solutions were diluted with water before extraction because at lower concentrations, below 0.5 mol·dm^{-3}, the partition coefficient of *o*-HAP toward toluene is in excess of 50. With these values of partition coefficient, it is possible to ensure complete transfer of *o*-HAP into the toluene phase. Since hydrotropes are highly water soluble organic salts and show no affinity toward toluene, there is no possibility of their transfer to the organic phase in the process. The organic extracts were pooled together, and the organic phase was then analyzed on a Chemito 8510 GLC unit using a 2-m SE-30 with 10% Carbowax column. The calibration charts were separately prepared for the quantitative analysis using the solvent area for the internal standard with an accuracy of $\pm 10 \times 10^{-3}$ mol·dm^{-3}. The repeated experiments showed a variation of 2.1% to maximum 3.8% in the solubility values of *o*-HAP for all hydrotropes. Nitrogen was used as carrier gas and the oven temperature was maintained at 373 K.

Results and Discussion

Solubility Study. Tables 1 and 2 give the solubility (in mol·dm^{-3}) of *p*-HAP and *o*-HAP in different hydrotrope solutions at temperatures, 303, 313, and 323 K. At low hydrotrope concentrations, the solubility increase is smaller but rises rapidly after a certain hydrotrope concentration. At higher hydrotrope concentrations, the rate of solubility increases with the hydrotrope concentration drops, giving an appearance of sigmoidal nature, which is common in most hydrotropic solubilization studies.[3] The solubility of *p*-HAP in aqueous NaPTS solutions at different temperatures is shown in Figure 1. The solubility behavior of both phenols in other different hydrotrope solutions was similar at different temperatures. The solubility increase was significant only beyond a minimum hydrotrope concentration of NaPTS at 0.4 mol·dm^{-3} at 303 and 313 K temperatures. The hydrotrope, because of its amphiphilic nature, is expected to form self-aggregates in aqueous solutions, which in turn coaggregate with the solute. As the hydrotrope concentration increases, due to the increased hydrophobic interactions with the hydrotrope molecules and/or

Table 1. Solubility of *p*-HAP (1) in Aqueous Solutions of Hydrotrope (2)

	S_1/mol·dm^{-3}		
c_2/mol·dm^{-3}	303 K	313 K	323 K
	Sodium *p*-Toluene Sulfonate (2)		
0.0	0.07 ± 0.04	0.14 ± 0.03	0.18 ± 0.04
0.1	0.11 ± 0.02	0.24 ± 0.07	0.41 ± 0.07
0.2	0.16 ± 0.05	0.3 ± 0.04	0.53 ± 0.07
0.4	0.23 ± 0.07	0.39 ± 0.08	0.71 ± 0.09
0.5	0.24 ± 0.08	0.41 ± 0.09	0.80 ± 0.16
0.8	0.29 ± 0.06	0.79 ± 0.07	1.40 ± 0.13
1.0	0.36 ± 0.07	0.91 ± 0.14	1.68 ± 0.19
2.0	0.59 ± 0.07	1.55 ± 0.08	2.57 ± 0.18
	Sodium *p*-Xylene Sulfonate (2)		
0.1	0.14 ± 0.076	0.25 ± 0.12	0.44 ± 0.19
0.2	0.19 ± 0.072	0.32 ± 0.13	0.71 ± 0.19
0.4	0.37 ± 0.069	0.46 ± 0.11	1.09 ± 0.16
0.5	0.49 ± 0.068	0.60 ± 0.14	1.76 ± 0.18
0.8	0.52 ± 0.069	0.95 ± 0.11	3.08 ± 0.45
1.0	0.80 ± 0.073	1.36 ± 0.14	3.74 ± 0.25
2.0	1.08 ± 0.07	1.94 ± 0.13	5.67 ± 0.29
	Sodium Cumene Sulfonate (2)		
0.1	0.15 ± 0.072	0.31 ± 0.126	0.59 ± 0.193
0.2	0.20 ± 0.073	0.48 ± 0.13	1.18 ± 0.195
0.4	0.37 ± 0.071	0.58 ± 0.13	2.08 ± 0.18
0.5	0.55 ± 0.08	0.72 ± 0.13	3.69 ± 0.19
0.8	0.73 ± 0.068	1.53 ± 0.133	4.84 ± 0.20
1.0	0.91 ± 0.072	1.90 ± 0.135	5.64 ± 0.27
2.0	1.59 ± 0.067	2.66 ± 0.13	7.54 ± 0.29

Table 2. Solubility of *o*-HAP (1) in Aqueous Solutions of Hydrotrope (2)

	S_1/mol·dm^{-3}		
c_2/mol·dm^{-3}	303 K	313 K	323 K
	Sodium *p*-Toluene Sulfonate (2)		
0.0	0.05 ± 0.004	0.11 ± 0.005	0.14 ± 0.026
0.1	0.08 ± 0.007	0.15 ± 0.012	0.33 ± 0.04
0.2	0.12 ± 0.019	0.19 ± 0.016	0.54 ± 0.04
0.4	0.20 ± 0.02	0.31 ± 0.04	0.73 ± 0.056
0.5	0.34 ± 0.038	0.40 ± 0.032	0.76 ± 0.059
0.8	0.48 ± 0.04	0.89 ± 0.071	1.45 ± 0.11
1.0	0.51 ± 0.05	1.21 ± 0.097	2.28 ± 0.187
2.0	0.89 ± 0.063	1.75 ± 0.13	3.77 ± 0.306
	Sodium *p*-Xylene Sulfonate (2)		
0.1	0.12 ± 0.025	0.20 ± 0.011	0.28 ± 0.012
0.2	0.22 ± 0.02	0.28 ± 0.017	0.69 ± 0.045
0.4	0.38 ± 0.09	0.40 ± 0.01	0.99 ± 0.07
0.5	0.49 ± 0.03	0.61 ± 0.04	1.73 ± 0.09
0.8	0.69 ± 0.04	1.02 ± 0.05	3.59 ± 0.22
1.0	0.81 ± 0.05	1.66 ± 0.09	4.50 ± 0.32
2.0	1.52 ± 0.09	2.20 ± 0.012	6.52 ± 0.30
	Sodium Cumene Sulfonate (2)		
0.1	0.13 ± 0.007	0.25 ± 0.02	0.49 ± 0.06
0.2	0.16 ± 0.009	0.42 ± 0.03	1.18 ± 0.12
0.4	0.34 ± 0.017	0.59 ± 0.035	2.08 ± 0.13
0.5	0.51 ± 0.025	0.71 ± 0.028	4.20 ± 0.38
0.8	0.71 ± 0.035	1.65 ± 0.08	5.55 ± 0.45
1.0	1.67 ± 0.09	2.82 ± 0.09	6.30 ± 0.66
2.0	3.52 ± 0.15	4.25 ± 0.19	8.09 ± 0.70

due to increased number of aggregates, more solute can be accommodated within the hydrotrope aggregates resulting in its apparent increased solubility. Around an 8-fold increase in the solubility of *p*-HAP in 2.0 mol·dm^{-3} NaPTS aqueous solutions from its water solubility of 0.073 mol·dm^{-3} at 303 K was observed. With the increase in temperature, there is no significant increase in the solubility of *p*-HAP in water (0.14 mol·dm^{-3} and 0.18 mol·dm^{-3} at 313 and 323 K, respectively), but the solubility enhancement in the 2.0 mol·dm^{-3} NaPTS solutions was 11- and 14-fold at 313 K and 323 K, respectively. Temperature, thus, has a remarkable effect on the solubility of HAPs in the presence of the hydrotrope. Temperature may affect the solubility of the

Table 3. Interaction Constants for HAPs and Hydrotropes for Association Model of Hydroropy

		p-HAP			*o*-HAP		
hydrotropes	*T*/K	K_S/mol^{-1}·dm^3	K_2/mol^{-1}·dm^3	std error in fit × 10^2	K_S/mol^{-1}·dm^3	K_2/mol^{-1}·dm^3	std error in fit × 10^2
NaPTS	303	3.9	0.10	9.81	40.9	0.12	3.02
	313	4.7	0.124	7.92	99.5	0.126	2.8
	323	5.7	0.125	9.12	141	0.127	3.02
NaXS	303	6.9	0.10	1.89	58.2	0.11	2.26
	313	7.9	0.13	0.76	144.1	0.135	2.10
	323	15.4	0.14	1.89	285	0.15	2.27
NaCS	303	9.4	0.12	3.78	67.6	0.14	1.89
	313	18.1	0.142	3.7	236	0.13	1.88
	323	24.0	0.145	2.77	370	0.145	1.78

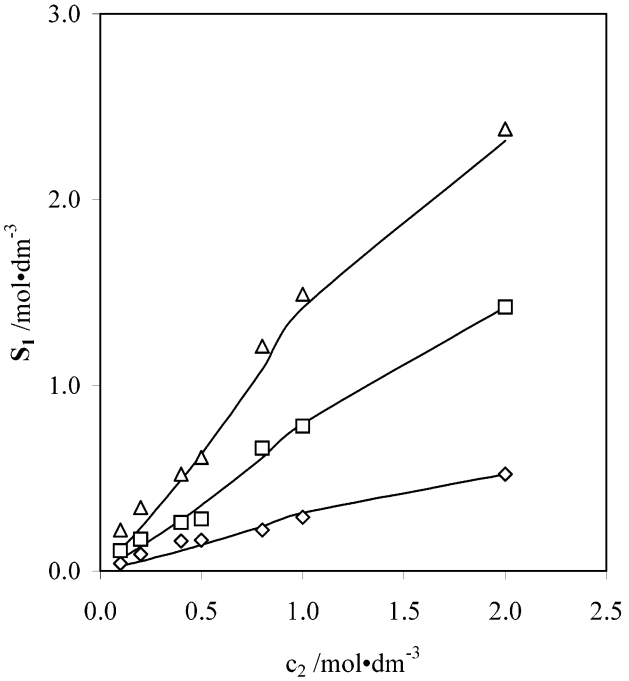

Figure 1. Solubility of *p*-HAP (1) in aqueous Na−*p*-Toluene Sulfonate (2) solutions at different temperatures (◇, 303 K; □, 313 K; △, 323 K).

solute due to the modification of the aggregate structures of the hydrotrope and also by modifying the intermolecular interactions between hydrotrope and solute. A similar increase in the solubility of *p*-HAP was observed in aqueous NaXS and NaCS solutions, but the amount of solubilized *p*-HAP increased significantly in these hydrotrope solutions. This increase can be attributed to the hydrophobicity of hydrotropes, which increases from NaPTS to NaCS with increasing number of carbon atoms in the alkyl group. The same trend in the solubility, as *p*-HAP, was observed for *o*-HAP also at different temperatures using the three hydrotropes. But the solubility increase is much more with *o*-HAP at the same hydrotrope concentration and temperature as compared to *p*-HAP.

The solubility values were fitted into a recently proposed Association model for the hydrotropic solubilization which illustrates the aggregation behavior of hydrotrope and subsequent interaction of a solute with the hydrotrope assemblies.[15] The model characterizes the hydrotrope−hydrotrope and hydrotrope−solute interactions with the mass-action law, with the assumption that hydrotrope molecules associate in a stepwise manner to form oligomers and multimers such that the association constant becomes weaker on addition of subsequent hydrotrope molecules. The association constant for an *n*-mer of hydrotrope with a monomer is related to the dimerization constant (K_2, mol^{-1}·dm^3), i.e., $K_n = K_2/n$.

The concentration of a monomeric hydrotrope molecule, [H_1], is related to the total hydrotrope concentration (C_S, mol·dm^{-3}) through the following equations

$$C_S = \sum_{n=1}^{\infty} n[H_n] \tag{1}$$

or

$$C_S = [H_1]\{2\exp(K_2[H_1]) - 1\} \tag{2}$$

Also the model assumes that the hydrotrope assemblies cosolubilize the solute, where an *n*-mer is capable to take up a maximum of "(n − 1)" solute molecules and that the solutes' association with the hydrotrope assemblies becomes weaker on addition of an extra solute molecule in the same manner as the hydrotrope aggregation process. The total solute concentration associated with all hydrotrope aggregates is given by eq 3

$$S_T = 2\,[S_1]\left(\frac{K_S}{K_2}\right)\{e^{K_2[H]} - (1 + K_2[H_1])\} \tag{3}$$

The hydrotrope−solute interaction constant (K_S, mol^{-1}·dm^3) and hydrotrope−hydrotrope interaction constant (K_2) were thus calculated for each pair of HAP and hydrotrope by fitting the experimental solubility data in eqs 2 and 3. The free solute concentration in the solution [S_1], (in mol·dm^{-3}) was taken equal to the solubility of *o*-HAP and *p*-HAP in water, at the corresponding temperatures. The values of K_S and K_2 for hydrotropes at different temperatures are given in Table 3, and the lines in Figure 1 indicate the fitted curves. The Association model inherently predicts an increase in the solubility of the solute. Table 3 shows that hydrotrope−hydrotrope association constant (K_2) to be much smaller than that of the hydrotrope−solute interaction constant (K_S) for all hydrotropes. Although the hydrotrope aggregates are formed in aqueous solutions, their aggregation tendency is much weaker than that of solute−hydrotrope coaggregation. With the increase in temperature, the interaction constants K_S and K_2 also increase. Probably temperature induces a significant change in the aggregate structures, thereby causing more solute to be solubilized in the hydrotrope solutions. Both K_S and K_2 increase in the order of NaPTS < NaXS < NaCS. This indicates that the solute−hydrotrope and hydrotrope−hydrotrope interactions are driven by hydrophobicity of the hydrotrope structure.[16] With the increase in the number of methylene groups in the hydrotrope structure, its hydrophobicity also increases and results in an increased solubility of the solute in the hydrotropic solutions. The comparison of the interaction constant K_S of two isomers, i.e., *o*-HAP and *p*-HAP, shows that K_S for *o*-HAP is higher than that for *p*-HAP. It signifies that *o*-HAP experiences

more hydrotropic effect on its solubility as compared to *p*-HAP. The hydrotrope−hydrotrope constant K_2 remains almost constant for both the isomers. Since the solute solubility in hydrotrope solutions is higher at high hydrotrope concentrations, dilution with water, in most cases, is used to recover the solute from the hydrotrope solutions. Since the temperature effect on solubility of solute is significant at a given hydrotrope concentration, it could be useful for recovery of the dissolved solute from the hydrotrope solutions by cooling instead of dilution by water as it will definitely be more economical.

The higher solubility of *o*-HAP compared to *p*-HAP is probably due to its planner and amphiphilic structure, while *p*-HAP does not show similar amphiphilicity because of two hydrophilic groups present at both ends of the aromatic ring. The hydrophobic interaction of *p*-HAP with the hydrotrope assemblies is thus poor as compared to that of *o*-HAP. The difference in the solubilities of *o*-HAP and *p*-HAP is not high. A mere 2-fold solubility difference was observed at 2.0 mol·dm^{-3} hydrotrope solutions at 303 K. Hence, only solubilization by hydrotrope solutions may not give effective separation of these isomers.

Conclusions

The solubility of *o*- and *p*-HAPs in aqueous hydrotrope solutions of sodium *p*-toluene sulfonate, sodium *p*-xylene sulfonate, and sodium cumene sulfonate increases in a differential manner with hydrotrope concentration and more with temperature. The enhancement in the solubility of *o*-HAP at a given hydrotrope concentration and temperature is almost twice that of *p*-HAP. More hydrophobic NaCS dissolves more amounts of *o*- and *p*-HAPs than those in aqueous NaXS and NaPTS solutions.

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