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Research Article

A STUDY ON THE PROPERTIES OF HYDROTROPE SOLUTIONS FOR THE ENHANCEMENT OF SOLUBILITY OF *P*-AMINOBENZOIC ACID THROUGH HYDROTROPY

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ABSTRACT

In the present investigation, the effect of various hydrotropes such as sodium salicylate, nicotinamide, sodium benzoate and urea under a wide range of hydrotrope concentrations (0 to 3.0 mol/L) and different system temperatures (303 to 333) K on the solubility of poor water soluble *p*-aminobenzoic acid has been investigated. The solubility enhancement of *p*-aminobenzoic acid by the hydrotropes was observed in increasing order as urea < sodium benzoate < nicotinamide < sodium salicylate. In order to elucidate the probable mechanism of solubilization, various solution properties such as viscosity, specific gravity, surface tension, refractive index and specific conductance of hydrotropic solutions were studied. The solubility data has been fitted in the Association model of hydrotropy to estimate the hydrotrope-hydrotrope (K_{hh}) and hydrotrope-solute (K_{hs}) association constants. The effectiveness of hydrotropes was measured in terms of K_{hh} and K_{hs}. In addition the solubilized *p*-aminobenzoic acid has been recovered by simple dilution with distilled water.

Keywords: *p*-Aaminobenzoic acid, Hydrotropy, Hydrotropes, Solubilization, Association model

INTRODUCTION

Hydrotropes are highly water 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]. 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. 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[2-6].

Hydrotropes have been used to solubilize organic compounds, drugs, biochemicals and petro-products. 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. Aqueous hydrotrope solutions provide safe and effective media for the extraction of natural products and for conducting organic synthetic reactions. The use of hydrotrope solutions in such industrial applications is attractive because of their easy availability, ready recovery of the dissolved solute by simple dilution with distilled water, absence of fire hazards etc.

The self-aggregation of hydrotropic agent is different from surfactant self-assemblies (i.e., micelles) in that hydrotropes form planar or open-layer structures instead of compact spheroid assemblies[7]. Hydrotropic agents are structurally characterized by having a short, bulky, compact moiety, such as an aromatic ring, while surfactants are characterized by long hydrocarbon chains. In general, hydrotropic agents have a shorter hydrophobic segment leading to higher water solubility compared to surfactants. Hydrotropy[8] is considered to be superior to other solubilization methods such as micellar solubilization[9,10], miscibility, cosolvency[11], and salting-in, because the solvent has high selectivity, and does not involve emulsification.

The effect of hydrotropes on the solubility and mass transfer coefficient for a series of organic acids and esters such as salicylic acid[12], stearic acid, 2-nitrobenzoic acid, butyl acetate, ethyl benzoate, amyl acetate, methyl salicylate and benzyl acetate was studied in our earlier publications[13]. It has been observed that in many two-phase reaction systems involving a sparingly soluble organic compound like *p*-aminobenzoic acid, the mass transfer coefficient was found to be very low solely due to the poor solubility of *p*-aminobenzoic acid in the aqueous phase. Since *p*-aminobenzoic acid serves as raw material/intermediate for a wide variety of chemicals and allied products[14] and the separation of *p*-aminobenzoic acid from any mixture seems to be difficult, this hydrotropic technique can be adapted to increase the solubility as well as to separate such mixtures effectively. Data on various aspects of hydrotropic study on the solubility for *p*-aminobenzoic acid + water system is reported for the first time.

MATERIALS AND METHODS

p-Aminobenzoic acid was purchased from M/s S. D. Fine Chemicals, Mumbai. Sodium salicylate, nicotinamide, sodium benzoate, and urea, of purity 99% each, were procured from M/s National Chemicals, Baroda.

Estimation of *p*-aminobenzoic acid

In the present study, UV spectrophotometric method was used for the estimation of *p*-aminobenzoic acid. The calibration curve of *p*-aminobenzoic acid was prepared in distilled water at 283 nm using double-beam spectrophotometer (UV-1701, Shimadzu, Japan).

Solubility study

The experimental setup for the determination of solubility values consisted of a thermostatic bath and a separating funnel. For each solubility test, 100 ml of a solution of the hydrotrope of known concentration was taken in a separating funnel and an excess amount of *p*-aminobenzoic acid was added. The separating funnel was immersed in a constant-temperature bath fitted with a temperature controller which could control the temperature within + 0.1 °C. The setup was kept overnight for equilibration. After equilibrium was attained, the solution was filtered from the remaining acid. The concentration of the dissolved acid in aqueous hydrotrope solutions was analyzed by UV-Vis spectrophotometer (1701, Shimadzu, Japan)[15-18]. All the solubility experiments were conducted in duplicate to check the reproducibility. The reproducibility was less than 2 %.

Properties of hydrotropic solutions

The various solution properties of hydrotropes such as viscosity, specific gravity, surface tension, refractive index and conductance were also studied in an attempt to reason out the increase in solubility of *p*-aminobenzoic acid with increase in hydrotrope concentration.

RESULTS AND DISCUSSION

Solubility

The solubility of *p*-aminobenzoic acid standard in water is 4.16×10^{-2} mol/L at 303 K, compared to 4.30×10^{-2} mol/L as reported by John[18]. Thus, the solubility value of *p*-aminobenzoic acid in water is in excellent agreement with the earlier reported values[19,20].

Experimental data representing the average of duplicate determinations on the effect of hydrotropes[21], i.e., sodium salicylate, nicotinamide, sodium benzoate and urea on the solubility of *p*-aminobenzoic acid are plotted in Figs 1- 4. Sodium salicylate is one of the hydrotropes used in this study. The solubility of *p*-aminobenzoic acid in water at 303 K in the absence of any hydrotrope is 4.16×10^{-2} mol/L (Fig. 1). It has been observed that the solubility of *p*-aminobenzoic acid in water increases significantly only after the addition of 0.25 mol/L of sodium salicylate in the aqueous solution. This concentration is referred to as the Minimum Hydrotrope Concentration (MHC).

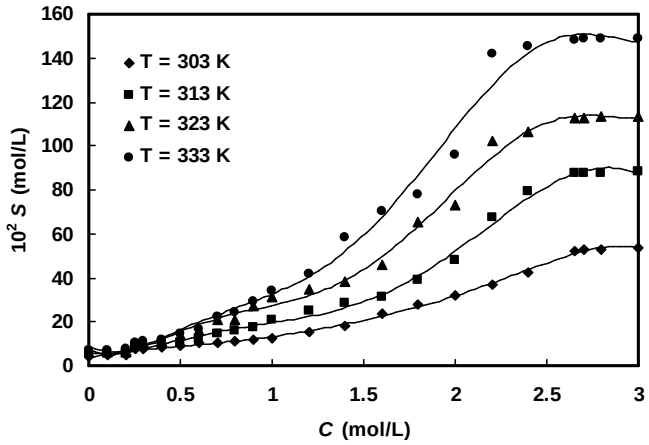

Fig. 1: Effect of sodium salicylate concentration (*C*) on the solubility (*S*) of *p*-aminobenzoic acid in water at different temperatures

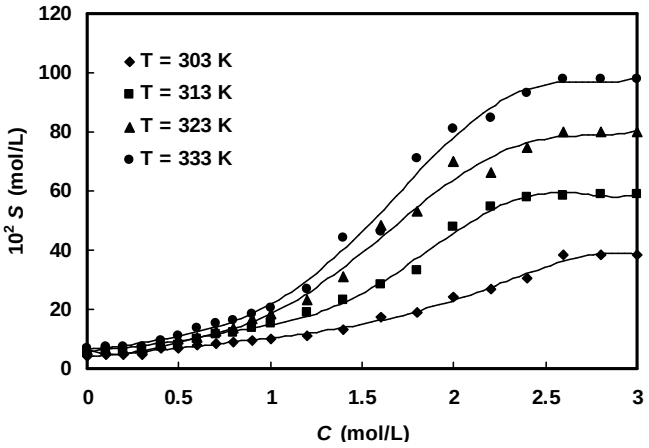

Fig. 2: Effect of nicotinamide concentration (*C*) on the solubility (*S*) of *p*-aminobenzoic acid in water at different temperatures

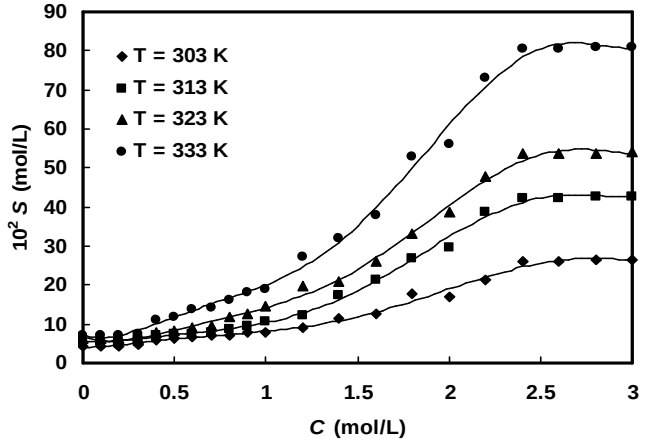

Fig. 3: Effect of sodium benzoate concentration (*C*) on the solubility (*S*) of *p*-aminobenzoic acid in water at different temperatures

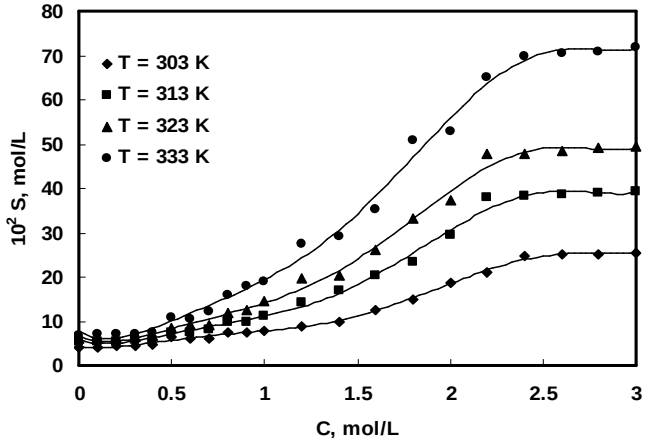

Fig. 4: Effect of urea concentration (*C*) on the solubility (*S*) of *p*-aminobenzoic acid in water at different temperatures

Therefore, it is evident that hydrotropic solubilization is displayed only above the MHC, irrespective of system temperature. Since hydrotropy appears to operate only at significant concentrations of hydrotrope in water, most hydrotropic solutions release the dissolved *p*-aminobenzoic acid on dilution with water below MHC. The knowledge of MHC values is necessary especially at industrial levels, as it ensures ready recovery of the hydrotrope for reuse.

The solubilization effect varies with concentration of hydrotrope (Fig. 1). In the present case, a clear increasing trend in the solubility of *p*-aminobenzoic acid was observed above the MHC of sodium salicylate. This increasing trend is maintained only up to a certain concentration of sodium salicylate in the aqueous solution, beyond which there is no appreciable increase in the solubility of *p*-aminobenzoic acid. This concentration of sodium salicylate (hydrotrope) in the aqueous solution is referred to as the maximum hydrotrope concentration (C_{max}). From the analysis of the experimental data, it is observed that further increase in hydrotrope concentration beyond C_{max} does not bring any appreciable increase in the solubility of *p*-aminobenzoic acid even up to 3.00 mol/L of sodium salicylate in the aqueous solution.

The saturation of the hydrotropic effect beyond C_{max} may be due to the non-availability of water molecules to form further aggregates comprising of additional MHC agglomerates. Similar to the MHC values, C_{max} values of hydrotropes also remained unaltered at increased system temperatures. The values of MHC and C_{max} of a hydrotrope with respect to *p*-aminobenzoic acid may be useful in determining the recovery of the dissolved *p*-aminobenzoic acid even to an extent of the calculated amount from hydrotrope solutions at any concentration between MHC and C_{max} by simple dilution with distilled water. This is the unique advantage of the hydrotropic solubilization technique.

From the experimental data plotted in Fig. 1, it can further be observed that, in order to achieve the particular solubility of *p*-aminobenzoic acid, say $52x10^{-2}$ mol/L, the sodium salicylate concentration should be 2.70 mol/L at 303 K, 2.00 mol/L at 313 K, 1.64 mol/L at 323 K and 1.40 mol/L at 333 K in the aqueous solution. Thus it can be seen that as the system temperature increases, the concentration of sodium salicylate required in the aqueous phase to achieve a particular solubility of *p*-aminobenzoic acid decreases. A similar trend has been observed for other systems also. It has also been observed that the solubilization effect of sodium salicylate was not a linear function of the concentration of the sodium salicylate. The solubilization effect of sodium salicylate increases with increase in hydrotrope concentration and also with system temperature[22].

A similar trend has been observed in the solubilization effect of other hydrotropes namely nicotinamide, sodium benzoate and urea. It has also been observed that the MHC values of hydrotrope used in this work range between (0.25 and 0.50 mol/L) and the C_{max} values of hydrotropes range between (2.40 and 2.65 mol/L) (Table 1). The highest value of solubilization enhancement factors φ_s, which is the ratio of solubility values in the presence and absence of a hydrotrope has been observed in the case of sodium salicylate as 21.43 at a system temperature of 333 K (Table 2).

Table 1: Minimum Hydrotrope Concentration (MHC) and maximum hydrotrope concentration (C_{max}) values for hydrotropes

Hydrotrope	MHC (mol/L)	C_{max} (mol/L)
Sodium salicylate	0.25	2.65
Nicotinamide	0.40	2.60
Sodium benzoate	0.40	2.40
Urea	0.50	2.40

Table 2: Maximum solubilization enhancement factor (φ_s) of *p*-aminobenzoic acid

Hydrotrope	φ_s			
	303 (K)	313 (K)	323 (K)	333 (K)
Sodium salicylate	12.50	15.90	18.40	21.43
Nicotinamide	9.18	10.65	13.01	14.14
Sodium benzoate	6.25	7.68	8.73	11.63
Urea	5.95	6.95	7.81	10.13

φ_s is the maximum enhancement factor for solubility

The experimental solubility values were fitted into an Association model proposed by Koparkar and Gaikar for the hydrotropic solubilization which illustrates the aggregation behavior of hydrotrope and subsequent association of a solute with the hydrotrope assemblies[23]. The model characterizes the hydrotrope-hydrotrope and hydrotrope-solute associations with mass-action law, assuming 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_{hh}, L/mol), i.e.,

$$K_n = K_{hh}/n.$$

The concentration of a monomeric hydrotrope molecule, [H_1], is related to the total hydrotrope concentration (C_s, mol/L) through the following equations

$$C_s = \sum_{n=1}^{\infty} nH_n \quad (1)$$

or

$$C_s = H_1[2\, e^{K_{hh}H_1} - 1] \quad (2)$$

Also the model assumes that the hydrotrope assemblies cosolubilize the solute, where an *n*-mer is capable to take up 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 Equation (3)

$$S_T = 2\left(\frac{K_{hs}}{K_{hh}}\right)[S_1]\left[e^{K_{hh}H_1} - (1 + K_{hh}H_1)\right] \quad (3)$$

The hydrotrope-solute association constant (K_{hs}, L/mol) and hydrotrope-hydrotrope association constant (K_{hh}) were thus calculated for *p*-aminobenzoic acid and hydrotrope by fitting the experimental solubility data in Equations (2) and (3). The free solute concentration in the solution [S_1], (in mol/L) was taken equal to the solubility of *p*-aminobenzoic acid in water, at the corresponding temperatures[24].

The values of K_{hh} and K_{hs} for hydrotropes at different temperatures are given in Table 3. The Association model inherently predicts an increase in the solubility of the solute. Table 3 shows that hydrotrope-hydrotrope association constant (K_{hh}) to be much smaller than that of the hydrotrope-solute association constant (K_{hs}) for all hydrotropes. Although the hydrotrope aggregates are formed in aqueous solutions, their aggregation tendency is much weaker than that of hydrotrope-solute co-aggregation. With the increase in temperature, the association constants K_{hs} and K_{hh} 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_{hh} and K_{hs} increase in the order of urea < sodium benzoate < nicotinamide < sodium salicylate. This indicates that the hydrotrope-hydrotrope and hydrotrope-solute associations are driven by hydrophobicity of the hydrotrope structure. With the increase in the number of carbon atom in the hydrotrope structure, its hydrophobicity also increases and results in an increased solubility of the solute in the hydrotropic solutions.

Table 3: Association constants (K_{hh}, K_{hs}) values for *p*-aminobenzoic acid and hydrotropes

Hydrotrope	*T* (K)	K_{hh} (L/mol)	K_{hs} (L/mol)	RMSE
Sodium salicylate	303	0.131	5.411	0.241
	313	0.133	7.236	0.445
	323	0.144	8.753	0.546
	333	0.154	10.536	0.716
Nicotinamide	303	0.092	3.792	0.253
	313	0.093	5.070	0.462
	323	0.105	6.339	0.569
	333	0.102	6.954	0.736
Sodium benzoate	303	0.064	2.630	0.272
	313	0.065	3.519	0.504
	323	0.067	4.039	0.624
	333	0.081	5.528	0.765
Urea	303	0.057	2.340	0.284
	313	0.059	3.209	0.509
	323	0.061	3.705	0.631
	333	0.072	4.893	0.785

RMSE: Root mean square error

In order to explain the theory of complex arrangement, a study on the solution properties like viscosity, specific gravity, surface tension, specific conductance and refractive index of hydrotropes for range hydrotrope concentrations (0-2.0 mol/L) has been carried out. Figs 5 - 9 show the plot of viscosity, specific gravity, surface tension, specific conductance and refractive index of hydrotrope solution versus hydrotrope concentration for different hydrotropes used.

From the Figures it can be seen that the trend in the change of solution properties with hydrotrope concentrations is a linear one up to the critical concentration corresponding to MHC values, after which a distinct deviation from linearity has been observed.

The positive deviation in the viscosity plot (Fig. 5) indicates that aggregate formation is associated with an increase in viscosity of hydrotrope concentration, which is in agreement with the self-association of phenolic compounds[25].

The plot of specific gravity versus hydrotrope concentration showed a negative deviation (Fig. 6) that indicates an increase in partial molal volume upon aggregation, and this increase in volume may be due to expansion of the hydrocarbon portion of the molecule or its partial removal from the high compressive force of water. The surface tension plot (Fig. 7) showed a moderate decrease in surface tension on increasing the hydrotrope concentration as hydrotropes are not surface active agents [26,27]. The deviation from linearity in specific conductance plot (Fig. 8) is strongly indicative of molecular aggregation[28].

The plot of refractive index versus hydrotrope concentration (Fig. 9) showed negative deviation. It was revealed from different studies that at lower hydrotrope concentration, there were weak ionic interactions while at higher hydrotrope concentration, the molecular aggregation seems to be the possible mechanism of hydrotropic solubilization[29,30].

Therefore, it can be concluded that the significant solubilizing effect of hydrotropes above MHC may be due to the fact that hydrotrope molecules probably associate into organized aggregates at this critical concentration. It may be suggested that the deviation from linearity of solution properties observed is an indication of aggregate formation, when the concentration surpasses this critical value. In other words, this deviation may be considered to be the characteristic of hydrotropic solubilization. Hence, the formation of aggregates of hydrotrope molecules with the attainment of MHC can be taken as a pre-requisite to display this phenomenon.

It may be further assumed that the formation of such aggregates creates a new surface environment with different solution properties like viscosity, specific gravity, surface tension, specific conductance and refractive index. This has been indicated in the study on solution properties also. Possibly the change in surface

tension and hence polarity at MHC enable the solute molecules to clinch to MHC aggregates to be retained in the aqueous phase. Such critical surface-active properties of hydrotrope aggregates seem to initiate the solubilization effect of hydrotropes.

The increase in the solubilizing effect with increase in hydrotrope concentration may be due to the more number of such aggregates available for interaction with solute molecules at the existing conditions of the aqueous phase.

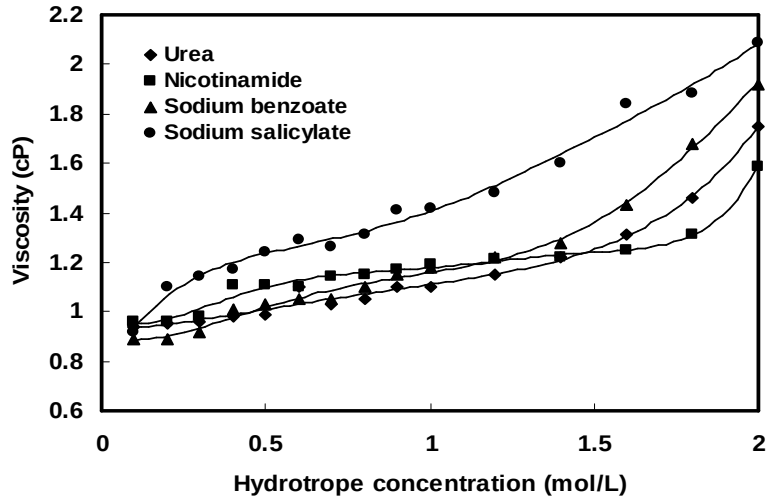

Fig. 5: Plot of viscosity versus hydrotrope concentration for different hydrotropes

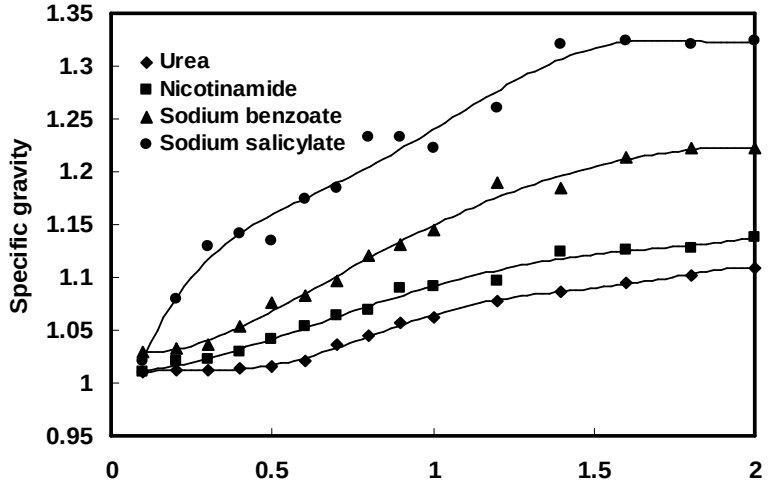

Fig. 6: Plot of specific gravity versus hydrotrope concentration for different hydrotropes

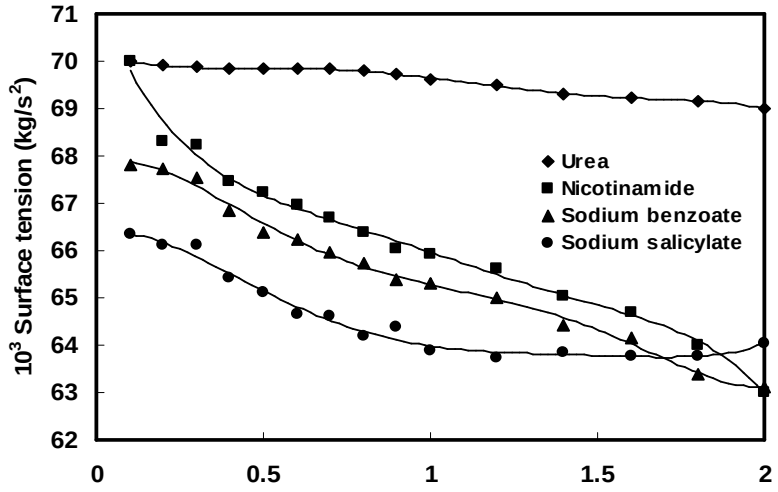

Fig. 7: Plot of surface tension versus hydrotrope concentration for different hydrotropes

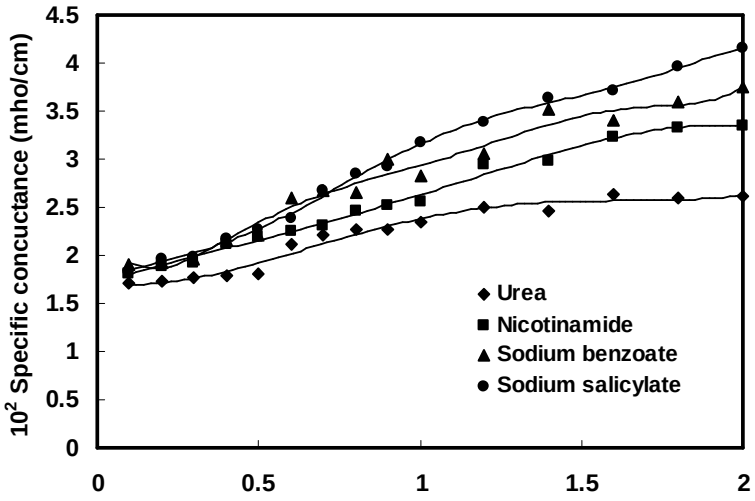

Fig. 8: Plot of specific conductance versus hydrotrope concentration for different hydrotropes

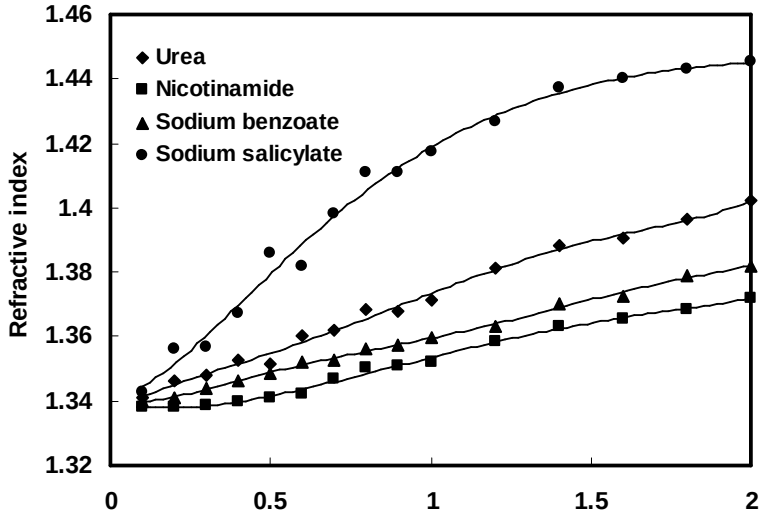

Fig. 9: Plot of refractive index versus hydrotrope concentration for different hydrotropes

This complex arrangement may be visualized as the formation of a stack of hydrotrope aggregates with that of solute molecules. It can also be visualized that such a staking arrangement of solute molecules are sandwiched between hydrotrope aggregates one upon the other. This stacking can be assumed as a sheet of solute molecules held captive between hydrotrope aggregates. However such a stacking arrangement need not have any geometric restrictions, that is to say that no regular pattern of stacking can be stressed upon. Further increase in the solubilizing effect of hydrotrope beyond maximum hydrotrope concentration C_{max} has been hampered because hydrotrope molecules are handicapped with the non-availability of water molecules to form aggregates. This explains the saturation of the solubilizing effect of hydrotropes beyond C_{max}, which can be observed from the experimental data.

It appears that the solute molecules after finding their way through the interface of hydrotrope aggregates are held hidden in the hydrotropic stack.Though, by nature, the solute and aqueous layers are immiscible because of difference in polarity, the hydrotrope aggregates are able to hold them within the possible hydrotropic stack, because of different solution properties acquired by them. Such a situation is not visible to the naked eye probably due to the negligible difference in the surface tension and other allied properties of the hydrotropic stack which contains the hidden solute and aqueous phase.

However, this arrangement seems to be a purely temporary one, because the solute particles contained within the hydrotrope stack can be brought out by simple dilution with distilled water, which alters the solution properties of hydrotrope stack. This causes the dissociation of hydrotrope molecules and the properties of hydrotrope solutions with decrease in hydrotrope concentration approach to that of water, similar to the situation below MHC. This phenomenon was observed experimentally by release of the dissolved solute from hydrotrope solutions at any concentration between MHC and C_{max} by simple addition with distilled water and hence possible re-use of hydrotrope solutions.

In general, the sort of host-guest interaction between the hydrotrope aggregates and solute molecules seems to contribute significantly to the overall stability of the solute-hydrotrope system.

Recovery of *p*-aminobenzoic acid from hydrotrope solutions

Hydrotropy can be considered to be a potentially and industrially attractive technique since the observed increase in the solubility is generally higher than that effected by other known solubilization methods. Easy recovery of the dissolved solute and the possible re-use of hydrotrope solutions make this method the most attractive one particularly at industrial levels.

Therefore, it is evident that hydrotropic solubilization is displayed only above MHC, irrespective of system temperature. Hydrotropy

does not seem to be operative below MHC, which may be a characteristic of a particular hydrotrope with respect to *p*-aminobenzoic acid. This MHC value assumes greater significance in the context of recovery of hydrotrope solutions. Since hydrotropy appears to operate only at significant concentrations of hydrotrope in water, most hydrotropic solutions release the dissolved *p*-aminobenzoic acid on simple dilution with distilled water, below MHC.

The knowledge of MHC and C_{max} values of each hydrotrope with respect to a particular acid assume greater significance in this study, since it indicates the beginning and saturation of solubilization effect of hydrotropes. The knowledge of MHC values is necessary especially at industrial levels as it ensures ready recovery of the hydrotrope for reuse. MHC is essential not only for observing significant solubilization, but also for consequent increase in mass transfer coefficient of acid.

The values of MHC and C_{max} of a hydrotrope with respect to a particular solute may be useful in determining the recovery of the dissolved solute even to an extent of calculated amount from hydrotrope solutions at any concentration between MHC and C_{max} by simple dilution with distilled water. The percentage recovery of *p*-aminobenzoic acid has been observed as 71.99 % for sodium salicylate, 66.73 % for nicotinamide, 62.83 % for sodium benzoate and 59.55 % for urea at system temperature 303 K.

CONCLUSIONS

The solubility of *p*-aminobenzoic acid, which is practically insoluble in water, has been increased to a maximum of 21.58 times in the presence of sodium salicylate as hydrotrope at a temperature T = 333 K with a corresponding increase in the mass transfer coefficient. This would be useful in increasing the rate of output of the desired product made from *p*-aminobenzoic acid. Among the hydrotropes sodium salicylate is found to exhibit stronger association with *p*-aminobenzoic acid and hence higher association constants i.e. K_{hh} = 0.154 L/mol and K_{hs} = 10.536 L/mol at system temperature 333 K. The recovery of the dissolved *p*-aminobenzoic acid from hydrotrope solution is ensured at any hydrotrope concentration between MHC and C_{max} by simple dilution with distilled water, which alters the solution properties of hydrotrope aggregates instantaneously affecting the MHC agglomerates. The highest percentage recovery of *p*-aminobenzoic acid has been observed as 71.99 % for sodium salicylate. This also facilitates the reuse of hydrotrope solution, which will eliminate the huge cost and energy normally involved in the separation of the solubilized *p*-aminobenzoic acid from its solution. The unprecedented increase in the solubilizing effect of hydrotropes is attributed to the formation of organized aggregates of hydrotrope molecules at a particular concentration.

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