

Effect of hydrotropes on solution behaviour of amphiphiles

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The hydrotropes are a special class of compounds that exhibit distinct solution properties. They may self-associate in aqueous medium, comparable to amphiphile self-association or micellization. They are efficient solubilizers and can influence the formation of micelle and microemulsion. In this review, the effect of hydrotropes on solution behaviour of amphiphiles has been presented with a brief mention of the essentials of hydrotrope action.

THE class of compounds that normally increase the aqueous solubility of sparingly-soluble solutes are called hydrotropes¹. Besides solubilization, hydrotropes have uses in vesicle preparation and selective separation, as stabilizer of o/w microemulsion, viscosity modifiers and as clearing agents in cloudy detergent formulation²⁻⁴. Alkylbenzene sulphonates based on toluene, xylene and cumene, polyhydroxy benzene, sodium salts of lower alkanols and derivatives of aromatic acids are generally considered to be effective hydrotropes⁵. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol⁶, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β -naphthols and salicylates, alkaloids like caffeine⁵ and nicotine⁷, ionic surfactants like diacids⁸, SDS (sodium dodecyl sulphate)⁹ and dodecylated oxidibenzene¹⁰. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive Π -orbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride¹¹.

The hydrotropes are known to self-assemble in solution⁵. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, etc.^{5,11}. In this review, an account of the influence of hydrotropes on solution behaviour of amphiphiles is presented. Their self-association

possibility and mode of action on phase transition of polymers are also briefly reported.

Influence of hydrotropes on amphiphile behaviour in solution

Phase-forming behaviour of surfactants

The phase-forming behaviour of micelle, microemulsion and liquid crystal-forming systems can be influenced by different additives (salts, polymers), including hydrotropes. A hydrotrope can modify the mixing behaviour of oil and water¹¹. The hydrotrope, vitamin C has been observed to change the solubility region of sunscreen E-557 in the CTAB/*n*-C₅H₁₁OH/H₂O system¹². Triangular phase diagrams in Figure 1 represent the manifestation of significant effects of hydrotropes on the phase behaviour of the ternary system water/TX-100/isooctane¹¹. The phase behaviour has distinctions: excepting pyrogallol, the others (NaSal, urea, proline and resorcinol) have produced conspicuous boundary zones between mono (1 ϕ) and biphasic (2 ϕ) regions. Resorcinol and proline have significantly reduced the single-phase zone; the residence of TX-100 in aqueous medium was less supported by proline than resorcinol. A hydrotrope can also bring about a structural transition from the liquid crystalline phase to a less ordered, isotropic fluid phase¹³⁻¹⁵. The action of sodium xylene sulphonate on didodecyl dimethyl ammonium bromide is conspicuous in this respect. It transforms the liquid crystalline phase either to a higher ordered cubic phase or a less ordered microemulsion depending on the hydrotrope/surfactant ratio¹⁴. The colloidal structure of a micellar system undergoes a major change in the presence of a hydrotrope producing thread-like micellar network reflected in its bulk property like rheology¹⁶⁻²⁰. The thread-like micellar network in the CTAB-NaSal system has been documented by TEM measurements^{16,19}. The mixed monolayers of surfactant-hydrotrope combination show less hydrophilic repulsion and a decreased micellar hydration conducive to sphere-to-rod transition. Hydrotropes thus have the ability to modify the viscosity of a surfactant-based product. The structural changes of amphiphile assemblies brought about by hydrotropes depend on their interaction with the amphiphiles and water under environmental condition.

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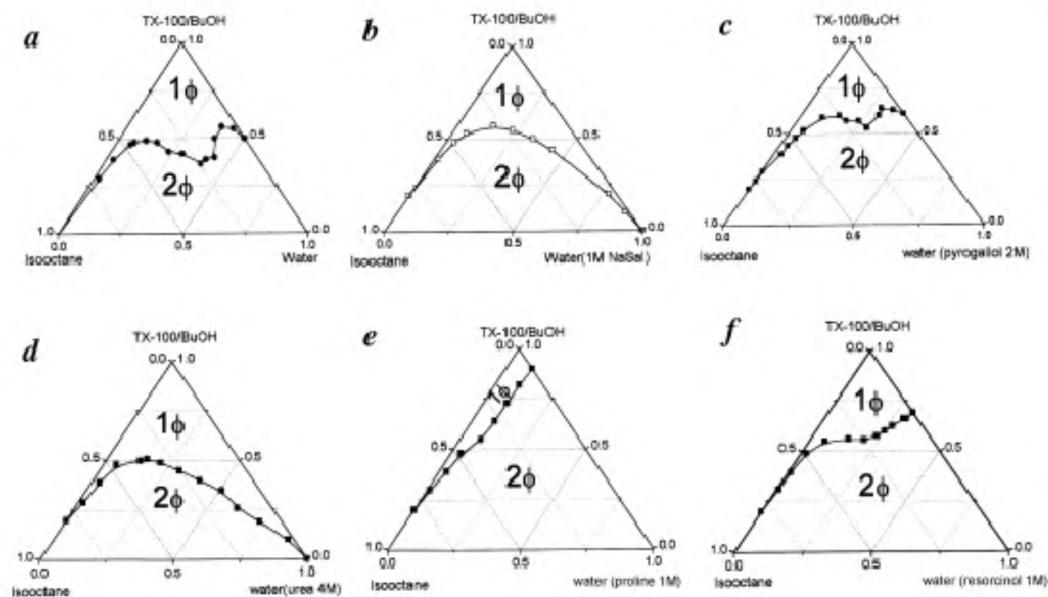


Figure 1. Ternary phase diagram of water/TX-100-Bu (1 : 1 w/w)/isooctane microemulsion-forming system in the presence of NaS (*b*), Pg (*c*), U (*d*), Pr (*e*), Rc (*f*) and in absence of hydrotrope (*a*) at 303 K. 1 ϕ Monophasic; 2 ϕ Biphasic. Apex value of unity refers to 100%.

The concentration of hydrotropes and their molar proportion with the amphiphiles are determining factors. While efficient complexation and an orientation favourable for intercomplex association may lead to higher ordered structure, random association and/or orientation should lead to dispersion with structure reduction. The issue is complex and warrants detailed probing.

On the cloud point of surfactant and polymer

Nonionic surfactants and polymers in their aqueous solutions may cloud or become turbid at and above a specific temperature by way of desolvation. Clouding should be prevented in practical processes where they are used. Hydrotropes have the ability to prevent or control the clouding process. It is known that short-chain alkyl benzene sulphonates, alkyl naphthalene sulphonates and sodium salicylate increase the cloud points (CPs) (liquid-liquid phase separation) of a nonionic surfactant or a neutral polymer^{11,18,21-23} and can thus be used to clear a cloudy detergent formulation. Table 1 presents the effect of proline, pyrogallol, resorcinol, and sodium salicylate on the clouding behaviour of TX-100 and methyl cellulose. While sodium salicylate increased CP, the other hydrotrope decreased it following the order of efficiency resorcinol > pyrogallol > proline. In Table 1, the effect of sodium *p*-toluene sulphonate (NaPTS) on the CP of ethylene oxide-propylene oxide (EO-PO) block co-polymers²⁴ has also been presented. The hydrotrope NaPTS has increased the CP of the block co-polymers. The increase was sharp for C₄(EO)₄-(PO)₁₁-OH, C₄(PO)₁₀-

(EO)₆-OH and C₁₂₋₁₄(PO)₄(EO)₅-OH and mild for C₁₂₋₁₄(EO)₉(PO)₆-OH, C₁₂₋₁₄(EO)₆(PO)₅-OH, HO-(EO)₃(PO)₂₈(EO)₇-OH and HO-(EO)₂(PO)₂₂(EO)₂-OH. NaPTS stabilized the polymers, preventing phase transition. Dhara and Chatterji²⁵ reported the influence of hydrotropes on the transition temperature (CP) and degree of swelling of poly(*N*-isopropyl acrylamide) and its hydrogel. There are also the salicylates which increased CP, whereas the other hydrotropes decreased it. The lowering of CP followed the order 4-methyl catecol > resorcinol > hydroquinone > catecol > pyrogallol. The order of the acids was *o,p*-dihydroxy benzoic acid > *p,m*-benzoic acid > salicylic acid > benzoic acid. Among the hydrotropes studied, dihydroxy benzoic acid was the most efficient CP-lowering agent. The salicylate anion increased the CP and *m*-hydroxy benzoate offered a minimum change. The influence was a cooperative process involving a number of interactions. Nicotinamide, tetrapropyl and tetrabutyl ammonium bromide also have shown a continuous effect of increased solubility of non-ionic surfactants (i.e. enhancement of CP) as the additive concentration is increased⁷. Attempts have been made to correlate the CP of the polymer with viscosity *B*-coefficients of ions in the light of making and breaking of water structure²⁶. The hydration of the hydrocarbon backbone of a polymer could also alter its CP.

The quantification of the phase separation process as in clouding has been recently attempted in terms of thermodynamics based on the mole-fractional solubility of the clouding species in the presence of hydrotropes^{27,28}. The enthalpy of the clouding process has been found to be significantly large and negative. Large negative entropy

Table 1. Clouding behaviour of TX-100, methyl cellulose and EO–PO block co-polymers in the presence of hydrotropes

[NaSal]/mol dm ⁻³	CP/°C	Proline/mol dm ⁻³	CP/°C	Resorcinol mol dm ⁻³	CP/°C	Pyrogallol mol dm ⁻³	CP/°C
TX-100 (1% w/w)							
0.0008	72.2	0.025	70.7	0.0125	66.8	0.025	68.1
0.002	73.3	0.050	70.5	0.025	62.0	0.05	64.6
0.004	74.6	0.125	69.5	0.050	51.5	0.10	58.5
0.010	77.4	0.50	63.3	0.060	47.4	0.15	53.0
0.020	79.6	0.75	58.7	0.075	40.5	0.20	48.1
0.040	82.4	1.50	45.5	—	—	0.25	42.7
0.100	90.5	—	—	—	—	0.30	37.5
Methyl cellulose (0.1% w/w)							
0.05	49.5	0.05	46.7	0.0125	46.5	0.025	46.1
0.1	52.0	0.15	45.7	0.025	44.0	0.050	44.5
0.15	53.0	0.25	43.5	0.05	40.0	0.075	42.5
0.20	57.5	0.50	41.0	0.075	38.0	0.100	39.7
0.25	59.5	1.01	39.3	0.100	37.0	0.125	38.8
0.50	70.5	1.50	39.3	0.125	35.5	—	—
0.60	74.7	—	—	—	—	—	—
EO–PO block copolymer (1 wt%)							
[NaPTS]/mol dm ⁻³	CP/°C ^a	CP/°C ^b	CP/°C ^c	CP/°C ^d	CP/°C ^e	CP/°C ^f	CP/°C ^g
0	53.0	46.2	41.5	30.0	26.9	22.7	15.4
0.14	55.4	46.2	46.2	32.3	25.4	22.7	20.0
0.25	58.5	50.0	50.0	33.8	25.4	23.9	26.2
0.50	66.2	54.6	54.6	40.0	28.5	24.6	34.6
0.75	73.8	61.5	58.5	43.9	30.0	27.7	45.4
1.05	84.6	73.1	63.1	49.2	35.4	29.6	58.5
1.50	—	91.5	68.5	54.6	42.3	34.6	77.7

^a, C₄(EO)₄-(PO)₁₁-OH; ^b, C₄(PO)₁₀-(EO)₆-OH; ^c, C_{12–14}(EO)₉(PO)₆-OH; ^d, C_{12–14}(EO)₆(PO)₅-OH; ^e, HO-(EO)₃(PO)₂₈(EO)₇-OH; ^f, HO(EO)₂(PO)₂₂(EO)₂-OH; ^g, C_{12–14}(PO)₄(EO)₅-OH.

From refs 11 and 24.

values obtained have evidenced efficient organization of the clouding species at the point of phase separation. In the presence of hydrotropes, the magnitudes of enthalpy and entropy have been found to decrease. This has suggested that the overall organization of the system diminished in the presence of hydrotropes. As a typical example, the ΔG_{cl}^0 , ΔH_{cl}^0 , and ΔS_{cl}^0 for methylcellulose were 38.8, –201 and –2.0 kJ mol⁻¹ (ref. 29) at 303 K.

Conductance percolation of water-in-oil microemulsions

The water-in-oil (w/o) microemulsions can undergo both volume and temperature-induced percolation of conductance³⁰. In this phenomenon, after a threshold droplet concentration at a constant temperature or after a threshold temperature at a constant droplet concentration, the conductance of the system may show a significant enhancement (100 to 1000 fold) by way of droplet association–dissociation process. This dynamic phenomenon is called percolation. Hydrotropes have been found to influence the conductance behaviour of w/o microemulsions, and their effects can be tested in this respect for under-

standing their influence on the structure and dynamics of the percolation-producing system. The aromatic hydrotropes, like Na-salicylate, are found to increase the ‘threshold temperature’ or ‘threshold volume’ of percolation by blocking the process of droplet fusion thus preventing mass exchange, an essential step for augmentation of the phenomenon³⁰. The polyhydroxy compounds on the other hand, may diminish the percolation threshold. The differential behaviours of polyhydroxy benzene depend on the variable position of the hydroxyl groups in the molecule¹¹. A detailed account entailing the mechanism of action of hydrotropes influencing the process of percolation has been recently proposed³¹. It has been shown that aromatic compounds having hydroxyl groups in the ortho position are incapable of enhancing the percolation threshold; those with meta substitution enhance the process and the para-substituted compounds enhance it the most. The threshold percolation temperature and the activation energy for percolation have been reported and the thermodynamics of clustering of droplets has also been discussed. Hydrotrope-assisted percolation behaviour¹¹ is depicted in Figure 2. The additive proline (Pr) has significantly assisted the process; resorcinol (Rc) and pyrogallol (Pg) are less effective, and are minorly differ-

ent from each other. The hydrotrope sodium salicylate (NaS) on the other hand, has appreciably retarded the process of percolation. The percolation-assisting hydrotropes have the ability to bridge efficiently two surfactant-coated droplets rendering easier fusion and mass exchange, resulting in large increase in conductance. The resisting hydrotropes block the negotiation between a pair of droplets hindering fusion and mass exchange, causing hindrance to the increase in conductance. The CP and percolation threshold are sensitive to molecular structure and interaction that may arise in the solution phase. Their measurements under different conditions (as with hydrotrope addition) could give useful information on the mechanism of action of the components. The area deserves further exploration.

Amphiphile self-association (micellization)

The hydrotropes are known to influence the self-association (micellization) of surfactants in solution. Sodium salicylate, pyrogallol, proline and procaine hydrochloride have been found to decrease the critical micellar concentration (CMC) of cetylpyridinium chloride (CPC) appreciably^{11,32}. The effect of changed proportions of proline, procaine hydrochloride and resorcinol with CPC on the CMC and interfacial adsorption of the mixed binary systems along with the free energy of micellization (ΔG_m^0)

and adsorption (ΔG_{ad}^0) is presented in Table 2. The CMC values of the mixed systems have decreased with increasing hydrotrope concentration, with decrease in the area minimum (A_{min}). ΔG_{ad}^0 is more negative than ΔG_m^0 ; the interfacial adsorption of the amphiphile in the presence of hydrotrope is more favourable than their association in the bulk. The results on the CTAB–NaSal system have also revealed similar behaviour (Table 3). The decrease in CMC is a consequence of efficient charge neutralization between the complexing ions CTA^+ and Sal^- , forming a 1:1 complex³³. The microcalorimetric method has evidenced two-step micellization of cetyltrimethylammonium bromide in the presence of sodium salicylate. On the other hand, a hydrotrope of large size and having substitution is detrimental to close packing by way of interaction with the amphiphile molecules producing enhanced solubilizing effect, inhibiting micelle formation¹⁰. The molecule of urea having hydrotropic property also inhibits micelle formation by way of disrupting hydrophobic bond³⁴.

Structural transition of aggregated amphiphile

The hydrotropes have the ability to cause structural changes of micelles. Ample work has been done on hydrotrope-assisted shape transition of spherical quaternary ammonium or pyridinium micelles to worm-like flexible micelles^{19,34–37}. The worm-like micelles exist in dynamic equilibrium with spherical micelles; the flexible micelles may further grow and overlap to form a quasistatic giant network producing viscoelastic effects^{38,39}. Because of their variable flow behaviour, nonlinear rheology has

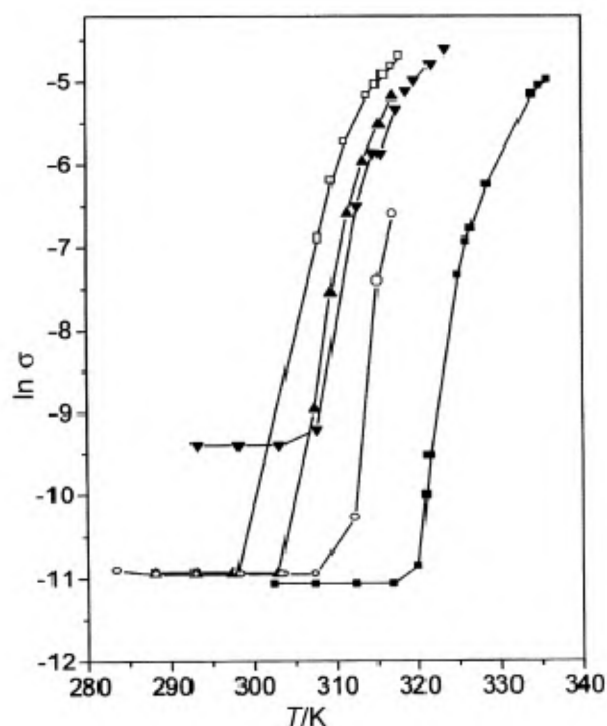


Figure 2. Temperature-induced conductance percolation in water/AOT/isooctane microemulsion system at water/AOT mole ratio 24.5 in presence of NaS (■), Pr (▼), Rc (□), Pg (▲) and in the absence (○) of additive.

Table 2. Critical micellar concentration (CMC), free energy of micellization, area minimum and free energy of adsorption at the air/water interface of pure CPC and its mixture with different hydrotropes at 303 K estimated from tensiometry

System	CMC $\times 10^4$ / mol dm^{-3}	ΔG_m^0 / kJ mol^{-1}	A_{min}/nm^2	ΔG_{ad}^0 / kJ mol^{-1}
CPC/Pr	10.0	–17.5	0.96	–31.6
0.95	7.2	–28.6	0.73	–39.9
0.80	1.0	–37.3	0.64	–49.8
0.50	0.9	–37.8	0.60	–52.7
0.20	0.9	–38.0	0.64	–51.0
CPC/PHCl				
0.95	9.6	–26.1	1.12	–44.3
0.90	7.9	–26.8	1.10	–46.4
0.75	7.6	–26.9	1.04	–44.9
0.50	5.7	–25.7	1.06	–46.3
0.25	5.5	–23.4	1.08	–44.3
CPC/Rc				
0.75	9.4	–27.4	0.83	–41.3
0.50	7.7	–29.2	0.72	–42.3
0.25	7.6	–29.6	0.72	–42.4

Pr, Proline; PHCL, Procaine hydrochloride; Rc, Resorcinol.
From ref. 11.

Table 3. Minimum hydrotope concentration (MHC) value of different hydrotropes determined by various experimental techniques

Hydrotrope	MHC/mol dm ⁻³					
	Viscosity	Surface tension	Dye solubilization	Conductivity	¹³ C NMR	Adiabatic compressibility
NaS	1.05 ^a	0.65 ^b	0.8 ^c	—	—	—
NaPTS	—	0.37 ^b	—	—	—	—
NaXS	—	0.40 ^b	0.4 ^c	—	—	—
NaCS	—	0.10 ^b	—	—	—	—
NaBMGS	—	0.70 ^b	0.8 ^c	—	—	—
Proline	0.75 ^a	—	2.5 ^c	—	—	—
Pyrogallol	1.05 ^a	—	—	—	—	—
Catechol	—	—	0.8 ^c	—	—	—
Resorcinol	0.8 ^a	—	0.7 ^c	—	—	—
Na-DHB ^d						
2,4	0.097	0.12		0.119	0.125	0.085
2,5	0.101	0.112		0.108	0.091	0.106
2,6	0.112	0.108		0.105		0.180
3,4	0.109	0.128		0.124	0.128	0.098
3,5	0.157	0.174		0.154		0.143

NaS, Sodium salicylate; NaPTS, Sodium *p*-toluene sulphonate; NaXS, Sodium xylene sulphonate; NaCS, Sodium cumene sulphonate; NaBMGS, Sodium butyl mono gluco sulphate, Na-DHB, Sodium dihydroxy benzoate.

^a, Ref. 11; ^b, Ref. 78; ^c, Ref. 77; ^d, Ref. 76.

been studied using such systems as models^{39,40}. Characterization of worm-like micelles^{16,34,41–44} and the role of counter-ions in their shape transition^{45–52} have been frequently studied and there remains scope for extending the study in the areas of interfacial adsorption and micellization, hydrodynamic behaviour and molecular complexation of surfactant in the presence of hydrotropes. Besides hydrotropes, simple salts like KBr⁵¹ and certain dye molecules⁵³ can also cause shape transition. NaCl-induced transition of spherical SDS micelle to rod-shaped micelle and micelles of diblock copolymers of vinyl ethers in aqueous solution have been also reported⁵⁴.

Counter-ion binding of micelles

The extent of counter-ion binding, counter-ion specificity, and location of the additive (hydrotrope) in the micelle play a major role on the shape transition behaviour of micelles. The added hydrotrope becomes a part of the micelle, and the effective charge on the micelle gets reduced making counter-ion-binding considerably less⁵⁵. N-14 NMR relaxation measurements have shown that Br[−] ions have a preference for cylindrical and Cl[−] ions for globular micelle. The meta/para chloro *o*-hydroxy benzoate in combination with CTAB produces worm-like micelles, while meta/para hydroxy *o*-chloro benzoate does not⁴⁶. A specific interaction may be established through the formation of charge-transfer complex with aromatic hydrotropes and ionic head group of the cationic surfactants^{47,48,55}. The growth of a rod-shaped micelle is driven by the preferential adsorption of counter-ions on the cylindrical entity^{45,50}. The sphere-to-rod transition has been found to be accompanied by enforced counter-ion binding leading to lowering of CMC and micellar ionization with the increase in hydrophobicity of the counter-ions.

The increasing hydrophobicity results in increasing counter-ion penetration into the interface and greater electrostatic interaction with surfactant head group⁴⁷. The extent of penetration into the surfactant layer varies with solute–solubilize combination. Bunton and coworkers⁴⁹ have reported similar results for the interaction between different cetyltrialkyl bromides and naphthalene-2-sulphonate. The ability of aromatic hydrotropes to stimulate the growth of the rod-shaped cationic micelle may arise from the interaction of delocalized electron cloud with the positive charge of the surfactant head group, while the increase in viscosity and aggregation number in the presence of nonpolar additives like aliphatic hydrocarbon is due to swelling of preexisting spherical micelle⁵⁰. It has been noticed by Ulmuis *et al.*⁴³ that the molecule which is solubilized in the outer region of a micelle considerably decreases the counter-ion binding, while additives solubilized in the interior have no such effect. The decreased counter-binding in the presence of interfacially adsorbed hydrotropes unfavourably affects the Gibbs energy of micellization by way of making the amphiphile self-association less spontaneous.

Mechanism of hydrotrope action

Neuberg¹ classified hydrotrope action to be distinct from micellar solubilization. Winsor⁵³ noted that hydrotropic salts are essentially the same as low molecular weight amphiphiles with marked hydrophilic solvent affinity, and proposed a mechanism as a supplement to the theory of micellization. Studies on the effect of hydrotropes on the phase behaviour of mixed systems of oil/water/hydrotrope have helped arrive at the above conclusion. Despite this, Hansen and Rosenholm⁵⁴ have considered hydrotrope action as different from normal solubilization be-

cause of the absence of extended association structures in such solubilized systems. Micellar solubilization and solubilization in presence of hydrotropes are markedly different with respect to the amount of solubilizer and solubilize. Based on the investigations by several researchers^{54–66}, the hydrotrope action has been understood in the light of medium effects, i.e. ‘co-solvency’ and ‘salting in’, coupling action between the solute and the hydrotrope, and the hydrotrope–solute complex formation or pair-wise association. Solubilization of solutes in the self-associated hydrotrope molecules as in self-associated amphiphiles, i.e. micelles has also been considered as a probable way of hydrotrope action.

Rosenholm and co-workers⁵⁴ and Lawrence⁵⁶ viewed hydrotrope action of alkanols as the effect of chain length upon the phase boundary of ternary liquid crystalline phase. Aqueous solubility of surfactant is limited due to the formation of liquid crystalline phase, which can be destabilized in the presence of a short-chain alcohol or a typical hydrotrope. The enhanced disorder as a consequence of the residence of hydrotrope in the regular structure of the condensed phase brings about a structural transition from the liquid crystal to o/w, w/o and bicontinuous regions^{9,12–15,57–61}. Guo *et al.*¹² distinctly observed that on addition of vitamin C in CTAB/pentanol/*p*-xylene/water system, the area of micellar and inverse micellar regions increased and ultimately coalesced, while the liquid crystalline region shrunked. Many formulations of pharmaceutical and health-care products need high concentration of hydrotrope acting as a ‘coupling agent’, to produce an isotropic fluid containing high concentration of surfactant.

The enhancement of both dissolution and permeation properties of drugs has been observed in the presence of hydrotropes^{62,63}. Hydrotrope–solute complex formation and ‘salting-in’ mechanism gain support from drug–hydrotrope interaction^{62–67}. The solubilization of a drug has been found to increase linearly with increasing [hydrotrope]^{63–65}. The stability constant of the complex formed has been correlated with hydrotrope structures and the extent of solubilization^{62–64}. Efficient solubilizers have been found to operate on the basis of both complex formation and salting-in mechanisms^{63,64}. Sodium salts of amino derivatives of aromatic acids are found to be more efficient solubilizers compared to the salts of hydroxy benzoic acid⁶². The extent of solubilization also varies with the relative position of the substituents in the molecule⁶³. Expansion of the ring in aromatic hydrotropes favours solubilization because of the increased interaction with the delocalized Π -orbital⁶³. Low enthalpy and entropy of pair-wise association between sodium benzoate and some drug molecules suggest that the association may be due to charge transfer or H-bonding⁶⁷.

With reference to the action of hydrotropes on the clouding of polymer poly(*N*-isopropyl acrylamide), it was found that the position of substitution on hydroxybenzene, hydroxy benzoates and benzene sulphonates

made the process different. The solubilization/destabilization of the polymer chain in solution was guided by a different combination of forces, viz. hydrogen bonding, van der Waals interaction, electrostatic interaction, hydrophobic interaction, etc. The energy difference between the collapsed state and the solvated state in each case is its contribution towards the overall energetics of the process. The complex nature of the process restricts quantification of individual contributions, making ample scope for future exploration.

Self-association of hydrotropes

In recent years, self-aggregation of hydrotropes in aqueous medium has been reported by a number of workers^{7,68–78}. The term minimum hydrotrope concentration (MHC) has been used in consonance with the CMC of surfactants. The MHC values of several hydrotropes are presented in Table 3. Rath⁷⁰ has emphasized the formation of intramolecular stack-type aggregation of hydrotropes. The aggregate formation of sodium salicylate has been evidenced from different solution properties (conductance, diffusion, density, viscosity and solubilization) at concentration $> 0.7 \text{ mol dm}^{-3}$ at 25°C (refs 11 and 73). Recently, Palepu *et al.*^{68,76} have determined the MHC values of Na-dihydroxy benzoate adopting viscosity, conductivity, compressibility, surface tension and ^{13}C NMR techniques. Like Rath⁷⁰, they have also considered stacking of hydrotropes as the process for self-association. From detailed physico-chemical studies, Balasubramanian and co-workers^{5,69,75,77,78} concluded that hydrotrope action is a collective molecular phenomenon involving the formation of non-covalent aggregates. According to them, there are (a) comparable microenvironmental features of hydrotrope assemblies with micelles, (b) surface activity of hydrotrope solutions are similar to micelle-forming surfactants, (c) sigmoidal solubilization curves show cooperativity in the process, and (d) open-layer assemblies of hydrotropes exist in their crystalline state.

The high concentration required for self-association of hydrotropes (i.e. high MHC values) strongly contrasts micelle formation and casts doubts on the formation of ordered assemblies as in micelles. Besides, the hydrotropes are essentially not efficient surface-active compounds, i.e. they do not appreciably lower the surface tension of water. Although viscosity measurements have supported a kind of self-association for proline, sodium salicylate, pyrogallol and resorcinol (Table 3), the microcalorimetric method has failed to give evidence of hydrotrope association, although the method is sensitive enough to register CMC of surfactants¹¹. This is evident from Figure 3a and b. In Figure 3a, the different heats of dilution of NaCl (a nonmicelle-forming salt) are plotted with [NaCl]. Similar results on CPC are presented (inset, Figure 3a), which show sharp change in the differential heats of dilution indicating self-association, i.e. micelle

formation. In Figure 3b, results on different hydrotropes do not evidence sharp transitions indicative of micelle formation. The hydrotropes have produced monotonous change like NaCl. Figure 4, presenting the relative viscosity–[hydrotrope] profiles for proline, sodium salicylate, resorcinol and pyrogallol, on the other hand, evidences crossing of two straight lines (a representation depicted in the inset) in favour of MHC formation¹¹. The hydrotrope urea has not shown such a behaviour; the relative viscosity increases linearly with [urea]. The hydrotropes have produced monotonous change in the thermal behaviour, no sharp change has been observed. The self-association of hydrotropes yielding a break at higher solute concentration is thus doubtful; this can be a common occurrence of a measured property due to activity and other effects. Further work is required for a conclusive decision on hydrotrope association. Until then, the concept of hydrotrope association and MHC must not be discarded, but should be used with reservation.

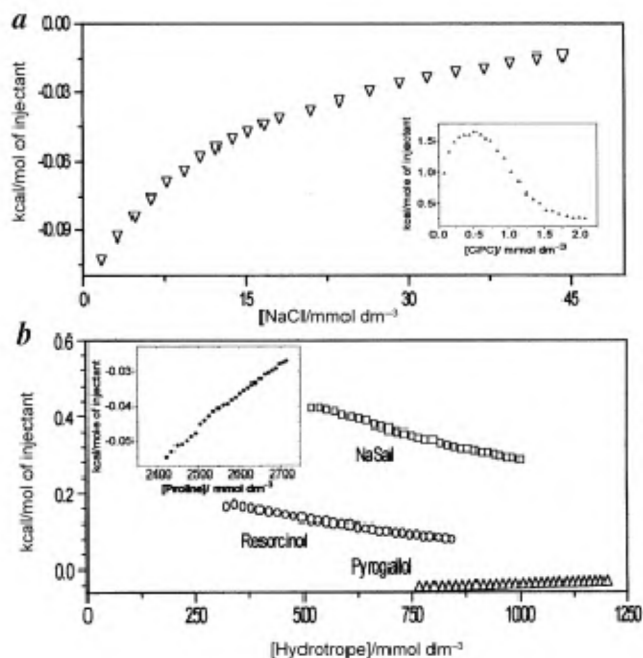


Figure 3. Differential enthalpy of dilution. *a*, NaCl (▽). (Inset) micelle-forming surfactant CPC (△). *b*, Hydrotropes, Pr (inset), NaS (□), Rc (○) and Pg (△) at 303 K.

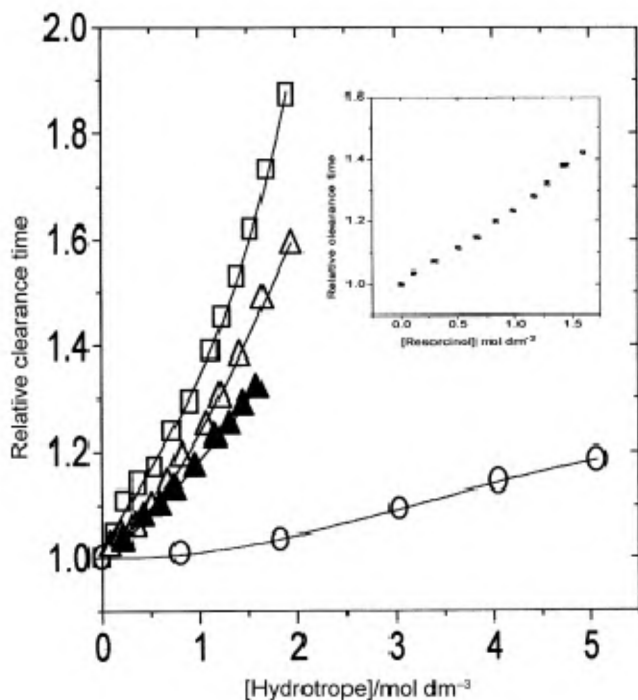


Figure 4. Relative clearance time (flow time with and without hydrotrope) vs concentration curve for different hydrotropes at 303 K. △, Pr; □, NaS; ■, Rc (inset); ▲, Pyrogallol; ○, Urea.

resorcinol and pyrogallol, on the other hand, evidences crossing of two straight lines (a representation depicted in the inset) in favour of MHC formation¹¹. The hydrotrope urea has not shown such a behaviour; the relative viscosity increases linearly with [urea]. The hydrotropes have produced monotonous change in the thermal behaviour, no sharp change has been observed. The self-association of hydrotropes yielding a break at higher solute concentration is thus doubtful; this can be a common occurrence of a measured property due to activity and other effects. Further work is required for a conclusive decision on hydrotrope association. Until then, the concept of hydrotrope association and MHC must not be discarded, but should be used with reservation.

Conclusion

It has been established that hydrotropes show interesting solution properties. It can (a) undergo specific interaction with amphiphile, (b) modify mixing behaviour of oil and water, (c) self-associate in water and (d) enhance aqueous solubility of different solutes. Although physico-chemical investigations on solution properties of hydrotropes have well-passed their infancy, further work is required to rationalize the phenomena encountered. Hydrotropes exhibit variable influences on microstructures of amphiphile aggregates. The liquid crystalline phase can be transformed into a higher or lower analogue. It may promote as well as inhibit micelle formation and can alter the liquid–liquid phase-separation temperatures of ethoxylated surfactant. In a microemulsion, it alters the solubility region and percolation threshold temperature. Packing requirement in the surfactant monolayer, extensive H-bonding with solvent molecules and the ability of complex formation may explain the selectivity in hydrotrope action. Hydrotropes have been found to manifest a change in their physical properties after a threshold concentration, i.e. MHC. Although there are evidences in favour of self-association of hydrotropes, conclusive evidence in favour of MHC and clear information on the nature of aggregation are still lacking.

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