CHAPTER 1

HYDROTROPY - AN OVERVIEW
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1.0. INTRODUCTION:

Hydrotropes are compounds that, at high concentrations, enhance the solubility in water of several hydrophobic substances. The term hydrotrope and the concept of hydrotropy were introduced by Neuberg (1916). He found that alkali metal salts of benzoic acid, salicylic acid, benzenesulfonic acid and its many derivatives, naphthoic acid, and various hydroaromatic acids are able to function as hydrotropes and the hydrophobic substances that he tried were alcohols, aldehydes, ketones, hydrocarbons and so on. Shortly thereafter, a few other papers describing the phenomenon of hydrotropy were published by Freundlich (1927, 1929), and Traube et al. (1927).

1.1. HYDROTROPY - DIFFERENT PERSPECTIVES:

1.1.1. Mckee's view: Mckee (1946) was interested in using hydrotropes for chemical engineering and industrial applications. He showed that concentrated aqueous solutions of soluble neutral salts of organic acids such as sodium benzoate (NaB), salicylate (NaS), benzenesulfonate (NaBS), p-toluenesulfonate (NaPTS), xylenesulfonate (NaXS), and cumenesulfonate (NaCS) increase the solubility of various organic and inorganic compounds in water. In contrast to the earlier views of Neuberg and others, who considered only organic compounds to function as hydrotropes, Mckee suggests that even some of the inorganic substances may be added to the class of hydrotropes. Some of these are alkali iodides, thiocyanates, oxalates and bicarbonates. But the current practice is not to include inorganic salts in the category of hydrotropes, the reasons for which are discussed in chapter 2.

In any event, Mckee brought out some important features of hydrotropy. He noted that
most hydrotropic solutions precipitate the solubilizate on dilution with water. This helps in recovering the hydrotrope for further use. He pointed out that NaXS is very useful in the paper-pulp manufacturing process, which appears to be less expensive than the customary alkaline process. The two important conclusions about hydrotropy that Mckee arrived at are: 1) a rather large concentration of the hydrotrope in water is required for it to display its action, and 2) the phenomenon is similar to "salting in" process. According to Mckee, the phenomenon of hydrotropy could be explained based on the theory of mixed solvents (Bancroft, 1935).

1.1.2. Booth and Everson's view: These authors used 40% NaXS solution in water to solubilize a variety of substances such as aliphatic and aromatic hydrocarbons, alcohols, ethers, aldehydes, ketones, amines, oils and so on and found this solvent to be an excellent hydrotrope (Booth and Everson, 1948). They had also compared the solubilizing ability of the o-, m-, and p-isomers of the xylenesulfonate towards a variety of hydrophobic substances and observed that all the three isomers exhibit comparable hydrotropic efficiency. However the meta isomer is preferable at lower temperatures due to its higher water solubility (Booth and Everson, 1950). Amongst Na benzenesulfonate, Na cymenesulfonate, Na toluenesulfonate and Na xylenesulfonate, the last one appears to have maximum solubilizing ability (Booth and Everson, 1949). The important point that has emerged from these studies is that the increased solubility brought about by xylenesulfonate is neither linear nor monotonic with increasing hydrotrope concentration, but displays a sigmoidal behaviour. This observation, as we will discuss in chapter 2, plays a major role in understanding the mechanism behind hydrotropy.

1.1.3. Winsor's view: Winsor (1948) made an attempt to relate hydrotropic action to solubilization and emulsification. He noted that a hydrotrope induces mutual solubilization of organic and aqueous liquids and regarded hydrotropy to be quite similar to cosolvancy.

1.1.4. Licht and Weiner's view: These authors obtained equilibrium solubility data at 30°, 40°, and 60° C for the system water-hydrotrope-benzoic acid. In order to look at the influence of similarity in structure between the solute (in the present case it is benzoic acid) and the
Hydrotrope, solubility data was obtained with six different hydrotropes. They, in the order of decreasing effectiveness, are: Na p-cymenesulfonate > o-xylenesulfonate > m-xylenesulfonate > p-bromobenzenesulfonate > p-toluenesulfonate > benzenesulfonate. Their interpretation of these results was that the increased solubility is due to "salting-in" effect rather than due to similarity in structure (Licht and Weiner, 1950). Their view of hydrotropy thus agrees with that of Mckee.

1.2. HYDROTROPY-SOME MECHANISTIC ASPECTS:

1.2.1. Complex formation: The importance of hydrotropes in pharmaceutical applications was realized by Brown and Riseman (1937), who showed that a mixture of the xanthine drug theobromine with sodium acetate was very effective in the treatment of angina pectoris. They noted that the hydrotropes NaS and Na acetate solubilize theobromine, whose solubility in water is markedly low, (3 mM or 1g in 200 ml of water). Its solubility is enhanced to 1 in 1.5 as an equimolar mixture with NaS. They attribute this enhanced solubility to a complex formation between the solute and the hydrotrope molecules. Subsequently Neish (1948) looked at the hydrotropic effect of caffeine (solubility, 0.1 M in water) in solubilizing sulfathiozole, sulfapyridine and so on. A few years later Guttman and Athalye (1960) had also shown that the vitamin riboflavin is solubilized by xanthines and related molecules. Of the several hydrotropes of interest, they looked particularly at the solubilizing effect of caffeine, theophylline, and dimethyluracil and concluded that complexing of the xanthine with riboflavin appears to be the primary factor in the solubilizing phenomenon.

1.2.2. Phase Diagrams of hydrotropes studied by Lawrence, Friberg and Pearson: Lawrence (1959) has constructed phase diagrams involving CTAB-water-caproic acid, whereas Friberg concentrated on the system NaXS-water-octanoic acid. The two essential features that result from these studies are (a) comparatively large concentration of the hydrotrope is needed vis-a-vis
surfactant, and (b) the amount solubilized by a hydrotrope is large compared to what is found with a surfactant.

These two characteristics are shown in Figure 1.1 (Friberg and Rydhag, 1970). Figure 1.1a shows the strongly enhanced solubility of octanoic acid in a Na xylenesulfonate solution for concentrations in excess of 20% by weight. The contrast between a solubility of less than 1% for concentrations at 15% of the hydrotrope and of more than 30% at higher concentrations reflects the typical properties of hydrotrope mediated solubilization. Figure 1.1b exposes the distinction of solubilization by the surfactant Na octanoate. In this case the solubilization is initiated at much lower concentration, but it remains at a modest level of below 8%. It has been shown by Shinoda (1963) that a surfactant with a shorter chain has an increased value of critical micellar concentration (CMC), beyond which solubilization is effected. A phenyl group corresponds to 3.5 methylene groups in a straight chain. Using this as the equivalence, the high hydrotrope concentration required to initiate solubilization (Figure 1.1a) is as expected.

In order to understand the differential solubilizing abilities displayed by hydrotropes and surfactants better, phase diagrams were constructed using the systems, water- octanoic acid- Na octanoate, and water- octanoic acid- Na xylenesulfonate. Figure 1.2 reveals the essential differences between the two systems mentioned above. The combination of octanoic acid and the surfactant gives rise to several phases, four of which are marked in the figure. Area A (Figure 1.3a) is the micellar solution from Figure 1.1b; area C is a liquid crystalline phase containing cylindrical surfactant associations stacked in a close-packed hexagonal array (Figure 1.3d); area D is lamellar liquid crystal (Figure 1.3c); and area E is an octanoic acid solution with inverse micelles (Figure 1.3b). The essential feature of the diagram is the lamellar liquid crystal region separating the normal micellar solution from the inverse one. This is in contrast to the conditions with the hydrotrope (Figure 1.2), for which only one solubility region of significance is found: a continuous isotropic liquid phase reaching from the aqueous corner to 80% octanoic acid without interruption. The reason for the "anomalously" high solubilization by a hydrotrope...
Figure 1.1 (a) The hydrotrope as a solubilizing agent is characterized by the high concentration needed to initiate solubilization and the large amounts solubilized at high hydrotrope concentrations. (b) A surfactant, on the other hand, is active at lower concentration (cmc) but the amount solubilized remains low at high concentrations (micellar solution).
Figure 1.2. The system water, sodium octanoate (solubilizer), and octanoic acid (---) contains an aqueous isotropic solution (A) with normal micelles (Fig. 1.3a), an octanoic acid isotropic solution (E) with inverse micelles (Fig. 1.3b), a liquid crystal (D) with lamellar structure (Fig. 1.3c), and a liquid crystal (C) of hexagonally close-packed cylinders (Fig. 1.3d). With sodium xylene sulfonate as the solubilizer (—) a single isotropic solution region is found.
Figure 1.3. The molecular organization in normal micelle (a), an inverse micelle (b), a lamellar liquid crystal (c), and a liquid crystal of hexagonally close-packed cylinders (d).
becomes apparent from these phase diagrams. Its solubility region is not interrupted by the formation of the liquid crystal; the shift from a water phase to an octanoic acid phase takes place continuously without a phase transition, which is not so in the case of surfactants. A hydrotrope is able to retard or inhibit the onset of the liquid crystalline phase.

1.2.3. Hydrotropy- effect of molecular structure: In order to understand the importance of molecular structural features of hydrotropes, a variety of solubilizing agents were chosen and their effect studied on the same representative lipophile, riboflavin (Yamamoto et al., 1955). Thiourea and its derivatives showed negligible effect and so did nicotinamide and isonicotinic acid. Hydroxybenzoic acid salts and related compounds were found to have very high solubilizing efficiency. The solubilizing effect of some of these hydrotropes is shown in Table 1.

Table 1: Solubility of riboflavin in aqueous hydrotropes (Yamamoto et al., 1955)

<table>
<thead>
<tr>
<th>HYDROTROPE</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
<th>5%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na benzoate</td>
<td>0.38</td>
<td>0.48</td>
<td>0.64</td>
<td>1.10</td>
<td>3.10</td>
</tr>
<tr>
<td>Na salicylate</td>
<td>0.53</td>
<td>0.96</td>
<td>1.30</td>
<td>2.90</td>
<td>7.70</td>
</tr>
<tr>
<td>(2-hydroxy benzoate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na gallate</td>
<td>0.67</td>
<td>0.92</td>
<td>1.46</td>
<td>2.85</td>
<td>7.34</td>
</tr>
<tr>
<td>(3,4,5-trihydroxy benzoate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na 3-hydroxy-2-naphthaoate</td>
<td>5.60</td>
<td>12.3</td>
<td>19.6</td>
<td>34.3</td>
<td>97.8</td>
</tr>
<tr>
<td>Na 4-picolinate</td>
<td>0.37</td>
<td>0.50</td>
<td>0.66</td>
<td>1.10</td>
<td>2.40</td>
</tr>
<tr>
<td>(pyridine-4-carboxylate)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

It can be noticed that the introduction of polar groups to NaB does not dramatically change hydrotropic efficiency, while changing from the benzene ring to the more hydrophobic
naphthalene moiety causes a tenfold improvement. The presence of the polarizable hetero atom
N reduces the hydrotropy of 4-picoline compared to that of Na benzoate. The importance of the
hydrophobic part of the hydrotrope can be realized from Table 1.

In a similar vein, Gans and Higuchi (1957) looked at the solubilizing ability of Na
salicylate, Na p-hydroxybenzoate, Na saccharin and Na p-aminobenzoate towards the antibiotics
tetracycline and oxy-tetracycline. It was found that tetracycline interacts better with all these
hydrotropes than oxytetracycline. With the exception of NaS, at concentrations below 0.5 M, all
other hydrotropes showed comparable solubilizing efficiency. It was observed that the
dependence of the hydrotrope concentration versus antibiotic solubility is not linear but
sigmoidal in nature (Booth and Everson. 1949). The authors suggest that hydrophobic
interactions and complex formation between the drug and hydrotrope as the causative factors for
the observed enhanced solubility.

1.2.4. Hydrotropy- thermodynamic parameters: Sego Ueda has studied the thermodynamics
of the interaction between riboflavin (and seven other solutes) and the hydrotrope Na benzoate
(NaB) and its hydroxy and amino derivatives. He showed a 1:1 aggregation between the solute
and the hydrotrope and determined the enthalpy and entropy of the process. The enthalpy change
upon 1:1 aggregation of riboflavin and NaB at 298 K was -7.2 kcal/mole and the entropy change
was -21.8 eu. These changes observed in the thermodynamic parameters may be regarded as the
driving force behind hydrotropy (Ueda, 1966a). In the subsequent two papers, he showed that
there is a perceptible decrease in the activity coefficient of the solute in the presence of the
hydrotropic agent, and that there are two main factors involved in hydrotropic action: molecular
association, and a hydrotrope mediated decrease in the activity coefficient of the solubilizate
(Ueda, 1966 b, c).

The idea of molecular association of hydrotropes was studied in some detail by Rath
(1965). Since several hydrotropes are aromatic in nature (NaCS, NaXS, NaS), the idea of
intermolecular association involving the stacking of the aromatic rings in the assembly, as a deck
of cards, has been pursued since his first report.

The connection between hydrotropy and pharmaceutics was summarized in detail by Elworthy et al. (1968). They suggested that the mechanism of action of hydrotropy is varied and perhaps different from micellar solubilization. Some of the important factors that govern hydrotropy are salting in, complexation, polarity effects (Paruta and Sheth, 1966), and the hydrophobic effect. The importance of hydrophobic interactions in hydrotropy was also investigated in some detail by various groups (Kostova and Markina, 1971; Mirgorod and Kulibaba, 1979; Danielsson and Stenius, 1971; Schwuger, 1972). It was shown that intermolecular association occurs in aqueous solutions of all straight chain alkanoates except acetate and propionate. True association colloidal behaviour was seen only with octanoates and higher homologues, while weaker association was noted in the case of lower ones (Danielsson and Stenius, 1971). Probably a hydrotrope molecule may be regarded as equivalent to either a short-chain amphiphile (Reinus, 1968; Danielsson, 1968), or even with bile salts (Fontell, 1965, 1968).

### 1.3. HYDROTROPY- STATUS A DECADE AGO:

#### 1.3.1. Self association of hydrotropes: Self-aggregation of hydrotrope molecules and its implications in the mechanism of hydrotropy was studied in some detail by Saleh and coworkers from Egypt (Badwan et al., 1980, 1983; Saleh et al., 1983, 1986, Saleh and El-khordagui, 1985). These authors constructed phase diagrams of water: cyclohexanol: hydrotrope (NaB or NaS) in one case and in the second system where the hydrotrope was replaced by a surfactant, Na dodecyl sulfate (SDS). From these phase diagrams they realized that hydrotropy is different from micellar solubilization, in terms of magnitude and qualitatively as well. The infrared spectrum of the C-H vibrational overtone region around 1.6-1.7 μ showed concentration dependant changes, including isobestic points. From this they concluded that there are two or more discrete species, which
have resulted due to self-aggregation of the hydrotrope molecules, at high concentrations. In a more elaborate study of the solubilization of benzodiazepine (diazepam) derivatives in NaS solution, they found that the diffusion rate, electrical conductivity, density, and the amount of diazepam solubilized all change critically beyond a concentration of 0.7 M NaS at 298 K. Based on these results, the authors suggested that NaS aggregates beyond a critical concentration into an intermolecular stacked assembly.

1.3.2. Classification of hydrotropes: Sales and his coworkers noted that the chemical structures of the conventional Neuberg hydrotrope molecules (of which NaB is the prototype) consist of two essential features: an anionic and hence water soluble group and a hydrophobic aromatic ring or ring system. Based on these features they proposed a new definition for hydrotropes as follows:

"Hydrotropic agents are freely soluble organic compounds which, at a concentration sufficient to induce a stack-type aggregate, considerably enhance the aqueous solubility of organic substances practically insoluble under normal conditions. These compounds may be cationic, anionic or neutral molecules".

The planar hydrophobic moiety is thought to be essential for inducing stack type aggregation whereas the hydrophilic ionic part helps in enhancing the hydrotrope solubility in water. If the role of the ionic group is only to increase the aqueous hydrotrope solubility, then even cationic or nonionic polar groups should serve the purpose. In order to test this, Saleh et al. studied the cationics, p-aminobenzoic acid (PABA) hydrochloride, procaine hydrochloride, and ducacaine hydrochloride and found them to be good hydrotropes, able to solubilize the representative lipophile riboflavin very effectively. It appears from our studies (to be reported in chapter 3) that the nonionics, resorcinol and pyrogallol are even better solubilizing agents. Data suggests that cationics solubilize riboflavin in water to the extent of 5-15 mM, while the nonionics solubilize to a maximum level of 50-100 mM.

The above definition of hydrotropes would seem to dictate that only organic molecules
having a planar hydrophobic ring system and polar groups attached to it should be considered as hydrotropes. If it is so, then the inorganic compounds such as KI, KSCN, NH₄CN, which Mckee considered as hydrotropes, will not come under the class of hydrotropes. This might be appropriate in the sense that these inorganic molecules bring in the solubilizing ability by the salting in process, which might or might not really be the operating mechanism behind hydrotropy. The second point about the definition is that it stresses the amphiphilic nature of the hydrotrope molecules, wherein the hydrophobic moiety is the “functional” part and the polar group aids in the high solubility of the hydrotrope itself in water. For example, the solubility of benzene in water is less than 10 mM, but introduction of the hydroxy group makes phenol soluble to the extent of 0.7 M, while the solubility of m-dihydroxybenzene (resorcinol) is 10 M in water. Third, the definition requires high concentration of the hydrotrope, sufficiently high as to form molecular aggregates, which are implicated to be the functional species in hydrotropy. The fact that molecular stacking occurs in the hydrotrope molecules reflects the planarity feature of the hydrophobic part of the hydrotrope molecule. Aliphatic and nonaromatic compounds would then be disqualified on this score. This restriction needs to be relaxed since aliphatic compounds such as Na 2-ethylhexylsulfate, and Na dihexyl sulfosuccinate (Hansen and Rosenhalm, 1986) have been used as effective hydrotropes. Two other linear chain hydrotropes that have come into prominence are Na n-butylmonoglycolsulfate (NaBMGS), and diacid or [5-(or 6-)-carboxy-4-hexyl-2-cyclohexen-1-yl] octanoic acid (Ward et al., 1975). Figure 1.4 shows the chemical structures of several of these hydrotropes.

1.4. APPLICATIONS OF HYDROTROPES:

1.4.1. Solubilizing agents in drug formulations: Hydrotropes have been used to prepare formulations of the drug temezapam and to stabilize the formulation by lyophilization (Woolfson et al., 1986). More recently hydrotropes were used in the formulations of the coronary
Figure 1.4. Structures of some hydrotropes
vasodilator drug nifedipine (Jain et al., 1988 a, b). The use of hydrotrope in these instances is to act as a nontoxic vehicle that solubilizes and keeps the drug in a stable homogeneous phase, rather than as an emulsion or a multiphase suspension. It was shown that hydrotropes enhance the absorption of the drug theophylline and the hormone insulin, when coadministered in the experimental animals (Nishihata et al., 1981, 1983). Hydrotropes are also found to be useful as vehicles for drugs administered through transdermal delivery (Osborne, 1988).

1.4.2. Biological applications: The effect of hydrotropes on the activity of the enzymes dehydrogenases (Kohn and Rekker, 1978) has been reported, so also the increased antibacterial action of cresols in hydro tropic solution (Ebian et al., 1987). Some hydrotropes can cause hemolysis of human erythrocytes (Saleh et al., 1987a). Saleh and coworkers also found that the hydrotropes Na benzoate (NaB) and Na salicylate (NaS) affect the structure of haemoglobin and this was attributed to the effect of the hydrotropic salts on the water structure at the Fe-histidine bond (Saleh et al., 1987b). The antiinflammatory effect of the hydrotrope aspirin (actually acetylsalicylic acid) has been attributed to an inhibition of prostoglandin synthesis (Kubota et al., 1979). The binding of hydro tropic acid (HTA) to plasma proteins was studied in intact, bile duct-caulated, bile duct-ligated, and the bile duct-cannulated as well as nephrectomized rats. The stereoselective excretion of HTA-G is regulated in the step from the liver into bile and blood (Yamaguchi and Nakamura, 1985). Of late, the ability of proline to function as a hydrotrope was looked at, since proline belongs to the class of compatible solutes, which help cells cope with the osmotic stress (Srinivas and Balasubramanian, 1995).

1.4.3. Catalysts in heterogeneous chemical reactions: The use of hydrotropes in this area has largely been pioneered by Sharma and coworkers (Janakiraman and Sharma, 1985; Pandit and Sharma, 1987; Sane and Sharma, 1987). While this is conceptually similar to micellar acceleration of chemical reactions, selectivity among the products is seen to a greater extent with hydrotropes. In the presence of the hydrotrope NaPTS, these authors have seen a tenfold to thousandfold increase in the alkaline hydrolysis rates of the arylbenzoates and of tridecyl formate.
Here NaPTS solubilizes the reactants and enhances the reaction rate. They had also looked at the oximation of cyclododecanone in the presence of hydrotropes. The cross-Cannizaro reaction of m-phenoxy-benzaldehyde and m-bromobenzaldehyde with formaldehyde was seen to be enhanced by as much as 177-fold in the presence of 30%(w/v) PEG 200 as the solubilizing agent. In this case, not only did the reaction rate increase, but selectivity amongst the products was also seen. The product m-phenoxybenzyl alcohol was formed with a selectivity of 79% over the coproduct m-phenoxybenzoic acid. In contrast, the cationic surfactants cetylpyridinium bromide and cetyltrimethylammonium bromide enhanced the reaction rate by a factor of only 5 or 6, and the product selectivity was also lower (53%). Thus, hydrotropy appears to be different from micellar solubilization and proved to be more advantageous. In our laboratory, NaCS was used in the maintenance of oscillatory chemical reactions (Balasubramanian and Rodley, 1988). A notable extension of the lifetime of the usual oscillator was observed.

1.4.4. Agents in the extractive separation of mixtures: Hydrotropes have been used in the extractive distillations and solvent extractions (Gaikar and Sharma, 1986; Mahapatra et al., 1988). Aqueous hydrotrope solutions have been used by them to separate components from mixtures of phenolic substances. It is not clear whether this is a general rule, but in these cases, the selectivity of separation appears to depend on the preferential association of one of the components of the mixture with the hydrotrope molecule. In extractive distillation, the added hydrotrope molecule modifies the vapour-liquid equilibration relationship by selective association with one of the components of the liquid mixture. This alters the relative volatility ratio \( r \), which is defined as the ratio of the components in the vapour phase to that in the liquid phase. The quantity \( r \) is thus an enrichment factor. Using NaPTS as the hydrotrope, it was shown that the \( r \) value of the 2,6-xylenol/p-cresol binary system improved from 1 to 3, with the molar ratio of the hydrotrope: total phenol as 1, and using a hydrotrope: total phenol mole ratio of 2 they achieved the \( r \) value of 3.9. Batch recovery of the substances by such extractive distillation was also done. The use of hydrotropes for such applications is particularly attractive because of
various factors, such as easy recovery of products, high selectivity, and the avoidance of emulsification problems normally encountered with surfactants.

1.4.5. Agents in the cleaning and washing processes: These processes are mainly concerned with the removal of "oily dirt", a complex mixture of hydrophobic substances from solid surfaces and fabrics. These phenomena depend to a high degree on the complex phase equilibria in the surfactant-water-"oily dirt" system (Raney and Miller, 1987).

Considering the number of applications hydrotropes have in various pharmacological, industrial and biological processes, it is important to delineate the mechanistic aspects and the structure-function relationships involved in hydrotropy. It is essential to understand the self-aggregation behaviour of hydrotropes and the intermolecular interactions involved therein in order to determine the nature and strength of these self-assemblies. Studies on the microenvironmental features offered by these hydrotropic assemblies is valuable and that could reflect on their solubilizing efficiencies. Since hydrotropy appears to operate at high concentrations, it might be possible to find similar structures in solution as well as in solid states; if it is so then crystal structure analysis of some of these hydrotropes would throw light on the actual nature of these aggregates. We turn to address some of these issues in the following chapters using a variety of methods such as surface tension, fluorescence, nuclear magnetic resonance and electron spin resonance spectroscopic techniques.