CHAPTER 5

MOLECULAR ORGANIZATION IN HYDROTROPE ASSEMBLIES
5.0. **INTRODUCTION:**

We have shown earlier that hydrotropy is a collective molecular phenomenon, brought about by the self-assembly of weakly amphiphilic molecules in water, and that is readily modulated by factors such as polarity, steric features, and related factors. The MHC values obtained for several hydrotropes are manifold higher than the CMC values of conventional surfactants, which suggests that the intermolecular interactions involved in the self-aggregation of hydrotropes are different and weak compared to that of surfactant micelles. Though it has been surmised that aromatic hydrotropes form stack-type assemblies which offer a less polar interior where lipophilic substances can be solubilized, the actual structure of these aggregates is not known in detail. Since intermolecular packing and interactions that occur in crystals would be expected to start manifesting themselves at high concentrations in solution, it is possible that there exists a similarity between the structure of the hydrotropic aggregate in solution and that obtained from the solid crystal.

We have shown that proline acts as a hydrotrope at a concentration of 3 M and beyond. The crystal structure of proline was determined by Kayushina and Vainstehein (1965) and they suggest an orderly packing or layering of the pyrrolidine rings. Similarly the crystal structures of some nonionic hydrotropes such as catechol, resorcinol and pyrogallol have been investigated (Brown, 1966; Wunderlicht and Mootz, 1971; Robertson, 1936) and the hydrotropic efficiency of these compounds was studied by us (Srinivas et al., 1991). Based on the expectation that crystal structure analysis of hydrotropes would be of considerable interest in a generalised understanding of the mechanistic aspects of hydrotropy, we have determined the crystal structures
of some anionic hydrotropes and the results are presented in this chapter. The hydrotropes that have been studied are: Na p-t-butylbenzenesulfonate (I), Na cumenesulfonate hemihydrate (II), Na p-toluenesulfonate hemihydrate (III), Na 3,4-dimethylbenzenesulfonate (IV). The intermolecular packing patterns that we see in these structures offer some clues about the mode of action of hydrotropes at the high concentrations at which they function.

5.1. MATERIALS AND METHODS:

The compounds used were of the highest purity available from commercial sources and were further purified by recrystallization.

5.1.1. Solubilization experiments: Solid fluorescein diacetate (FDA) was added to the hydrotrope solutions (the concentration of each hydrotrope being kept at 4 times its respective MHC value) and equilibrated for several hours in a constant-temperature shaker. The suspension was centrifuged and the concentration of FDA determined spectrophotometrically at 480 nm, using a Hitachi model 330 instrument.

5.1.2. Methods used in X-ray crystal structure analysis and its parameters: The experimental conditions were: MoKα radiation, graphite monochromator, 2θ<sub>max</sub>=480, omega scan. Each structure was solved by direct methods and refined by Siemens-Shelxtl-Plus program system and Shelxl-93. Compound I: Na p-t-butylbenzenesulfonate dihydrate, C<sub>10</sub>H<sub>13</sub>O<sub>3</sub>NaS.2H<sub>2</sub>O, M= 240.23, monoclinic, space group C2/c, a=39.985 (5), b=6.161(1), c=10.802(2)Å, β=102.12(1)°, V=2601.7(7)Å<sup>3</sup>, Z=8, ρ<sub>calc</sub> 1.227 Mg/cm<sup>3</sup>; 1694 independent reflections, 1265 observed reflections with I≥3σ(I), data to parameter ratio 8.4 :1; R=4.3%, Rw=4.7%. Compound II: Na cumenesulfonate hemihydrate, C<sub>9</sub>H<sub>12</sub>O<sub>3</sub>NaS, M=231.24, orthorhombic, space group Pbc<sub>a</sub>, a=16.051(6), b=6.563(2), c=40.24(2)Å, V=4239(3)Å<sup>3</sup>, Z=16, ρ<sub>calc</sub> 1.449 Mg/cm<sup>3</sup>; 3323 independent reflections, 2007 observed reflections with Fo≥4σ(Fo), data to parameter ratio 7.49 :1; R=5.5%, Rw=13.0%. Compound III: Na p-toluenesulfonate hemihydrate, C<sub>7</sub>H<sub>8</sub>O<sub>3</sub>NaS, M=203.18, monoclinic, space group P2(1)/c, a=17.81(2), b=14.588(11), c=6.686(7)Å,
\[ \beta = 90.45(6) \circ, V = 1737(3) \text{Å}^3, \ Z = 8, \ \text{cal} \ 1.544 \text{Mg/cm}^3; \ 1380 \ \text{independent reflections, 1103 observed reflections with } F_0 \geq 4\sigma(F_0), \ \text{data to parameter ratio} \ 4.65:1; \ \text{R}=5.8\%, \ \text{Rw}=14.6\%. \]

Compound IV: Na 3,4-dimethylbenzenesulfonate trihydrate, C_{8}\text{H}_{9}\text{O}_{3}\text{NaS.3H}_{2}\text{O}, \ M=501.52, monoclinic, space group \ P2(1)/n, \ a=7.128(2), \ b=6.352(2), \ c=24.844(5)\text{Å}, \ \beta=90.28(2)\circ, \ V=1124.8(5)\text{Å}^3, \ Z=4, \ \text{cal} \ 2.961 \text{Mg/cm}^3; \ 1474 \ \text{independent reflections, 1381 observed reflections with } I \geq 3\sigma(I), \ \text{data to parameter ratio} \ 9.5:1; \ \text{R}=3.7\%, \ \text{Rw}=4.7\%.

5.2. RESULTS AND DISCUSSION:

5.2.1 Two structural types: Analysis reveals two types of crystal structures. In type A, represented by compounds I, II and III, the molecules are packed in a two-dimensional sandwich manner, the aromatic portions associating end-to-end to form a broad and extended hydrophobic region (Figures 5.1 to 5.3). The ionic regions are knitted together in a hydrophilic two-dimensional network. In type B, compound IV has a comparable structure except that rings from adjacent layers intermesh to give a more dense hydrophobic region (Figure 5.4). This latter structure was also observed for sodium 2,4,5-trimethylbenzenesulfonate (P. J. Steel, unpublished).

The two structural types, A and B, correlate with the benzene ring substitution pattern. The mono para-substituted compounds form the more open A layer structure, while those with ortho- and or meta- substitution form the B structure. Formation of the latter may be the result of stronger lateral hydrophobic interactions, favoured by the presence of the ortho-, or meta-methyl groups.

This suggests that A-type hydrotropes would show greater solubilizing properties than B-type ones, in lieu of the more open and more extended hydrophobic layer size. In a test of this prediction, we measured the solubility values of fluorescein diacetate in Na cumenesulfonate, Na p-toluenesulfonate and Na xylenesulfonate and found them to be in the order 20: 7.5: 4,
Figure 5.1. Cell packing for Na p-t-butylbenzenesulfonate dihydrate (I)
Figure 5.2. Stereo diagram for packing of Na cumenesulfonate hemihydrate (II)
Figure 5.3. Stereo diagram for packing of Na p-toluenesulfonate monohydrate (III)
Figure 5.4. Cell packing for Na 3,4-dimethylbenzenesulfonate trihydrate (IV)
which is in keeping with the prediction.

5.2.2. Aromatic stacking absent: Of significance is the general absence of a direct overlay of aromatic rings at the normally observed distance of 3.4 Å. This is in contrast to the suggestion of Saleh and El-Khordagui (1985) who thought stacking to be an important feature of hydrotrope aggregation. Rather, the rings fill the hydrophobic region in a more twisted, staggered and intermeshing manner, as shown in the figures for structures II, III and IV (Figures 5.2, 5.3 and 5.4). While some overlay of adjacent rings does occur for structure I (Figure 5.1) these are staggered with respect to each other. As a consequence, lateral packing is more compact in all cases, as indicated by the cell-repeat for the relevant axis (corresponding to two intermolecular separations) being less than 6.8 Å. This feature provides an indirect explanation as to why both aromatic ring sulfonates and aliphatic chain ones display comparable solubilizing features, as observed for sodium n-butylmonoglycolsulfate and sodium p-toluenesulfonate (Balasubramanian et al., 1989). The common feature would be cluster association of the nonpolar organic regions to form a hydrophobic layer that allows association of Na⁺, SO₃⁻ and water entities to occur, as observed in the structures reported. With aromatic ring stacking not being a crucial factor, the length of the hydrophobic component may be the key factor. The latter could be achieved by a range of both aromatic and aliphatic entities.

The ionic association involves coordination of oxygens from the sulfonate group as well as oxygens from water molecules. The precise details vary amongst the structures studied, but the overall effect is similar. A separate hydrophilic network extending in two dimensions is formed.

5.2.3. Open sandwich-type dynamic cluster arrangement: The overall stabilization of the sandwich arrangement is therefore a combination of favourable ionic network formation, combined with hydrophobic layer clustering of the nonpolar regions. This affords an overall planar configuration of the hydrophobic and hydrophilic regions. Such an arrangement corresponds to an opened-up micelle having greater accessibility to the hydrophobic regions than in a micelle.
The arrangement is akin to that of a lamellar liquid crystal (Balasubramanian and Friber, 1993).

The observed solid-state structure is considered to indicate the operative molecular detail for hydrotrope action (Balasubramanian and Friberg, 1993). This relates to the fact that relatively high concentrations of hydrotrope are required to initiate solubilization. Since crystals seed and form from such concentrations the observed structural detail would reflect the solution state structure existing at that point. Thus, hydrotrope solutions may be deduced to contain dynamic aggregate clusters having essentially the sandwich structure found in the solid state. The characteristic solubilizing properties of hydrotropes may be understood in terms of this configuration. Entities having low water solubility could readily become solubilized by entering the hydrophobic layers of micro units. These would, in turn, stabilize the layered structure, producing a cooperative effect. Direct evidence for such an effect is provided by the sigmoidal character of solubility curves (Balasubramanian et al., 1989; Srinivas and Balasubramanian, 1995; Srinivas et al., 1991). Furthermore, the observed open-layer structure is consistent with the (occasionally seen) significantly higher solubilizing feature of hydrotropes than observed for micelles (Balasubramanian and Friberg, 1993).

Thus the crystal structure analysis of the anionic hydrotropes appears to offer a clue to the mode of action of hydrotropes and more such studies on other diverse class of compounds such as cationic and aliphatic hydrotropes would be useful to generalize the phenomenon of hydrotropy.