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Hydrotropic solutions

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Abstract

Hydrotropes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Often strong synergistic effects are observed when hydrotropes are added to aqueous surfactant or polymer solutions. Recent studies regarding the effects of hydrotropes on phase behavior, aggregation, surface tension, viscosity, solubility, and microstructure formation are reviewed. Novel applications of hydrotropes as molecular probes and for controlled release of pharmaceuticals are also discussed.

Keywords: Hydrotrope; Sodium tosylate; Sodium salicylate; Phase behavior; Cloud point; Micelle transition; Branched micelle; Surfactant polymerization; Controlled release; Molecular probe

1. Introduction

Hydrotropes are a diverse class of molecules first described by Neuberg [1,2] almost a century ago. They are characterized by an amphiphilic molecular structure and an ability to dramatically increase the solubility of sparingly soluble organic molecules in water, often by several orders of magnitude [3,4]. The most common molecular characteristics of a hydrotropic molecule are a saturated hydrocarbon ring and an ionic moiety; however, hydrotropes can adopt many forms. Fig. 1 illustrates a small sample of the diverse molecules classified as hydrotropes. They have been well studied since their discovery and Friberg and Blute [5] report a detailed description of their historical development and industrial applications. Several recent review articles [6–8] also touch on the importance of hydrotropes and their many synergistic properties when combined with other amphiphilic molecules. Despite this extensive study and the numerous commercial and pharmaceutical applications many ambiguities regarding their classification and molecular association still exist.

The ability of hydrotropes to increase the solubility of organics in water is often strongest when the hydrotrope concentration is sufficient to induce the formation of associated structures. The concentration at which self association begins is denoted as the minimum hydrotrope concentration (MHC) [9••,10•–13] and is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility. The relatively high concentrations required to reach the MHC, however, often restrict the commercial application of hydrotropes. A novel approach to reducing the MHC was reported by Kumar et al. [14•] who successfully reduced the MHC of several hydrotropes with the addition of salts, *n*-alcohols, or urea. Recently, interest in mixed hydrotrope/surfactant and hydrotrope/polymer solutions has grown because of the presence of novel microstructures and the many synergistic effects on the phase behavior, viscosity, and solubility of organics at relatively low hydrotope concentrations.

The nature of hydrotrope aggregate formation in water is essential to make a tighter connection between microscopic assembly and the corresponding macroscopic behavior; unfortunately, the ways hydrotropes assemble are still not well understood. X-ray studies [10•] of the four hydrotropes sodium *p*-tert-butylbenzenesulfonate, sodium cumenesulfonate, sodium *p*-toluenesulfonate, and 3,4-dimethylbenzenesulfonate suggest that three dimensional aggregates form that contain concentrated localized hydrophobic regions. These hydrophobic regions are responsible for the increased solubility of organics in water. These four hydrotropes were found to associate by either end-

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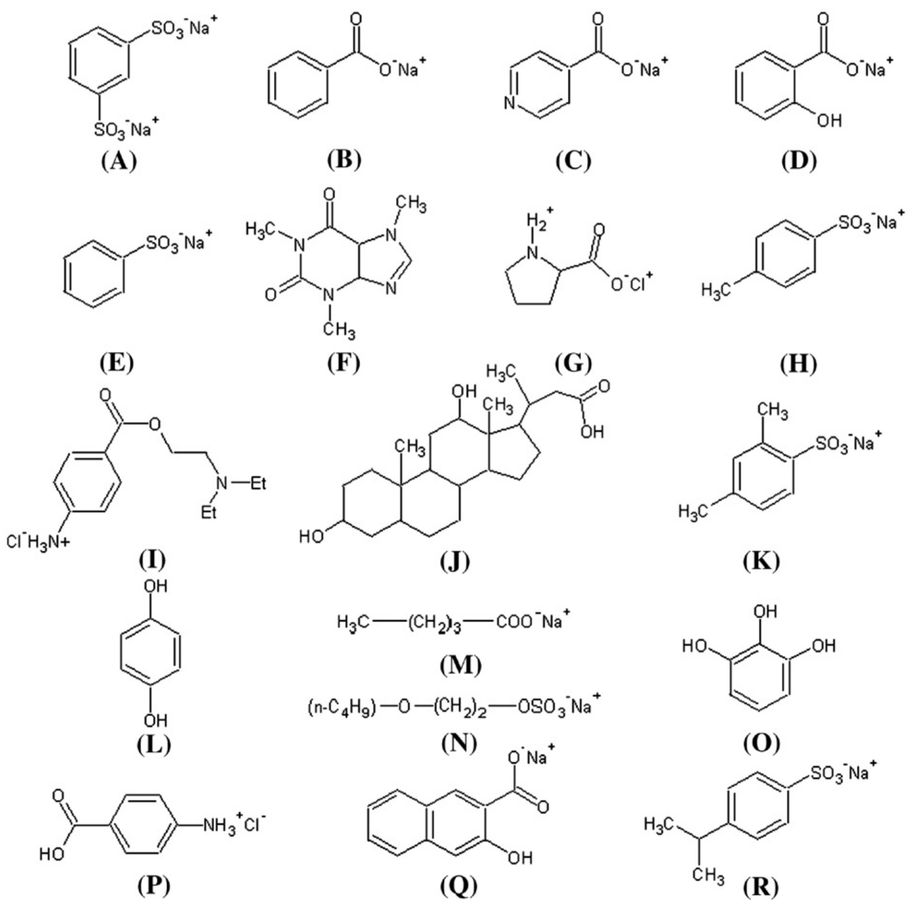

Fig. 1. Common hydrotropic molecules: sodium 1,3-benzenedisulfonate (A), sodium benzoate (B), sodium 4-pyridinecarboxylate (C), sodium salicylate (D), sodium benzene sulfonate (E), caffeine (F), proline, HCl (G), sodium *p*-toluene sulfonate (H), procaine, HCl (I), pregnane-20-carboxylic acid, 3,12-dihydroxy (J), sodium *p*-xylene sulfonate (K), resorcinol (L), sodium *n*-pentanoate (M), sodium butyl monoglycol sulfate (N), pyrogallol (O), 4-aminobenzoic acid, HCl (P), sodium 3-hydroxy-2-napthoate (Q), sodium cumene sulfonate (R).

to-end assembly of the hydrophobic rings, or by formation of adjacent layers of overlapping hydrophobic rings. The second method of association results in more densely packed hydrophobic regions, and the authors hypothesize that this results in poorer solubility of organic additives. Small angle neutron scattering (SANS) experiments [11] suggest hydrotropes with aromatic rings associate via ring stacking into ellipsoidal structures. However, scattering from the aggregates was not detected until a concentration eight times the MHC. Microcalorimetric experiments [15•] were conducted on five hydrotropes in an effort to measure the enthalpy change associated with aggregate formation at the MHC. No measurable enthalpy was observed, which suggests either no aggregation at the MHC occurs, or that the heat associated with aggregation is far below the enthalpy change associated with standard micelle formation.

Hydrotropes can be differentiated from surfactants because their hydrophobicity is not sufficient to create well organized self-associated structures, such as micelles, even well above the MHC. The molecular structure or macroscopic property that defines the distinction between hydrotropes and surfactants is, however, not clear. A study of alkylbenzenesulfonates synthesized with varying hydrocarbon tail lengths [9••] was designed to define the tail length at which the transition from hydrotrope to surfactant occurred. Surface tension and solubility experiments suggested molecules with a hydrocarbon tail length of four or greater behaved like surfactants. The insertion of molecules to probe the hydrophobicity of the microenvironment, however, did not show the abrupt formation of hydrophobic regions indicative of micelles. Rather a gradual transition from a water-like solution for short chains to highly localized hydrophobic regions for long chains was observed. This result suggests a smooth transition, with the alkylbenzenesulfonates forming large loosely associated aggregates for molecules with tails of three and four carbons. A similar study [16,17] utilized small angle neutron scattering (SANS) to probe the microstructure present in microemulsions containing *n*-alkyl polyglycol ether surfactants of varying sizes to establish a transition to surfactant-like behavior.

Another approach to understanding the categorization of hydrotropes is that of Bauduin et al. [18••], who proposed a unified concept of solubilization of organic dyes for the surfactant sodium dodecyl sulfonate (SDS), the hydrotrope sodium xylene sulfonate (SXS), and a series of solvosurfactants and cosolvents. As expected, SDS exhibited a characteristic sigmoidal shape for the solubilization of dyes as a function of surfactant concentration. Addition of the other molecules