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Hydrotropic agents: a new definition

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Summary

The term hydrotropic agent was first introduced by Neuberg (1916) to designate anionic organic salts which, at high concentrations, considerably increase the aqueous solubility of poorly soluble solutes. In the present study, an attempt is made to extend the definition of the term to include cationic and non-ionic organic compounds bearing the essential structural features of Neuberg's hydrotropes. The results obtained indicate that model planar cationic compounds such as *p*-aminobenzoic acid hydrochloride and procaine hydrochloride, and neutral molecules such as resorcinol and pyrogallol confer typical hydrotropic properties.

Introduction

Hydrotropic agents, according to the definition first put forward by Neuberg (1916), are metal salts of organic acids which at fairly high concentrations, considerably increase the aqueous solubility of organic substances normally slightly soluble in water. However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds (McKee, 1946; Elworthy et al., 1968; Thoma and Arning, 1976). Such indiscriminate use has resulted in further confusion in an already confused field and a more precise definition of the term 'hydrotropic agent' is still sought. This should involve a systematic determination of the characteristics of the hydrotropic agent molecule specifically relevant to the hydrotropic effect.

The chemical structure of the conventional Neuberg's hydrotropic salts (prototype, sodium benzoate) consists generally of two essential parts, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is obviously

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involved in bringing about high aqueous solubility which is a prerequisite for a hydrotropic substance. The type of anion or metal ion appeared to have a minor effect on the phenomenon (Neuberg, 1916). On the other hand, planarity of the hydrophobic part has been emphasized as an important factor in the mechanism of hydrotropic solubilization (Poochikian and Gradock, 1979; Badwan et al., 1983). This should imply that hydrotropic agents are molecules having a planar hydrophobic structure brought into solution by a polar group. Hence, it seems rational to propose that molecules with a planar hydrophobic part and a polar group, which is not necessarily anionic, can act as hydrotropic agents. The present study was undertaken to test this hypothesis by assessing the hydrotropic properties conferred by three model cationic agents, namely *p*-aminobenzoic acid-HCl, procaine-HCl and cinchocaine-HCl and two non-ionic compounds, resorcinol and pyrogallol.

Materials and Methods

Solubilization study

The solubilizing effect of *p*-aminobenzoic acid-HCl [1] (PABA-HCl), procaine-HCl [2], cinchocaine-HCl [3], resorcinol [4] and pyrogallol [5] was tested using riboflavine as a solubilizate. The study was carried out at 30 ± 0.2°C under exclusion of light. The amount of riboflavine in solution was determined spectrophotometrically at 445 nm after equilibration for 24 h. The interference of the solubilizers with the absorbance readings of riboflavine was negligible. The pH of the solutions was recorded at the beginning and end of the experiment.

To exclude the effect of pH, riboflavine solubility was determined in hydrochloric acid solutions of pH ranging from 1.2 to 4.0 under similar conditions.

Conductance measurement

The resistance of PABA-HCl, procaine-HCl and cinchocaine-HCl solutions was determined using a conductivity bridge [6]. Measurements were recorded after the solutions had equilibrated in a water bath at 30 ± 0.1°C. The specific and equivalent conductances were then calculated using the constant of the conductance cell used.

Viscosity and specific gravity

The viscosities of resorcinol and pyrogallol solutions (0.3–2.2 M) were determined relative to water at an ambient temperature of 20°C using an Ostwald viscometer. The specific gravity of solutions of the two substances (0.1–2.5 M) was determined at the same temperature. Relative viscosity and specific gravity data presented are the averages of 5 determinations.

[1] Prepared by dissolving PABA in ether and passing dry HCl gas, the precipitated PABA HCl was filtered and recrystallized from an alcohol–ether mixture.
[2] Procaine-HCl BP, Orgamol Talfar, Switzerland.
[3] Warld Blenkinsop, U.K.
[4] Prolabo, Rhône-Poulenc, France.
[5] E. Merck, Darmstadt, F.R.G.
[6] Conductivity Bridge Model PM-70 CB, Sybron Barnstead, U.S.A.

Effect on gel formation

One gram of each of the five substances under study was dissolved in 5 ml distilled water. Gelatin[7] (100 mg) was added and the mixture was heated on a boiling water bath for 10 min until gelatin had completely dissolved and kept at 4°C overnight.

Results and Discussion

In a previous study (Badwan et al., 1983), it has been shown that the phenomenon of hydrotropy could be correlated with a break in the solution properties of benzoate hydrotropic agents at relatively high concentration. Such a deviation has been attributed to a stacking-type association of the hydrotrope molecules favoured by the planarity of their structure. In the present work, the solution properties of three model cationic and two non-ionic agents were investigated in an attempt to test their possible hydrotropic behaviour.

The solubilizing effect and conductance of aqueous solutions of PABA-HCl, procaine-HCl and cinchocaine-HCl were studied as a function of concentration. Solubilization data for riboflavine (Fig. 1) show that the solubility diagrams corresponding to PABA-HCl and procaine-HCl exhibit a positive deviation from linearity

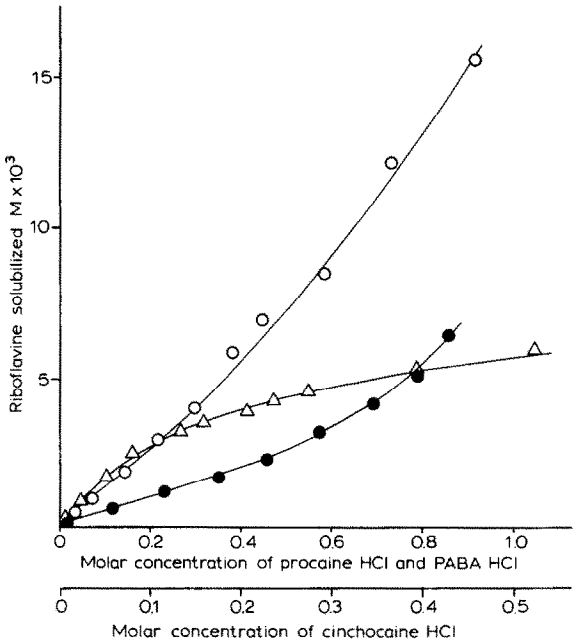

Fig. 1. Solubilization of riboflavine by procaine-HCl (○), PABA-HCl (●) and cinchocaine-HCl (△).

[7] Veb Laborchemie Apolda, D.D.R.

while a negative deviation is obtained in the case of cinchocaine. Positive deviation implies a greater solubilizing power at higher concentrations and is characteristic of hydrotropic solubilization (Elworthy et al., 1968). Results of the solubilization study thus suggest that PABA-HCl and procaine-HCl behave as hydrotropic agents while cinchocaine does not. Solubility diagrams with positive deviation have been also reported for the solubilization of some acids by amine salts (Conine, 1965). The author interpreted the results on the basis of a sudden change in the solution properties of the amine salts at a concentration referred to as the solute critical micelle concentration. However, the possible type of molecular association was not clearly indicated.

The increase in the solubility of riboflavine in the three systems under study cannot be even partly attributed to a pH effect as riboflavine solubility determined in hydrochloric acid solutions of pH ranging from 1.2 to 4.0 remained almost constant (about 11.2 mg/100 ml). The lowest pH value recorded for the solubilizing solutions was 1.2.

The specific conductance of solutions of the three cationic agents was measured as a function of concentration. Relatively concentrated solutions were used as the hydrotropy phenomenon is generally associated with a high solute concentration. Apparent discontinuities are obtained in the specific conductance plots of PABA-HCl and procaine-HCl over the concentration range tested, 0.2–1.0 M (Fig. 2A). Deviation from linearity in conductance plots is strongly indicative of molecular aggregation (Mukerjee, 1967). The lack of a clear discontinuity in the cinchocaine plot (Fig. 2A) suggests the absence of an abrupt change in the solution properties of this agent in the concentration region used.

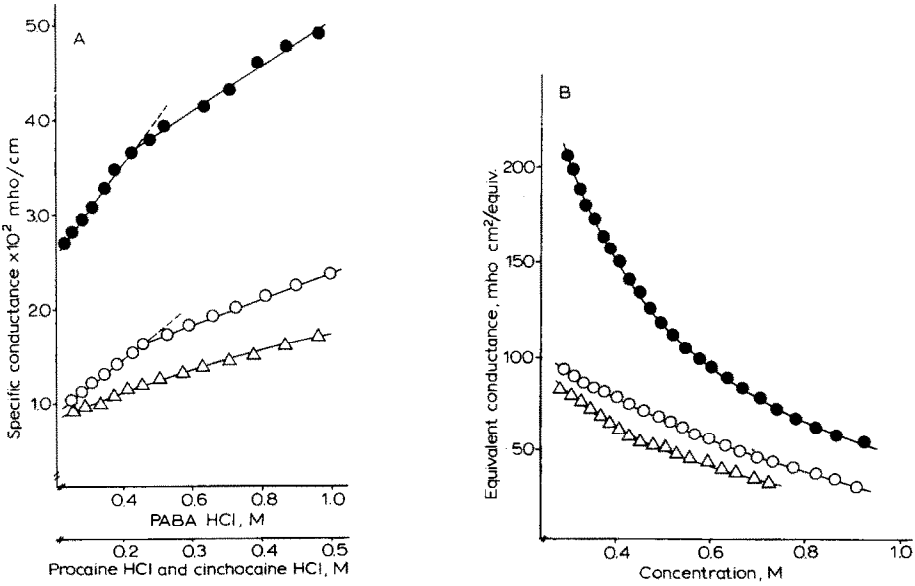

Fig. 2. A: specific conductance plots of PABA-HCl (●), procaine-HCl (○) and cinchocaine-HCl (△). B: equivalent conductance plots of PABA-HCl (●), procaine-HCl (○) and cinchocaine-HCl (△).

The equivalent conductance of the three agents was then plotted versus $\sqrt{C}$ as the plot of such a molar property is truly indicative of aggregate formation. Fig. 2B shows a gradual decrease of the equivalent conductance over an extended concentration region. This pattern suggests a weak aggregating tendency which should result in slow multiple equilibria between aggregates of different sizes. However, it has been reported that cinchocaine aggregates by a micellar process similar to that observed in conventional surface active agents rather than by a stepwise stacking, the reported CMC being 0.06 M (Eckert et al., 1964; Farhadieh et al., 1967). Hence, the molecular interaction resulting in the slow decrease of the equivalent conductance of cinchocaine at higher concentrations might be different from that exhibited by hydrotropic agents. This is supported by the different solubilizing behaviour of cinchocaine-HCl solutions compared to that of PABA-HCl and procaine-HCl solutions (Fig. 1).

It could be assumed that the rigid planar structures of PABA and procaine allow these molecules to aggregate by a free plane-to-plane association pattern (Mukerjee, 1974) while the side-chains in cinchocaine are likely to act as a structural barrier to such an association. As the interaction of substrate molecules with the hydrotrope aggregates is thought to be a possible mechanism of hydrotropic solubilization (Badwan et al., 1983), the non-hydrotropic behaviour of cinchocaine might be attributed to the lack of this particular type of aggregation. Accordingly, hydrotropy is not restricted to anionic agents as reported originally by Neuberg (1916), freely soluble cationic agents may also be hydrotropic provided that their structural features allow a plane-to-plane stacking.

The second point of interest in this study was the possibility of extending the definition of hydrotropic agents to include non-ionic substances. Since the ionic groups on hydrotropic agent molecules are concerned mainly with bringing about solubility in water, non-ionic planar structures that are freely soluble in water may thus be proposed as a new class of hydrotropic agents. Resorcinol and pyrogallol have been selected to test this assumption using solubilization, viscosity and specific gravity data.

Solubilization of riboflavine by resorcinol and pyrogallol resulted in typical hydrotropic solubility diagrams (Fig. 3) indicating the hydrotropic behaviour of these neutral molecules.

Viscosity data were plotted according to the equation:

$$\frac{\eta}{\eta_0} = 1 + BM + CM^2$$

where M is the molar concentration of the solute. The coefficients B and C can be evaluated from the intercept and slope of the plot of $\eta/\eta_0 - 1/M$ versus M. This equation has been employed to represent and analyze viscosity data of non-electrolytes at moderate to high concentration (Herskovits and Kelly, 1973). The C parameter can be used to represent the contribution of solute–solute interactions to the relative viscosity.

The viscosity plots of resorcinol and pyrogallol (Fig. 4) show inflection points, the

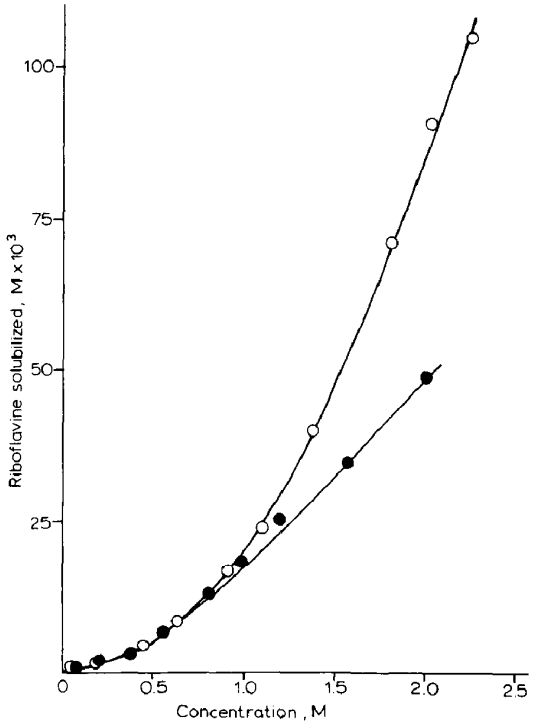

Fig. 3. Solubilization of riboflavine by resorcinol (○) and pyrogallol (●).

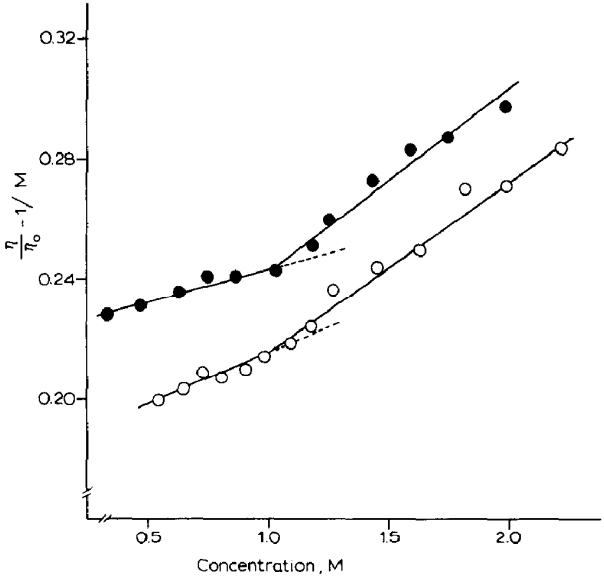

Fig. 4. Viscosity plots of resorcinol (○) and pyrogallol (●).

coordinates of which were determined by regression analysis. The values of the C parameter before and after the inflection point are 0.020 and 0.061 for pyrogallol; and 0.033 and 0.054 for resorcinol. Since the C parameter is a measure of molecular interaction, the increase of the value of C at higher concentrations suggests molecular aggregation of resorcinol and pyrogallol. This is not entirely surprising since phenol, cresols and some other phenolic compounds were reported to associate in the liquid state, the extent of association being affected by the substitutions interfering in the flat-on-flat packing (Thomas, 1960).

The aggregation of resorcinol and pyrogallol is also supported by discontinuities in specific gravity plots (Fig. 5).

Moreover, hydrotropic agents were shown to affect macromolecular systems. For instance, these agents render coagulable protein uncoagulable on heating, convert starch into a paste on the cold, inhibit the gelling of substances like gelatin and reversibly denaturate methemoglobin (Neuberg, 1916; Roche and Combette, 1937; Feigen and Trapini, 1954). In the present work, inhibition of gelling of a gelatin solution was used as an additional simple experiment to test the hydrotropic properties of the substances under study. The results shown in Table 1 suggest the interference of PABA-HCl, procaine-HCl, resorcinol and pyrogallol in the gelling process, thus confirming the hydrotropic behaviour of these agents, while gelling of the system containing cinchocaine indicates a non-hydrotropic behaviour.

In conclusion, the present work strongly suggests that the phenomenon of hydrotropy is not confined to the metal salts of organic acids as first pointed out by

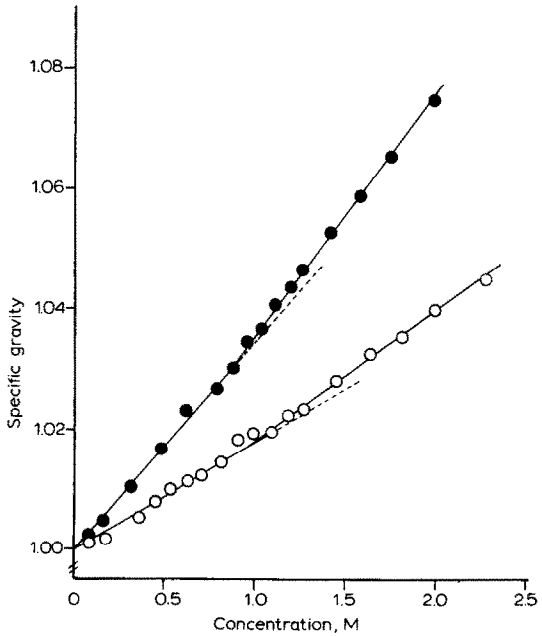

Fig. 5. Specific gravity plots of resorcinol (○) and pyrogallol (●).

TABLE 1

EFFECT OF CATIONIC AND NON-IONIC AGENTS (20%) ON THE GELLING OF A 2% GELATIN SOLUTION

Agent	Effect
Procaine-HCl	Inhibition
PABA-HCl	Inhibition
Cinchocaine-HCl	No effect
Resorcinol	Inhibition
Pyrogallol	Inhibition

Neuberg (1916); certain cationic salts and neutral molecules may be equally involved. The following definition of hydrotropic agents is, thus, proposed: 'hydrotropic agents are freely soluble organic compounds which at a concentration sufficient to induce a stack-type aggregation, considerably enhance the aqueous solubility of organic substances, practically insoluble under normal conditions. These compounds may be anionic, cationic or neutral molecules'. However, further characterization of hydrotropic agents will be the subject of subsequent studies.

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