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Investigations on the mechanism of aqueous solubility increase caused by some hydrotropes

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Abstract

The effects of nicotinamide, sodium *p*-toluenesulfonate and tetrapropyl and tetrabutyl ammonium bromides on the cloud points of non-ionic surfactant solutions and on the solubility of an apolar dye were determined. They all revealed a continuous effect of increased solubility as the additive concentration increases. Surface tension and heats of dilution were also measured for these solutions and the results support the view of a continuous hydrotrope self-association, which is then proposed as a key process to their ability of increasing aqueous solubility of apolar compounds. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

While most compounds when dissolved in water decrease the solubility of a second component, some present opposite behaviour, leading to considerable solubility increases. The occurrence of such phenomena led to the terminologies 'salting out', referring to reduced solubility, and 'salting in' for the reverse effect. Compounds that cause increase in aqueous solubility are sometimes called hydrotropes, or chaotropes [1]. Both 'salting in' and 'salting out' effects present many practical applications, for instance in separation processes (precipitation of proteins, separation of isomers using hydrotropes) [2], development of pharmaceutical formulations [3], increase of cloud points of detergent solutions [4], changes in reaction rates [5] among others.

Many different compounds have been used as hydrotropes, including urea, guanidinium chloride, nicotinamide, tetraalkyl ammonium halides, aromatic sulfonates, sodium thiocyanate [6–9]. There have been various theoretical and experimental efforts aiming at an explanation for these effects and the available proposed mechanisms may be summarised according to three schemes. The first one assumes that the additives and the solute interact strongly, similar to complex formation, and that this complex would then present a higher aqueous solubility. This proposal finds support from some molecular dynamics simulations [10], crystallographic studies on solid complexes [11] and solubility studies [6]. An opposite hypothesis assumes that such additives insert themselves in the structure of liquid water, changing it, therefore the

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names 'structure-breaker' and, oppositely, 'structure-maker' [12]. A third alternative involves the self-association of the additives to form aggregates that may act as micelles affecting the solubility and properties of the other solutes [13]. This proposal is supported by experimental data pointing out that some of these hydrotropes, as tetrabutyl ammonium bromide [14], nicotinamide [15] and some aromatic sulfonates [13] associate in aqueous solutions.

Another view, which is somewhat related to the aggregation proposition, was suggested by Breslow [5] and assumes that these additives act in a bridge-like manner, concentrating themselves around the hydrophobic solute, but without any specific interaction with it. The solubility increase would then result from a decrease in the Gibbs energy of the system due to the more favourable solvent–additive interaction in relation to the previous solute–solvent interaction. Nevertheless, one has to bear in mind the wide range of compounds that act as hydrotropes. Considering such a diversity, it sounds reasonable that more than one of the proposed mechanisms might be ascribed to the action of different additives or to changes of a specific property.

We have previously investigated the role of urea on the increase of aqueous solubility of some apolar compounds [16]. We have targeted the proposed hypothesis that this effect be caused by the formation of a solute–urea complex [6]. Careful calorimetric measurements have shown that the changes in enthalpy associated with such an interaction were too small to be atributted to any kind of specific interaction involved in this complex formation. Moreover, we found out that the solubility increase, analysed both in terms of Gibbs energy or entropy, increases linearly with the solute size indicating a geometrical cause closer to the proposal of Breslow [5].

In this work, we have performed a systematic evaluation of the effects of four hydrotropes on different properties: solubility of an apolar dye, cloud points of non-ionic surfactant solutions, solution surface tension, and compared those results to the hydrotropes dilution enthalpies in water. The examination of different solution properties aims at verifying the generality of the hydrotrope behaviour, as well as at providing some insight on their mechanism of action. More specifically, these results will be analysed in terms of the variations of the measured effects as function of the additive concentration, in order to verify the existence of proposed critical aggregation region [13].

2. Experimental

The non-ionic surfactants Brij 30 ($C_{12}EO_4$), Aldrich, p.a.; Renex 80 (ethoxylated nonylphenol, $n = 8$ EO groups), a gift from Oxiteno, Brazil, and L61 ($EO_2PO_{33}EO_2$), donated by ICI Surfactants, UK, were used as received. The additives tetrapropyl (TP) and tetrabutyl (TB) ammonium bromides and sodium *p*-toluenesulfonate (TS), purchased from Aldrich, and nicotinamide (NT), from Fluka, were all of the best grade available. They were used without further treatment, but being kept in a desiccator over P_2O_5. Water used throughout was freshly bi-distilled over $KMnO_4$ in a glass apparatus.

The cloud temperatures (cloud points) were determined visually by controlled heating (ca. 1 K/min) of the well stirred samples. The temperatures were measured by a thermocouple with a precision of 0.1 K. This procedure has been used before [17] and produces values in accordance with the ASTM method [18] and a reproducibility of better than 0.5 degree.

Methyl yellow (Profile Testing Laboratories, NJ) suspensions in aqueous additive solutions were sonicated, kept at 298.1 ± 0.1 K for at least 24 h and filtered. Following this, the dye solubility was determined by measuring the absorbance of diluted solutions at 440 nm using a HP 8452 spectrophotometer.

The solution surface tensions were determined by using an automatic Sigma 701, KSV tensiometer and the Wilhelmy plate method, in a temperature-controlled reservoir (298.1 ± 0.1 K). The solution surface purity was ensured by a constant reading of surface tension [19]. The surface tension of the purified water ($\gamma = 72.0$ mN m^{-1}) is in agreement with the literature value [20].

The additive enthalpies of dilution were determined by calorimetric titration using a Thermometric 2277 isothermal calorimeter at 298.15 K. Previously calibrated 20 μl aliquots of an additive solution were added to 1–3 ml of water. The additive concentrations in the syringe were: NT (3 mol dm^{-3}), TB (2 mol dm^{-3}), TP (1 mol dm^{-3}) and TS (2 mol dm^{-3}). The heat of dilution was determined by using the electrical calibration method. This procedure was chemically calibrated by measuring the heats of dilution of aqueous sucrose solutions, which were found in close agreement to the literature values [21]. All the reported values are averages of at least two independent titrations.

3. Results and discussion

3.1. Cloud point measurements

The cloud point changes for 1% Brij 30 and Renex 80 aqueous solutions are shown, respectively, in Figs. 1 and 2 (the effects for L 61 solutions are smaller). Each surfactant solution presents a different trend of additive efficacy: Brij 30, TS > TB > TP, NT; Renex 80, TS, TB > NT,TP and L61, NT > TS,TB > TP. Different efficacies were also verified in a previous study with a series of block copolymers [17], and might be due to different aggregation states of each surfactant at their clouding temperatures. This early study has also shown that these additives are not so efficient in increasing the solubility of the more hydrophobic polypropylene oxides and, therefore, their effect should be related to the hydration of the ethylene oxide groups.

The cloud point changes are observed to increase with the additive concentration, but, in some cases (Fig. 2), the effects are remarkable event at low additive contents (less than 0.1 mol dm^{-3}). These changes for L61 and Renex 80 solutions are continuous and show no evidence of critical additive aggregation. For Brij 30 solutions with TS and TB, though, some inflexion points occur at intermediate additive concentrations, followed by a steep increase of the cloud points as the additive concentration increases. However, the peculiarity of this behaviour, being only observed for Brij 30 solutions, suggests that it is not a general phenomenon of these additives solutions.

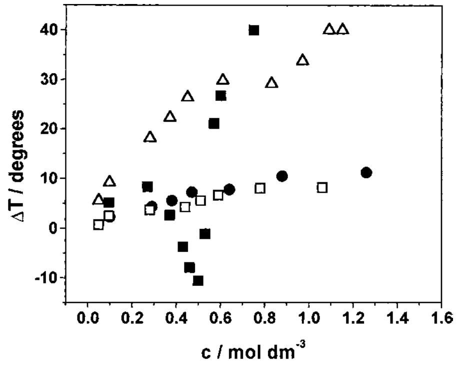

Fig. 1. Clouding temperatures of solutions containing Brij 30 (1.0%) and ● NT, □ TP, ■ TB and △ TS.

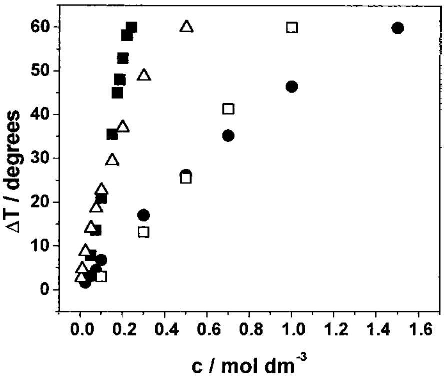

Fig. 2. Clouding temperatures of solutions containing RENEX 80 (1.0%) and ● NT, □ TP, ■ TB and △ TS.

In order to verify the existence of specific polymer–additive interactions, we have determined the enthalpies of transfer for a series of these block copolymers from water to 0.5 mol dm^{-3} additive solutions [22]. Some of these results are presented in Table 1, expressed in terms of moles of polymer molecules. If one assumes that more than one interaction occurs per polymer molecule, these values would be even smaller, being too small to be attributed to any specific interaction or complex formation. In addition, the variety of additive chemical structures, including anions, cations and neutral molecules makes difficult

Table 1
Enthalpies of transfer of the block copolymers from water to 0.5 mol dm^{-3} additive solutions[a]

Polymer	$(\Delta H)_t$ (kJ mol^{-1})		
	TP	TB	TS
L31	1.05	−10.89	2.08
L35	−7.75	−167.6	−12.18
L43	−3.99	−43.89	–
L64	−0.68	−88.84	–

[a] Expressed per mol of polymer.

the proposition of any general mechanism of complex formation. The only exception is for tetrabutyl ammonium bromide solutions, where significant enthalpies of transfer were obtained. The possibility of cation–polymer interaction is ruled out by the negligible enthalpy values determined for tetrapropyl ammonium bromide solutions. One possible explanation arises from previous studies that indicated a larger tendency to self-association of the more hydrophobic homologues [14], leading in some cases, to the formation of liquid biphase systems [23]. This larger changes in enthalpy might then be related to the occurrence of TB association, somewhat induced by the presence of the surfactant.

3.2. Solubility of methyl yellow

Solubility measurements have been extensively performed in hydrotropes aqueous solutions, since the early observations of Licht and Weiner [24]. Srinivas and Balasubramanian [25] have investigated the solubility of apolar compounds in water with hydrotropes, observing an abrupt solubility increase at certain additive concentrations. Similar profiles have been observed for surface tension measurements, leading these authors to propose the occurrence of additive aggregation as their mechanism of action.

The increase of methyl yellow aqueous solubility due to the presence of the additives is shown in Fig. 3. The additive efficacy follows TB > TP > NT > TS, tetrabutyl ammonium bromide being much more effective than the others. This sequence is different from the ones observed for the additive effects on the cloud points of surfactant solutions. The change in solubility is again monotonic, increasing exponentially with the additive concentration. These results confirm the ability of these compounds to make apolar compounds more soluble in water, but there is no evidence of any critical phenomena. They rather seem to support a continuous process.

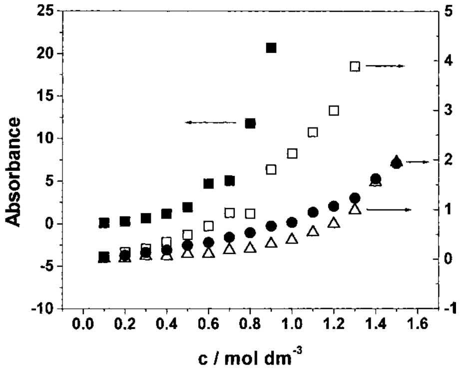

Fig. 3. Solubility variation of methyl yellow in the presence of: ● NT, □ TP, ■ TB and △ TS. The absorbances for TB solution were calculated from more dilute solutions.

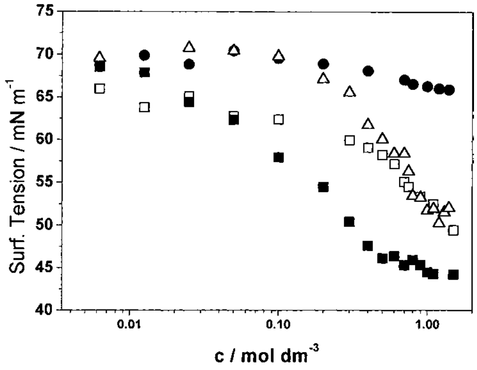

Fig. 4. Surface tension variation for solutions of ● NT, □ TP, ■ TB and △ TS.

3.3. Surface tension measurements

The solution surface tension was determined at increasing additive concentration and the results are shown in Fig. 4. Not all the substances with reported hydrotopic activiy are also surface active as, for instance, KSCN and KI. Balasubramaniam et al. [13], however, reported a significant surface activity for some hydrotropes (aromatic organic anions), which also present breaks in the surface tension versus concentration curve, which they have ascribed to additive aggregation. As these discontinuities occured close to points of steep increases in solubility caused by these compounds, this was proposed as their mechanism of action. The curves represented in Fig. 4 resemble the ones reported by Balasubramanian et al., revealing a significant surface activity of the four tested hydrotropes.

However, one has to bear in mind that the Gibbs adsorption isotherm Eq. (1) predicts an exponential decrease of the surface tension for solutions where the solute presents a positive surface excess concentration:

$$\Gamma = -\frac{1}{RT}\left(\frac{\partial \gamma}{\partial \ln c}\right) \qquad (1)$$

where Γ is the solute surface excess concentration, R and T, respectively, the gas constant and absolute temperature, γ the solution surface tension and C, its concentration.

This exponential decrease may, sometimes, be wrongly interpreted as a sign of critical aggregation. Therefore, as pointed by Speight and Andersen [26], the existence of a c.m.c. should be supported by a break in the γ versus $\ln C$ plot, as shown in Fig. 4. The application of this approach to the present data disregard any critical aggregation phenomena, except, perhaps, for TB at higher concentrations (ca. 0.7 mol dm^{-3}). The effectivity in reducing the solution surface tension follows the sequence TB > TP > TS > NT. Once again, these experimental data do not conform to the proposition of critical additive aggregation.

3.4. Calorimetric measurements

Calorimetry has been routinely employed to study solute–solute interactions [27], and specifically to investigate the phenomenon of self-association [28,29]. Solute–solute interactions are indicated by deviations from the infinite dilution enthalpies (either of dilution or mixing) and have been quantitatively analysed according to modified MacMillan–Meyer theories [30]. Micellisation is verified as a distinctive break in the heat of dilution (or mixing) curves as the surfactant concentration passes the critical micelle concentration and the enthalpies of micellisation can be calculated from the difference of the slopes before and after c.m.c. [31]. In some cases, as for instance, butoxyethanol [28] or some block-copolymers [32] in water, signs of self-association have been observed even before the atributted c.m.c. and the determination of the micellisation enthalpies has to be performed through some model analysis. However, even in those more complex aggregation processes, a discontinuity is always observed in the c.m.c. region.

The differential and integral enthalpies of mixing derived from the titration experiments for the four studied hydrotropes are shown in Figs. 5 and 6. A first analysis reveals that for all the substances, there is indication of solute–solute interaction, with no limit enthalpy of mixing (infinite dilution) being observed even at low concentrations (below 0.1 mol dm^{-3}). The dilution of nicotinamide is endothermic, whereas for the other three, this process is exothermic. As the solute concentration increases, due to solute–solute interaction, all the differential enthalpies seem to tend to zero.

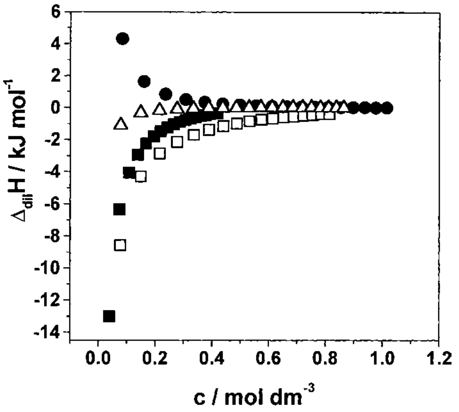

Fig. 5. Differential enthalpies of dilution for: ● NT, □ TP, ■ TB and △ TS.

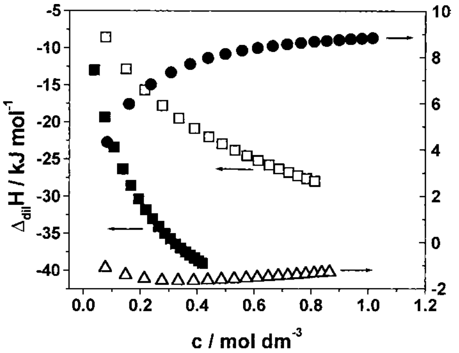

Fig. 6. Integral enthalpies of dilution for: ● NT, □ TP, ■ TB and △ TS.

This dilution process may be rationalised as a sum of three independent processes, according to:

$$(\Delta H)_{\mathrm{dil}} = (\Delta H)_{\mathrm{deaggr}} + (\Delta H)_{\mathrm{solv}} + (\Delta H)_{\mathrm{w/w}}$$

where $(\Delta H)_{\mathrm{deaggr}}$ represents the energy required to separate solute molecules, $(\Delta H)_{\mathrm{solv}}$ the enthalpy change for the solute solvation (or hydration), and

$(\Delta H)_{w/w}$ the energy for releasing the water molecules that will interact with the solute.

In this equation, the first term is positive (as energy should be added to the system to break the solute–solute interactions), and the last process which also requires energy for the cavity formation inside the solvent. The solvation process, however, is exothermic, as all the solutes interact favourably with water molecules, either by hydrogen bonding or through electrostatic interaction. Therefore, the net process will be endothermic or exothermic depending on the energy balance of (deaggregation + (water–water interaction)) versus solute solvation. For the electrically charged solutes, the solvation term seems to prevail and the overall enthalpy of mixing is negative. With the neutral solute nicotinamide, however, the hydration is not so energetic or enthalpy of solute deaggregation is high, and the process is endothermic.

Another interesting feature revelead in Fig. 5 is that for all cases, the dilution enthalpy approaches zero as the solute final concentration increases. This behaviour may be ascribed to the reduced number of solute–solute interactions that are disrupted when the solute is transferred from the more concentrated solution in the syringe to the final solution in the ampoule. Therefore, these results confirm the existence of significant solute–solute interaction in the concentration range where hydrotrope activity is verified, but once again, they support the view of a continuous process rather than a critical aggregation, as the one observed for surfactants. In addition, these calorimetric experiments indicate that above a certain concentration range (0.8–1.0 mol dm^{-3}), most of these solutes are already associated and only negligible enthalpy changes are observed in relation to their more concentrated solutions (ca. 1–3 mol dm^{-3}). This invariance in dilution enthalpy indicates that negligible interacion occurs among the solute aggregates. The concentration at which this plateau region is reached may be taken as the estimate of solute tendency to self-associate, and follows the sequence NT > TS > TB > TP. Interestingly, this sequence is different from the efficacy ones observed from the previous effects.

4. Conclusion

The investigation on the hydrotrope activity of four substances revealed that the sequence of efficacy depends on the process and on the solutes studied. Considering that the structure of liquid water may depend on the nature of the solute and solubilising process, these effects can not be separated of disrupting the water structure. Another observation, for the case of some EO–PO–EO block copolymers is that no significant enthalpy change is detected when the polymers are transferred from water to hydrotrope solutions. The only exception, tetrabutyl ammonium bromide, is probably due to its self-association induced by the presence of the polymer. This lack of enthalpy change, plus the variety of chemical structures of the studied hydrotropes, seem to disregard the hypothesis of complex formation between solute and additive. Surface tension and heat of dilution measurements show no sign of critical aggregation phenomena, but rather of a continuous solute self-association in the region where hydrotropic activity is observed. These findings support the view that hydrotrope aggregation is a part of their mechanism of action. However, due to the continuous nature of this process and to the size of the polymers whose solubility they affect, the resulting picture is more in line with Breslow's proposal of a type of preferential solvation, where the hydrotrope molecules accomodate around the solute, turning its solvation more favourable.

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