Water, a unique medium for organic reactions
Buurma, Niklaas

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Hydrolysis in Aqueous Solutions Containing Hydrotropes

The effect of added hydrotropes on the rates of neutral hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole 4.1 has been studied, together with the molality dependence of the \(^1\)H-NMR spectra of the hydrotropes in aqueous solution. Hydrotropes include sodium 4-alkylbenzenesulfonates 4.2a-e, sodium 4-methoxybenzenesulfonate 4.2f, sodium 4-hydroxybenzenesulfonate 4.2g, caesium benzenesulfonate 4.3, benzamidinium chloride 4.4, phenyltrimethylammonium bromide 4.5a and benzyltrimethylammonium bromide 4.5b. All hydrotropes, except 4.2g, induce strong rate retarding effects, indicative of strong interactions with 4.1 and of remarkably strong hydrophobic interactions between aromatic moieties. Most hydrotropes show neither spectroscopic nor kinetic evidence for cooperative aggregation in the molality range studied, i.e. from 0 to 1.4 mol kg\(^{-1}\). Cooperative aggregation is absent because the hydrophobic moieties are too small for hydrophobic interactions to overcome electrostatic repulsion. Lack of aggregation results in high availability of hydrophobic binding sites, thereby accounting for the high solubilising power characteristic for hydrotropes. However, sodium 4-n-propylbenzenesulfonate 4.2d and sodium 4-n-butylbenzenesulfonate 4.2e show cooperative self-association forming highly dynamic, loose micellar-type structures.

4.1 INTRODUCTION

4.1.1 HYDROLYSIS OF 1-BENZOYL-3-PHENYL-1,2,4-TRIAZOLE IN THE PRESENCE OF SELF-ASSOCIATING COSOLUTES

The procedures as set up in Chapters 1 and 2 are valid for non-reacting and non-catalytically active cosolutes and are normally used for dilute cosolutes so that only pairwise (1:1) interactions have to be considered. As described in Chapter 3, a range of basic cosolutes either catalyse hydrolysis or react with the activated amides and the basic pattern underlying the reactivity of basic compounds has been explored.
The next topic under study is the effect of self-association of cosolutes. Equation 1.9, describing the rate-retarding effects resulting from 1:1-interactions, is derived from general equations which include the possibility of higher than 1:1-interactions. Further quantities related to $G(c)$-values can be defined incorporating these higher-order interactions. Normally, however, molalities are intentionally kept low and cosolute hydrophobicity is kept within limits in order to prevent higher than 1:1-interactions.

Many organic cosolutes, however, are rather hydrophobic which can lead to a higher propensity to self-associate. This tendency to self-associate is expected to show up in deviations from linearity in plots of $\ln[k(m_c)/k(m_c=0)]$ as a function of cosolute molality $m_c$.

### 4.1.2 Hydrotopes

In the present study of the effect of self-association of cosolute molecules, we used hydrotopes as cosolutes. Hydrotopes normally comprise hydrophilic and hydrophobic moieties, with the hydrophobic moiety being typically too small to induce micelle formation. The extent and mechanism of self-association are under debate with both non-cooperative step-wise self-aggregation and cooperative self-aggregation ($\textit{vide infra}$) being suggested.

Hydrotopes induce a characteristic steep increase in aqueous solubilities of sparingly soluble hydrophobic compounds around a certain hydrotrope concentration, after which solubilities remain unchanged. The sudden increase in solubilisation by hydrotopes after a certain threshold concentration, called the minimum hydrotrope concentration (MHC), has been attributed to a cooperative process. This involves cooperative self-aggregation of the hydrotopes since the threshold concentration for solubilisation appears to be rather solubilisate insensitive. This cooperativity is disputed, however, as is the exact mechanism of solubilisation by hydrotopes.

Solubilisation by hydrotopes differs from that of typical salting-in compounds and cosolvents in that the increase in solubility is sigmoidally dependent on hydrotrope concentration. Salting-in cosolutes and cosolvents usually cause a monotonic increase in solubility without a levelling off at higher concentrations. Compared to micelle-forming surfactants, hydrotopes are more effective in solubilising organic solutes and can be more selective. Further, self-aggregation of hydrotopes most probably differs from that for micelles (Chapter 5). A crucial difference between micelle-forming surfactants and hydrotopes...
becomes clear from phase diagrams of their respective aqueous solutions. Aqueous solutions of hydrotropes lack the lamellar liquid crystal region found in solutions of micelle-forming surfactants. This lamellar region separates the normal micellar solution from the inverse micellar one. Instead, the phase diagrams of aqueous solutions of hydrotropes display a single continuous isotropic liquid phase.\cite{5,14,15}

The solubilising power of hydrotropes was recognised as early as 1916 by Neuberg.\cite{16} The potential use of hydrotropes in industry was stressed in 1946 by McKee.\cite{17} However, hydrotropes have received much less attention in the chemical literature than micelle-forming surfactants (Chapter 5). Despite this lack of attention, hydrotropes have been applied in liquid household detergents, shampoos, degreasing compounds and printing pastes, as well as used to extract pentosans and lignins in the paper industry and as an additive for glues used in the leather industry.\cite{18} Arguably, there are numerous areas that could benefit from the use of hydrotropes.\cite{4,5}

For organic synthesis in aqueous solutions, the use of hydrotropes can be beneficial, as for example, in the microwave-enhanced Hantzsch dihydropyridine ester synthesis,\cite{19} and the Claisen-Schmidt reaction\cite{20} in aqueous solution. In addition, hydrotropes enhance rates of reactions in multiphase transformations,\cite{21} which can lead to autocatalysis in the biphasic alkaline hydrolysis of aromatic esters.\cite{22}

Apart from their use as solubilising agents for organic synthesis in aqueous solutions, hydrotropes could also find application in formulations of pharmaceuticals\cite{23-27} (a number of pharmaceuticals turned out to be hydrotropes themselves\cite{28,29}) and in extraction and separation processes.\cite{13,30,31} In fact, most of the recent research into the action of hydrotropes has been performed in the latter two subjects. In addition, the effect of hydrotropes on micelle-forming\cite{32,33} and vesicle-forming\cite{34-36} surfactants and copolymers\cite{37-40} in aqueous solution has been investigated, as well as the influence on oil-in-water (OW) microemulsions\cite{41,42} and related cleaning and washing processes. Their biological action has also received attention.\cite{5}
In order to probe noncovalent interactions between hydrophobic solutes, we have studied the effects of sodium 4-alkylbenzenesulfonates $4.2\text{a-e}$, 4-methoxybenzenesulfonate $4.2\text{f}$, 4-hydroxybenzenesulfonate $4.2\text{g}$, caesium 4-methylbenzenesulfonate $4.3$, benzamidinium chloride $4.4$, aromatic ammonium bromides $4.5\text{a-b}$ and $N$-cyclohexyl-2-pyrrolidinone $4.6$ (Scheme 4.1) on the water-catalysed hydrolysis (Chapter 1) of 1-benzoyl-3-phenyl-1,2,4-triazole $4.1$ (Scheme 4.2).

These hydrotropes are not sufficiently basic to act as general bases in the hydrolysis of $4.1$, nor are they nucleophilic enough to act as nucleophiles (with the possible exception of $4.2\text{g}$) in the nucleophilic substitution of $4.1$ (Chapter 3). Furthermore, we determined the molality dependence of the $^1\text{H}$-NMR-spectra of benzenesulfonates $4.2\text{b,d}$ and $e$ in $\text{D}_2\text{O}$ in order to examine the self-association of the hydrotropic cosolutes in a probe-independent way.
4.2 RESULTS AND DISCUSSION

4.2.1 AN OVERVIEW OF RATE EFFECTS OF HYDROTROPES ON HYDROLYSIS OF 1-BENZOYL-3-PHENYL-1,2,4-TRIAZOLE

All tested hydrotropes, except 4.2g, induce strong rate retardations (Figure 4.1). The hydrotropes 4.2d and 4.2e, bearing longer alkyl chains, show sigmoidal dependence of ln[k(m_c)/k(m_c=0)] on molality of added hydrotrope, indicative of cooperative self-association.

![Graph](image1)

**Figure 4.1**: The effect of different hydrotropes on the hydrolysis of 4.1. Left: alkylated benzenesulfonates 4.2a (o), 4.2b (•), 4.2c (V), 4.2d (♦), 4.2e (Δ). Right: 4.2f (♦), 4.2g (V), 4.3 (o), 4.4 (x), 4.5a (•) and 4.5b (Δ).

4.2.2 KINETICS OF REACTIONS IN DILUTE SOLUTIONS OF HYDROTROPES

For all hydrotropes, plots of ln[k(m_c)/k(m_c=0)] against molality of hydrotrope (Equation 1.9) were constructed for the molality range up to 0.3 mol kg\(^{-1}\) (0.1 mol kg\(^{-1}\) for 4.2e). This molality range was chosen in order to avoid possible complexities in the data due to 2:1 and higher order interactions. All plots show a linear dependence of ln[k(m_c)/k(m_c=0)] on molality of hydrotrope (Figure 4.2).
This pattern accords with the results of Friberg et al.\textsuperscript{43} who showed that the vapour pressure of phenylethyl alcohol decreases linearly with the mole fraction of added sodium xylenesulfonate up to mole fractions of the latter of at least 0.5 mol\% (0.25 mol kg\textsuperscript{-1}). The slopes of the plots of $\ln[k(m_c)/k(m_c=0)]$ vs. $m_c$ for the dilute region yield the $G(c)$-values given in Table 4.1.

### Table 4.1: $G(c)$ values of hydrotropes 4.2a-g, 4.3, 4.4 and 4.5a-b at 298K.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Hydrotrope</th>
<th>$G(c)$ / J kg mol\textsuperscript{-2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2a</td>
<td>-1475±25</td>
</tr>
<tr>
<td>4.2b</td>
<td>-1950±50</td>
</tr>
<tr>
<td>4.2c</td>
<td>-2408±37</td>
</tr>
<tr>
<td>4.2d</td>
<td>-2858±30</td>
</tr>
<tr>
<td>4.2e</td>
<td>-3456±6</td>
</tr>
<tr>
<td>4.2f</td>
<td>-2551±116</td>
</tr>
<tr>
<td>4.2g</td>
<td>~0</td>
</tr>
<tr>
<td>4.3</td>
<td>-1909±6</td>
</tr>
<tr>
<td>4.4</td>
<td>-1443±27</td>
</tr>
<tr>
<td>4.5a</td>
<td>-715±26</td>
</tr>
<tr>
<td>4.5b</td>
<td>-1153±8</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Errors are standard errors based on a least-squares fit of kinetic data using Equation (1.9).

All $G(c)$-values are large and negative (apart from that for 4.2g), indicating strong inhibition of hydrolysis by substrate-solute interactions involving added
hydrotopes. In terms of the model leading to Equation 2.1, the observed pattern is consistent with the formation of relatively stable encounter complexes with equilibrium constants of formation $K_{ec}$ larger than unity, except in the cases of 4.5a and 4.5b. The values for $K_{ec}$ are comparable to those found by Ueda.\(^{44}\) For encounter complexes between 4.1 and 4.5a and 4.5b, $\Delta G_{ec}$ is larger than 0 kJ mol\(^{-1}\) ($K_{ec}<1$ kg mol\(^{-1}\)) with respect to the individually solvated molecules. Previously, significantly negative $G(c)$-values were also reported for the effects of added aromatic $\alpha$-amino acids and derivatives of aromatic $\alpha$-amino acids on rate constants for hydrolysis of 4.1,\(^{45-47}\) despite the possibility of nucleophilic substitution (Chapter 3). In combination with the present results, we suggest that hydrophobic interactions involving aromatic molecules are particularly strong.

Thermodynamics of solution of aromatic molecules in aqueous solutions are different from that of aliphatic molecules in that standard Gibbs energies of transfer from the gas to the aqueous phase are negative for aromatic molecules, whereas they are positive for aliphatic molecules. This is an enthalpic effect, attributed to the aromatic ring being able to accept hydrogen bonds from hydration-shell water molecules.\(^{48,49}\) In addition, interactions between aromatic molecules themselves are more favourable than those between comparable aliphatic molecules.\(^{48}\)

![Figure 4.3](image_url)  
**Figure 4.3:** $G(c)$ as a function of the number of methylene units in the alkyl-chain of hydrotropic cosolutes 4.2a-e.

For hydrotropes 4.2a-e, $G(c)$ varies linearly with the number of methylene groups in the alkyl chain (Figure 4.3), in accord with the Savage Wood Additivity of Group interactions (SWAG) theory.\(^{50}\) The decrease in $G(c)$ per methylene unit, viz. -500±131 J kg mol\(^{-2}\), is large when compared with previously reported estimates. Typically, increments for undisturbed methylene units are in the order of -100 J kg mol\(^{-2}\),\(^{51,52}\) although values up to -340 J kg mol\(^{-2}\) have been observed for the less hydrophobic substrate 1-benzoyl-1,2,4-triazole.\(^{53}\)
The remarkably high group contribution of the methylene group to the present \( G(c) \)-values is attributed to a synergistic effect of the aromatic benzenesulfonate moiety and of the methylene groups. Sodium benzenesulfonate itself is a potent inhibitor of the reaction, as can be seen from the \( G(c) \) for \( 4.2a \). In terms of the analysis leading to Equation 2.1, the observed strongly negative \( G(c) \) corresponds to a rather stable encounter complex which inhibits the reaction (Chapter 2).\(^{54}\) Further hydrophobic stabilisation of this encounter complex by elongating the alkyl chains of the added hydrotropes increases the rate retarding effect.

Surprisingly, the rather polar \( 4.2f \) induces rather a strong rate retardation, comparable to that of \( 4.2c \). Apparently, the methylene unit or oxygen is “invisible” to hydrophobically interacting species. Previously, shielding of hydrophobicity by hydrophilic groups has been attributed to the prevention of the formation of a hydrophobic hydration shell.\(^3\) We contend that the methyl and phenyl moieties prevent formation of a hydrophilic hydration shell around the oxygen, resulting in the oxygen’s hydration shell becoming part of a slightly disturbed hydrophobic hydration shell of its neighbouring groups. Hence the oxygen is masked as a hydrophilic moiety in 1:1 hydrophobic interactions.

For the hydroxy-substituted benzenesulfonate \( 4.2g \), \( G(c) \) is positive but small. General-base catalysis by the deprotonated phenol is expected to be negligible as the \( pK_a \) of \( 4.2g \) was found to be 8.6 by titration of a 0.5mol% solution. Using the LFER as derived in Chapter 3, Figure 3.9, kinetic data for nucleophilic substitution by phenolates of \( p \)-NPA\(^{55}\) and the \( pK_a \), we estimate the second-order rate constant for nucleophilic attack of \( 4.2g \) on \( 4.1 \) to be 5 kg mol\(^{-1}\) s\(^{-1}\). At pH 4.0 and unit cosolute molality, 25 \( \mu \)mol kg\(^{-1}\) of phenol is deprotonated leading to a rate increase of approximately \( 1.3 \times 10^{-4} \) s\(^{-1}\), which corresponds to a \( G(c) \) of +162 J kg mol\(^{-2}\). This accounts for the observed small positive \( G(c) \). However, it also indicates that (the remaining) protonated \( 4.2g \) has a negligible rate-retarding effect. The lack of hydrophobic interaction between \( 4.2g \) and \( 4.1 \) is opposite to that of \( 4.2f \). Here, the hydrophobic nature of the phenyl ring is masked by the hydration shells of the hydrophilic sulfonate and hydroxy group, making the phenyl ring unavailable for hydrophobic interactions. Similar behaviour has been found for L-proline, where 4-hydroxylation results in a total loss of hydrotropic behaviour.\(^{56}\) The mole fraction solubilities of phenol and methoxybenzene, being \( 1.78 \times 10^{-2} \) and \( 1.75 \times 10^{-3} \), respectively,\(^{57}\) show that the phenolic compound is far more hydrophilic than the methoxy-substituted benzene.
To investigate the effect of the relative electron density in the aromatic ring, non-alkylated hydrotropes 4.2a, 4.4, 4.5a and 4.5b were studied. Aromatic interactions are strongest for donor-acceptor systems, followed by acceptor-acceptor systems whereas electron-rich aromatic species do not stack well because the aromatic π-electron clouds repel each other.\(^5\) Kinetically, at low molality, non-alkylated cationic hydrotrope 4.4 strongly resembles non-alkylated anionic hydrotrope 4.2a. The average chemical shifts of the aromatic protons show that the electron density in the aryl rings of 4.2a and 4.4 is similar (Table 4.2).

Based on the higher average NMR chemical shift, the aromatic ring of the non-alkylated cationic hydrotrope 4.5a is more electron deficient than that of 4.2a and 4.4. Considering that both aromatic rings in 4.1 are relatively electron deficient, 4.5a is expected to interact more weakly with 4.1, leading to a less negative \(G(c)\), as borne out in practice.

<table>
<thead>
<tr>
<th>Hydrotrope</th>
<th>(\delta / \text{ppm} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2a</td>
<td>7.68</td>
</tr>
<tr>
<td>4.2b</td>
<td>7.52</td>
</tr>
<tr>
<td>4.2c</td>
<td>7.55</td>
</tr>
<tr>
<td>4.2d</td>
<td>7.54</td>
</tr>
<tr>
<td>4.2e</td>
<td>7.55</td>
</tr>
<tr>
<td>4.2f</td>
<td>7.41</td>
</tr>
<tr>
<td>4.2g</td>
<td>n.d.(^a)</td>
</tr>
<tr>
<td>4.3</td>
<td>n.d.(^a)</td>
</tr>
<tr>
<td>4.4</td>
<td>7.68</td>
</tr>
<tr>
<td>4.5a</td>
<td>7.72</td>
</tr>
<tr>
<td>4.5b</td>
<td>7.55</td>
</tr>
</tbody>
</table>

\(^{(a)}\) n.d.: not determined

Structurally related 4.5b, having a lower average chemical shift, is intermediate in \(G(c)\). Even though \(G(c)\) shows no correlation with the average chemical shift of the aromatic protons, the lack of correlation with average chemical shifts alone is caused by the fact that the trimethylammonium moiety of 4.5b is not directly attached to the aromatic ring. The hydrophilic hydration shell around the ionic
moiety will therefore not overlap as strongly with the hydration shell of the aromatic ring as is the case for 4.2a, 4.5a and 4.4. Consequently, the hydrophobicity of the aromatic ring is less attenuated for 4.5b, causing $G(c)$ to be more strongly negative than expected on the basis of electron density in the aromatic ring alone, which is indeed observed.

As noted above, the dilute molality range in which the $G(c)$-values have been determined was chosen to avoid 2:1 and higher order interactions. To check the validity of this assumption, the molality dependence of the $^1$H-NMR spectrum of 4.2b was examined. The short-chain benzenesulfonate 4.2b shows an almost linear dependence of the chemical shift of the meta hydrogen on molality in aqueous solution indicating the absence of cooperative aggregation. The decrease in chemical shift of the meta hydrogen is caused by the decrease in interhydrotrope distances upon increasing cosolute molalities and the accompanying weak non-cooperative interaction between the individual hydrotrope molecules. As a result of the increasing molality, both intermolecular aromatic ring current effects and the decreasing polarity of the solution cause an upfield shift.

In addition, aggregation into loose micellar-type aggregates would have been associated with a difference in $G(c)$ between 4.2b and 4.3. Larger aggregates will bind counterions as a result of the increasing charge density with increasing aggregation number. Replacing sodium counterions by caesium counterions is known to enhance association: a less unfavourable dehydration of the caesium cations leads to more efficient stabilisation of the double (or higher) positive charge in the dimer (or higher aggregates). In the dilute solutions for which $G(c)$ have been determined, this is not observed.

The equilibrium constants for hydrotrope self-association also indicate the prevalence of 1:1 interactions. The equilibrium constant for encounter complex formation (Chapter 2) between 4.1 and any of the investigated hydrotropes does not exceed 3 kg mol$^{-1}$. We therefore contend that the equilibrium constant of association between individual hydrrotropic molecules does not exceed 1 kg mol$^{-1}$ for the investigated systems, since binding between the hydrolytic probe and hydrotropic cosolute is only governed by favourable hydrophobic interactions, whereas binding between two hydrotropic cosolute molecules is counteracted by electrostatic interactions. We assume the equilibrium constants for formation ($K_{ass}$) of the (n+1)-mer from the n-mer to be less than 1 kg mol$^{-1}$, assuming non-cooperative association (Scheme 4.3, cf. Section 2.2.7).
Scheme 4.3

Using an upper value of 1 kg mol\(^{-1}\) for \(K_{\text{ass}}\), we calculated the compositions, in terms of monomer and oligomer molalities,\(^{61}\) of solutions in which the total hydrotrope molality ranges between 0 and 0.3 mol kg\(^{-1}\) (Figure 4.4).

![Figure 4.4: Molalities of monomers (o) and of oligomers (●) as a function of the molality of a weakly self-associating solute.](image)

At all total hydrotrope molalities \(m_c\), the molality of monomeric hydrotropic cosolute ([monomer]) is smaller than the total molality of hydrotropic cosolute. However, in the range between 0 and 0.3 mol kg\(^{-1}\), the total molalities of monomers and oligomers combined, \(\Sigma_n[n\text{-mer}]\) is only about 20% less than the total hydrotrope molality and it varies almost linearly with total hydrotrope molality. Therefore, 1:1-interactions still prevail. For the expected values of \(K_{\text{ass}}\) smaller than 1 kg mol\(^{-1}\), 1:1-interactions will be the main contribution to \(G(c)\).

4.2.3 Kinetics of Reactions in Moderately Concentrated Solutions of Hydrotropes

In the higher molality range from 0.3 mol kg\(^{-1}\) up to 1.5 mol kg\(^{-1}\), kinetic data for hydrolysis in the presence of 4.2d and 4.2e indicate strong self-association of the hydrotropes, most probably even cooperative self-association, as indicated by the markedly non-linear, almost sigmoidal plots of ln\([k(m_c)/k(m_c=0)]\) vs. \(m_c\). This sigmoidal-like pattern is not observed for the shorter-chain benzenesulfonates 4.2a-c and the other hydrotropes. For example, in the case of sodium 4-methylbenzenesulfonate, an archetypal hydrotrope, ln\([k(m_c)/k(m_c=0)]\) is linearly dependent on hydrotrope molality, the deviation being towards higher values of

99
$\ln[k(m_c)/k(m_c=0)]$ at higher molalities. This pattern is generally observed for non-associating cosolutes.

![Figure 4.5](image)

**Figure 4.5:** The effect of different non-alkylated hydrotropes on the hydrolysis of 4.1. Hydrotropes: 4.2a (o), 4.4 (x), 4.5a (♦) and 4.5b (Δ).

Unfortunately, the interpretation of the observed plots of $\ln[k(m_c)/k(m_c=0)]$ as a function of hydrotrope molality is hampered by the difference in interpretation of deviations from linearity according to the equations in Chapters 1 and 2. According to Equation (1.9), a linear plot of $\ln[k(m_c)/k(m_c=0)]$ versus molality indicates the prevalence of 1:1-interactions in the corresponding molality range. Deviations to higher values of $\ln[k(m_c)/k(m_c=0)]$ at higher molalities then signify a tendency to (weakly) self-associate. This self-association effectively reduces the interactions between cosolute and hydrolytic probe if the shielding of potential interaction sites occurs without the dimer (or higher aggregates) having a stronger rate-retarding effect than the monomer. According to Equation 2.1, however, curves of $\ln[k(m_c)/k(m_c=0)]$ as a function of molality are non-linear for 1:1-interactions. According to this equation, linearity actually is a result of weak cosolute self-association.

For the non-alkylated hydrotropes, plots of $\ln[k(m_c)/k(m_c=0)]$ versus molality are linear or deviate towards higher values of $\ln[k(m_c)/k(m_c=0)]$ at higher molality. This result not only excludes the possibility of cooperative self-association in this molality range, it also indicates that $K_{ass}$ (for non-cooperative association between the hydrotropes) is small, most probably significantly smaller than 1 kg mol$^{-1}$, as we assumed on the basis of the kinetic data obtained for dilute solutions (*vide supra*). The linearity of plots of $\ln[k(m_c)/k(m_c=0)]$ vs. molality up to high molalities therefore indicates that high molalities of hydrotropes are achievable in aqueous solution, without significant association or phase separation. The fact that $K_{ec} > K_{ass}$ corroborates the conclusion that interactions with uncharged molecules are not hindered by charge repulsion and that interaction between apolar non-ionic
solubilisates and ionic hydrotropes is much stronger than interactions between hydrotropic molecules. Consequently, if the hydrophobic moiety of the hydrotrope is made less hydrophobic, for example by introduction of a hydroxy-substituent, a strong decrease in hydrotropic activity is observed.\textsuperscript{56}

The lack of strong self-association results in the presence of many “single hydrophobic binding sites”, facilitating the dissolution of apolar molecules. Therefore, solubilising effects of hydrotropes are normally larger than those of surfactants. We also note that these single hydrophobic binding sites can participate in rather strong hydrophobic interactions with apolar solutes, making hydrotropes different from typical salting-in solutes.

The transition from weak association to cooperative association is apparent from a marked change in the molality dependence of $\ln\left[\frac{k(m_c)}{k(m_c=0)}\right]$. Weak association is accompanied by higher values of $\ln\left[\frac{k(m_c)}{k(m_c=0)}\right]$ than expected on the basis of linear behaviour at higher cosolute molalities. Cooperative association, however, is accompanied by sigmoidal plots of $\ln\left[\frac{k(m_c)}{k(m_c=0)}\right]$ against molality.\textsuperscript{62} First, the slope of plots of $\ln\left[\frac{k(m_c)}{k(m_c=0)}\right]$ vs. $m_c$ becomes more negative, a pattern attributed to stronger cooperative binding of 4.1 to small self-associated clusters of added cosolute molecules. A levelling off at higher molalities is the result of the substrate being almost completely bound. For 4.2d and 4.2e, the hydrophobic moieties are large enough for hydrophobic interactions to overcome the electrostatic repulsion. As a consequence, small and weakly organised clusters are formed. For both hydrotropic molecules and hydrolytic probe, it now becomes possible to interact favourably with more than one hydrophobic moiety and cooperative binding starts to take place. In fact, 4.2d and 4.2e are the link between hydrotropes and surfactants.

**Figure 4.6**: Chemical shift of the meta protons in the aromatic ring of 4.2b (o, +0.03 ppm), 4.2d (v) and 4.2e (x). Molalities were calculated after correction for the density difference between H$_2$O and D$_2$O.
In accord with the kinetic data, 4.2d and 4.2e show a sigmoidal dependence of the chemical shift of the meta protons as a function of the molality (Figure 4.6), revealing a critical molality of association. The observed critical hydrophobic interaction molalities (CHIMs) are 0.5 molal and 0.25 molal for 4.2d and 4.2e, respectively, in accord with the molalities obtained from the kinetic experiments.

In addition to ionic hydrotropes, a few nonionic hydrotropes have been examined previously. As nonionic molecules lack repulsive electrostatic interactions, they are more generally expected to show cooperative self-association at low molality. Indeed, \(N\)-cyclohexyl-2-pyrrolidinone 4.6 has been shown to have a rate retarding effect very similar to that observed for 4.2d and 4.2e.52,64

The absence of a clear CHIM for the studied hydrotropes is remarkable and in sharp contrast with solubilisation experiments. One of the reasons for not observing a clear CHIM may be that the concentration of hydrolytic probe has been kept some 3 orders of a magnitude lower than the concentrations of dyes and drugs in typical solubilisation experiments. Introducing relatively high concentrations of hydrophobic materials may well induce clustering of the hydrotrope monomers, even when clustering is not occurring in the absence of hydrophobic solubilisates. This conclusion is in accord with results of a study of Horvath-Szabo et al.11 on the solubilisation of lecithin by sodium dimethylbenzensulfonate. They concluded that instead of cooperative self-association of sodium dimethylbenzensulfonate (SXS), “a cooperative interaction between lecithin and SXS is responsible for the phenomena”. Similarly, Ueda44 found that solubilisation at low concentrations of solubilisate occurs by one to one complexation, whereas at the higher solubility limits, one to one complexation was no longer sufficient to account for the increased solubilities of apolar compounds. Significantly, da Silva et al.66 have shown that non-linear increases in solubilising power and other properties of hydrotrope solutions are not necessarily suggestive of any critical phenomenon.

4.3 CONCLUSIONS

In the present study, we have examined the effect of a series of charged hydrotropes on the water-catalysed hydrolysis of 4.1. We find that typical hydrotropes stabilise the apolar substrates in aqueous solution by forming encounter complexes with equilibrium constants in the range between 1 kg mol\(^{-1}\) and 3 kg mol\(^{-1}\). These equilibrium constants are in most cases larger than the equilibrium constants for self-association between hydrotrope monomers as a result of charge repulsion.
between the latter. The balancing of favourable hydrophobic interaction and unfavourable charge repulsion results in the hydrotropes being soluble over a large molality range. The mode of action of a hydrotrope differs from the mode of action of a salting-in compound since a hydrotrope contains a hydrophobic moiety, albeit small, that is able to participate in relatively strong hydrophobic interaction with an uncharged apolar molecule. As soon as the hydrophobic moieties are large enough for the hydrophobic interaction to overcome the charge repulsion, cooperative self-association takes place, presumably producing highly dynamic and loose micellar-type aggregates.

4.4 EXPERIMENTAL

4.4.1 KINETIC EXPERIMENTS

Aqueous solutions were prepared by weight immediately before use. Water was distilled twice in an all-quartz distillation unit. Reactions were monitored at 25.0±0.1°C using appropriate wavelengths to avoid overlap with strong absorption bands of the cosolutes used. Reactions were followed for at least six half-lives using a Perkin-Elmer lambda 2, lambda 5 or lambda 12 spectrophotometer. Good to excellent pseudo-first-order kinetics were obtained, the error in the rate constants being 2% or less. Between 4 and 7 µl of a stock solution containing 1-benzoyl-3-phenyl-1,2,4-triazole 4.1 in cyanomethane were injected into about 2.7 ml of reaction medium in a 1.000 cm path length stoppered quartz cuvette. The resulting concentrations of hydrolytic probe were about 10⁻⁵ mol dm⁻³ or less. The pH of every solution was determined using a SENTRON ISFET pH probe and was adjusted to 3.9±0.3 using aqueous HCl. The pH was checked again at the end of each kinetic run and was found to be still well within the pH-range in which solely water-catalysed hydrolysis takes place.

4.4.2 MATERIALS

1-Benzoyl-3-phenyl-1,2,4-triazole,67 sodium 4-n-butylbenzenesulfonate68 and sodium 4-methoxybenzenesulfonate69 were prepared according to literature procedures. p-Toluenesulfonic acid monohydrate, 4-ethylbenzenesulfonic acid, phenyltrimethylammonium bromide and benzyltrimethylammonium bromide were obtained from Aldrich, benzamidinium chloride was from Sigma, caesium hydroxide hydrate was from Acros and 4-n-propylbenzenesulfonyl chloride was from Lancaster.
and all were used as received. Sodium 4-methylbenzenesulfonate and sodium
4-ethylbenzenesulfonate were prepared by neutralising the corresponding acid
using a sodium hydroxide solution, followed by filtration and evaporation of the
solvent. Caesium 4-methylbenzenesulfonate was prepared analogously using CsOH
hydrate. All prepared salts were tested and found pure using $^1$H-NMR and
 elemental analysis. All hydrotropes were stored in a desiccator over $\text{P}_2\text{O}_5$ or KOH.
NMR spectra were recorded on Varian Gemini 200 ($^1$H: 200MHz) and VRX 300 ($^1$H:
300MHz) spectrometers, with HOD set to 4.79 ppm. In the determination of the
molality dependence of the $^1$H-NMR spectra of 4.2b, 4.2d and 4.2e, methanol was
added as a second reference. The signal of methanol did not shift with respect to
the set signal of HOD.

Sodium 4-\textit{n}-propylbenzenesulfonate (4.2d). 4-\textit{n}-Propylbenzenesulfonyl chloride
(15g, 65 mmol) was suspended in 1M aqueous NaOH and stirred vigorously for 2
days at 40°C. The resulting acidic solution was neutralised and the solvent
evaporated, resulting in a 1:1 sodium 4-\textit{n}-propylbenzenesulfonate/NaCl mixture
(18.2 g, 65 mmol). The mixture was extracted continuously overnight in a Soxhlet
apparatus using \textit{n}-propanol. Only part of the 4-\textit{n}-propylbenzenesulfonate was
extracted to avoid contamination with NaCl. The absence of sodium chloride was
confirmed using a silver nitrate precipitation test. $^1$H-NMR (D$_2$O): $\delta$ (ppm): 0.88 (3H,
CH$_2$CH$_2$CH$_3$, t), 1.61 (2H, CH$_3$CH$_2$CH$_3$, sextet), 2.64 (2H, CH$_3$CH$_2$CH$_3$, t), 7.36 and
7.71 (4H, phenyl, AB-system); anal. calcd. for C$_9$H$_{11}$SO$_3$Na, %: C, 48.64; H, 4.99; S,
14.43; found %: C, 48.30; H, 4.84; S, 14.30.

4.5 ACKNOWLEDGEMENTS

Elemental analyses were performed by H. Draayer and J. Ebels of the analytical
section of this department.
4.6 REFERENCES AND NOTES

(6) Schobert, B. Naturwissenschaften 1977, 64, 386.
(10) Balasubramanian et al. (reference 9) observed that the hydrotrope concentration at which the sudden rapid increase in solubility of a hydrophobic solubilisate occurs, coincides with a break in a plot of surface tension as a function of hydrotrope concentration. However, as pointed out by Da Silva et al. (reference 66), cooperative aggregation (e.g. micellisation) is accompanied by a break in a plot of surface tension as a function of the logarithm of concentration. Horvath-Szabo et al. (reference 11) showed that in a plot of surface tension as a function of the logarithm of hydrotrope activity, no break occurs at the activity at which the sudden increase in solubilisation occurs.
(18) Usage of sodium dimethylbenzenesulfonate (mixture of isomers) according to the National Toxicology Program (US).


(55) Bruce, T. C. and Lapinski, R. J. Am. Chem. Soc. 1958, 80, 2265-2267.


(61) Compositions were calculated iteratively. $K_{\text{nas}}$ was set to 1 mol kg$^{-1}$ for all association steps up to 20-merisation. Molalities of 20-mers were low enough to cut off the calculation for higher order aggregates.

(62) As pointed out by Mukerjee (reference 8), sigmoidal plots of solubilising effect versus concentration of solubilising agent are not necessarily indicative of cooperative self-aggregation of the solubilising agent. Likewise, sigmoidal curves of $\ln[k(m_c)/k(m_c=0)]$ as a function of molality $m_c$ can be the result of stepwise association (Equation 2.7). For the present case, however, either the hydrotrope self-association or the binding of the hydrolytic probe to the hydrotrope assemblies (or both) should be unexpectedly high (in comparison with the 1:1-interaction) to reproduce the observed curves.


