Effects of overlap of hydration shells on noncovalent interactions in aqueous solution
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1998

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
CHAPTER 3

Effects of Cationic Group Hydration on Noncovalent Interactions

3.1 Introduction. Properties of alkylated ammonium bromides in aqueous solution

In the previous chapter the effects of cosolutes containing a polar group were investigated to some extent. Attention is now turned to the effects of cosolutes containing charged groups. The interesting results arising from the study of Noordman et al., which revealed for the first time how an anionic group affects the hydrophobic interactions of \( n \)-alkylsulfates with 1-benzoyl-1,2,4-triazole, initiated a similar investigation of the effects of cationic solutes on intermolecular hydrophobic interactions.

Symmetric tetraalkylammonium halides are an obvious choice since they were previously identified as good models for studying hydrophobic phenomena, in part because of their relatively simple structure, the availability of series of cations with different alkyl chain lengths and their high solubilities in water. Indeed, the solution properties of these ‘hydrophobic salts’ have been the subject of intense research for more than three decades. The early investigations pointed indirectly to increased ordering of hydration water around the hydrocarbon groups of these ions in water. Later, other experimental studies confirmed this increase in structure of water induced by these hydrophobic salts and up to several years ago “structure-making” (“breaking”) terminology has been used to explain their aqueous solution properties. More recently, however, experimental results have been interpreted without resorting these concepts.

With the goal of obtaining direct evidence for enhanced water-water interactions around these salts, Turner, Soper and Finney systematically studied aqueous solutions of tetramethyl-, tetrapropyl- and tetrabutylammonium halides in aqueous solution by sophisticated neutron diffraction techniques using isotope substitution (NDIS), focusing on the pair correlations between water-water, water-cation and cation-cation. Their results were a breakthrough and indicated clearly that there is little difference in the average 3-D hydrogen-bond structure around the tetraalkylammonium cations, which implies that the structural enhancement of water commonly associated with hydrophobic hydration is small or even absent. This conclusion was also supported by a recent molecular dynamics simulations study of
tetraalkylammonium halides in aqueous solution. In addition, this study suggested that the hydrogen bonds between water molecules in the hydration shell are somewhat shorter and more linear in character than those in the bulk. This is not surprising, since alkylated ammonium salts lead to considerable electrostriction (contraction) of the solvent.

However, water in the first hydration shell of tetraalkylammonium halides is dynamically different from bulk water. The translational motion of water molecules is hindered in the hydration shell, as was shown by water self-diffusion coefficients and NMR studies and is also in accord with the early discovery of the high viscosities of tetraalkylammonium salt solutions.

Ion pairing could have some influence on the hydration structure around the cations, especially since the interactions involving ions in aqueous solution are long-range. However, it is assumed that ion pairing in dilute aqueous solutions containing tetraalkylammonium salts is negligible and that the cations and anions are at least solvent separated and possess independent hydration shells.

The aim of the present kinetic study is to investigate the effects of the cationic ammonium hydration on hydrophobic interactions of the solute apolar alkyl groups with the hydrolytic probe 1-benzoyl-1,2,4-triazole (BT) (see Chapter 2) in dilute aqueous solutions. In addition to the tetra-n-alkylammonium bromides (1), n-alkylammonium (2), n-alkyltrimethylammonium (3) and n-alkyldimethylammonium (4) bromides have also been used as cosolutes.

The questions prompting this study were:
1. Are these ionic solutes really hydrophobic ions, i.e. are they able to interact via hydrophobic interactions with BT?
2. What are the effects of varying the alkyl group R from methyl to n-hexyl on hydrophobic interactions with the kinetic probe in terms of additivity of group interactions?
3. In connection with question 2, how extensive is the ammonium group hydration and what is its effect on hydrophobic interactions?
3.2 Kinetic solvent effects of alkylated ammonium bromides on the water-catalysed hydrolysis of 1-benzoyl-1,2,4-triazole

The kinetic medium effects of the hydrophobic salts 1-4 on the hydrolysis of 1-benzoyl-1,2,4-triazole at pH 4 and 25°C have been measured at different molalities. Generally, rate constants were obtained up to a concentration of 1 molal of added cosolute, except for \( n \)-hexylammonium and \( n \)-hexyldimethylammonium bromide, which were measured up to a limit of 0.5 molal, because these salts showed evidence for aggregation above this concentration. These concentrations are expected to allow the formation of at least one independent layer of water around each cation\(^{20,9e} \). Like anionic cosolutes\(^1 \), the cationic alkylammonium bromides retard the hydrolysis of BT. As an example, the medium effects on the neutral hydrolysis of BT, expressed as the dependence of \( \ln(k/k_0) \) on the molality of added tetra-\( n \)-alkylammonium bromides, are shown in Figure 3.1. The tetra-\( n \)-alkylammonium bromides produced excellent linear correlations between \( \ln(k/k_0) \) and the molality of added salt indicating pairwise (i.e. 1:1) interactions with BT. The salts 2-4 showed a similar linear dependence on molality. \( G(c) \) values were obtained from the slopes of these plots and are compiled in Table 3.1.

In terms of the SWAG approach\(^{21} \), each functional group in one molecule interacts with every functional group in the other molecule. Each of these interactions has a characteristic effect on the pairwise Gibbs energy interaction parameter \( G(c) \). It has been shown that the SWAG-approach is also applicable to the interactions between electrolytes and non-electrolytes\(^{22} \), amongst

![Figure 3.1 Kinetic medium effects on the pseudo-first-order rate constant for hydrolysis of BT at pH 4 and 25 °C, plotted as \( \ln(k/k_0) \) versus the molality of ammonium bromide (●), tetramethylammonium bromide (▲), tetraethylammonium bromide (●), tetra-\( n \)-propylammonium bromide (▼) and tetra-\( n \)-butylammonium bromide (◆).](image-url)
others between tetraalkylammonium bromides and DMF. In the case of alkyl-substituted ammonium bromides, G(c) is composed of contributions due to \( n \) Table 3.1. G(c) values (J kg mol\(^{-2}\)) for tetra-\( n \)-alkylammonium, \( n \)-alkylammonium, \( n \)-alkyldimethylammonium and \( n \)-alkyltrimethylammonium bromides as cosolutes in the water-catalysed hydrolysis of 1-benzoyl-1,2,4-triazole. Standard deviations in G(c) in parenthesis.

<table>
<thead>
<tr>
<th>R</th>
<th>( R_4\text{N}^+\text{Br}^- )</th>
<th>( \text{RNH}_3^+\text{Br}^- )</th>
<th>( \text{RN}^+\text{H(Me)}_2\text{Br}^- )</th>
<th>( \text{RN}^+\text{(Me)}_3\text{Br}^- )</th>
</tr>
</thead>
<tbody>
<tr>
<td>methyl</td>
<td>-324 (4)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>-324 (4)</td>
</tr>
<tr>
<td>( n )-propyl</td>
<td>-655 (7)</td>
<td>-471 (26)</td>
<td>-415 (8)</td>
<td>-436 (6)</td>
</tr>
<tr>
<td>( n )-butyl</td>
<td>-1190 (13)</td>
<td>-486 (4)</td>
<td>-527 (16)</td>
<td>-512 (14)</td>
</tr>
<tr>
<td>( n )-pentyl</td>
<td>n.d.</td>
<td>-631 (6)</td>
<td>-625 (10)</td>
<td>-575 (13)</td>
</tr>
<tr>
<td>( n )-hexyl</td>
<td>n.d.</td>
<td>-735 (7)</td>
<td>-696 (8)</td>
<td>-782 (6)</td>
</tr>
</tbody>
</table>

\(^a\)Not determined

methylene moieties in the alkyl chain, the ammonium ion and the bromide ion. In the case of perfect additivity, the increment in G(c) of the cosolutes depends solely on the difference in the number of CH\(_2\)-groups. In Figure 3.2, the G(c) values for the tetra-\( n \)-alkylammonium bromides are plotted versus the number of CH\(_2\)-groups (where the contribution of a CH\(_3\)-group equals the contribution of 1.5 CH\(_2\)-group and the contribution of 3 CH-groups\(^{23}\)). Obviously, there is no constant contribution of the CH\(_2\)-group to the kinetic medium effect throughout the series. Hardly any effect on the G(c) value is observed when the alkyl chain length increases from zero to two carbon atoms per chain; \( i.e. \) from ammonium bromide to tetraethylammonium bromide. Most probably, these methylene groups are not available for hydrophobic interactions with the hydrophobic groups of BT. This sensitivity is due to the hydrophilic hydration sphere of the ammonium headgroup, which extends to the third carbon atom in the \( n \)-alkyl chain. The influence of ionic hydration shells on the

![Figure 3.2 Medium effects of tetra-\( n \)-alkylammonium](image)
bromides on the hydrolysis of BT at 25 °C and pH 4. Plot of $G(c)$ values versus number of CH$_2$-moieties in the cosolute. The hydrophobicity of nearby methylene groups agrees very well with kinetic solvent effect studies of aqueous solutions containing sodium $n$-alkylsulfates$^1$, $n$-alkylpyrrolidinones$^{24}$ and $\alpha$-amino acids$^{25}$. Gianni et al.$^{26}$ recently analysed partial molal volumes of organic electrolytes at infinite dilution by a simple additivity scheme from which they also concluded that the region of influence of a polar group does not extend beyond the $\beta$ carbon atom of the alkyl substituent. The kinetic observations are also supported by Hirata et al.$^{27}$, who investigated the micellisation behaviour of double-headed surfactants in which two quaternary ammonium species $(C_{10}H_{21}N^+\text{(CH$_3$)$_2$})$ are linked by a hydrocarbon spacer. The results indicated that surfactants having spacers of 4 methylene moieties and shorter behave as normal micelle forming surfactants whereas 6 methylene moieties and longer show deviating behaviour. Methylene moieties in the short spacers do not cause these deviations because they are not significantly hydrophobically hydrated due to the strong hydrophilic hydration of the two ammonium head groups.

Despite the absence of hydrophobic interactions between the short-chain alkylammonium bromides and BT, a retardation of the hydrolysis is observed. For the longer-chained compounds the retardations are mainly the result of a dominant stabilisation of the more hydrophobic initial state of the hydrolysis by these cosolutes through hydrophobic interactions (these alkylated ammonium salts are generally viewed as hydrophobic species$^{28,29}$). The retardations caused by the short-chain compounds must have another origin (even though there is convincing evidence that, for example, the tetramethylammonium cation is a hydrophobic species according to neutron diffraction experiments$^{30}$). Even ammonium bromide has a rate retarding effect on the neutral hydrolysis of BT, $G(c) = -307 (7)$ J kg mol$^{-2}$, despite the absence of any hydrophobic groups. One would actually anticipate an increase in rate due to a stabilisation of the polar transition state by favourable electrostatic interactions with the charged group, which is not screened by alkyl groups in the case of ammonium bromide. It is noted, however, that it was observed previously that an anionic group can have a retarding effect on the hydrolysis of BT. In the case of sodium $n$-alkylsulphates$^1$, $G(\text{OSO}_3^-)$ is approximately -600 J kg mol$^{-2}$. Recently, Berendsen et al.$^{31}$ calculated the proton transfer rate constant for the rate determining step in the water-catalysed hydrolysis of a carboxylic ester, $p$-methoxyphenyl dichloroacetate, by means of MD simulations and Density Matrix Evolution (DME). The water-catalysed hydrolysis of this substrate proceeds via the same mechanism$^{32}$ as the water-catalysed hydrolysis of BT. They observed that only a few of the many possible water orientations which lead to reaction can account for the experimental rate constant. As a possible explanation for the observed
retardations in the presence of the (alkylated) ammonium bromide(s) it is suggested that the strict orientational requirements for the water molecules in the activated complex are more pronounced when these water-demanding salts are added to the aqueous solution. Ammonium bromide is extensively hydrated, mainly through hydrogen bonding to the four polarised N-H groups, and competes with the transition state for water molecules, *i.e.* a salting out effect is operative particularly for the transition state. However, in view of the MD simulation\(^1\), a more likely explanation lies in the reduced (translational) mobility of the water molecules due to the presence of the cosolutes, *i.e.* the water molecules in the hydration shells are less dynamic and it simply takes more time to find the configuration necessary for the reaction to occur. The larger negative contribution to the G(c) value by the OSO\(_3\)-group\(^1\) might be rationalised in terms of the reduced shielding of the charge relative to that for the alkylated ammonium ions. Consequently, the anions have a larger influence on the 3D hydrogen-bond network of water than the cationic ammonium bromides. However, this influence does not reach further than the influence of the cations; both affect the hydration of the alkyl groups up to the γ-C atom.

For the other three series of ammonium bromides G(c) values have been obtained for compounds with alkyl chains longer than two carbon atoms only (see table 3.1) and therefore the results cannot provide additional evidence for the assumption that the cationic charge reduces the apparent hydrophobicity of neighbouring methylene moieties. However, outside the destructive influence of the cationic charge, additivity of CH\(_2\)-group interactions is more likely to occur. In Figure 3.3, all G(c) values have been plotted versus the total number of CH\(_2\)-groups. The relationships are fairly linear (except for the tetraalkylammonium bromides), indeed suggesting additivity of CH\(_2\)-group interactions with BT for methylene moieties which are independently hydrated. The slopes of these plots give an indication for the strength of these noncovalent pairwise group interactions and are compiled in Table 3.2. As can

\[ \text{Figure 3.3. } G(c) \text{ values for the tetraalkylammonium (■), alkylammonium (▲), alkyldimethylammonium (○) and alkyl} \]
trimethylammonium bromides (\textit{N}) as a function of the total number of CH$_2$ groups in the solutes.

be seen, the slopes (G(CH$_2$)) are the same within experimental error, except for

Table 3.2 Pairwise Gibbs energy interaction parameters for the CH$_2$-group in the various series of cosolutes.

<table>
<thead>
<tr>
<th>Solutes</th>
<th>G(CH$_2$)$^a$ J kg mol$^{-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_4N^+$ Br$^-$</td>
<td>116 (19)</td>
</tr>
<tr>
<td>$RNH_3^+$ Br$^-$</td>
<td>125 (12)</td>
</tr>
<tr>
<td>$RN^+H(\text{Me})_2\ Br^-$</td>
<td>94 (7)</td>
</tr>
<tr>
<td>$RN^+\text{Me}_3\ Br^-$</td>
<td>110 (24)</td>
</tr>
<tr>
<td>alcohols</td>
<td>90 (3)$^b$</td>
</tr>
</tbody>
</table>

$^a$Only data for solutes with alkyl substituents larger than ethyl have been taken into account. $^b$Taken from ref. 33.

the alkylidimethyl ammonium bromides. The G(CH$_2$) values are slightly higher than the value obtained for pairwise interactions between linear alcohols and BT, but this is not surprising since that value is based on the difference between ethanol and 1-propanol and it is now clear that the alkyl moieties of those two solutes are not completely independently hydrated, due to the influence of the hydroxyl group.

To illustrate more clearly that only methylene moieties outside the hydration sphere of the ionic group (\textit{i.e.} further than two carbon atoms away from the ionic group) are available for hydrophobic interactions with the substrate, the G(c) values for $n$-alkylidimethylammonium bromides are plotted again versus the number of CH$_2$-moieties in Figure 3.4, but now leaving space for extrapolation towards zero methylene groups. If the argumentation above is correct, the group interaction

![Figure 3.4](image-url) Medium effects of $n$-alkylidimethylammonium bromides on the hydrolysis of BT at 25°C. Plot of G(c) versus number of CH$_2$ moieties. Extrapolation according to the SWAG-approach (5 CH$_2$-moieties = CH$_2$CH$_2$N(H)Me$_2$).
parameter for the $\text{CH}_2\text{CH}_2\text{N}^+(\text{H})\text{Me}_2\text{Br}^-$-group should be similar to the G(c) value for ammonium bromide. This value is obtained by extrapolation of the linear correlation shown in Figure 3.4 to where $n(\text{CH}_3)$ equals five. This gives a value for $\text{G}(\text{CH}_2\text{CH}_2\text{N}^+(\text{H})\text{Me}_2\text{Br}^-)$ of -282 J kg mol$^{-2}$. This is in satisfactory agreement with the experimental G(c) value for ammonium bromide of -307 (7) J kg mol$^{-2}$, again supporting that hydrophobic groups in close proximity to a polar group are masked for hydrophobic interactions with the kinetic probe. A similar extrapolation of the data for the $n$-alkylammonium and $n$-alkyltrimethylammonium bromides gives values for $\text{G}(\text{CH}_2\text{CH}_2\text{N}^+\text{H}_3)$ of -300 J kg mol$^{-2}$ and for $\text{G}(\text{CH}_2\text{CH}_2\text{NMe}_3)$ of -245 J kg mol$^{-2}$, respectively. The deviation of the latter value for $n$-alkyltrimethylammonium bromides is probably due to the less pronounced apolar group additivity (i.e., a larger error in extrapolation).

Now that it is established that the noncovalent interactions of alkylated ammonium bromides with linear alkyl chains shorter than 3 linear C-atoms with BT are governed primarily by the headgroup hydration, it is worthwhile to plot the alkyl chain length of the salts 1-4 versus the G(c) value, irrespective of the substitution pattern of the ammonium head group (i.e., how many methyl groups (or even ethyl groups, in the case of tetra-$n$-alkyl ammonium bromides) it contains in addition). This is shown in Figure 3.5. As anticipated, the data for the various series of cosolutes nearly overlap each other. Thus, once more, it is illustrated that the kinetic probe hardly distinguishes between an ammonium, a methyl-, dimethyl- or trimethylammonium head group and even a triethylammonium group in the case of tetraethylammonium bromide. In the case of tetra-$n$-propyl ammonium bromide, the cationic hydration looses its dominance. Clearly there is a difference between solutes bearing one or four $n$-propyl groups and this distinguishes the tetra-$n$-alkyl ammonium salts from the other series.

In view of these results it is expected that the alkylethylammonium bromides will show overlap with the data in Figure 3.5. Unfortunately, such data are not available.

As mentioned in the introduction, there is a vast amount of thermodynamic data

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**Figure 3.5.** G(c) parameters for tetraalkylammonium (■).
alkylammonium (▲), alkyldimethylammonium (O) and alkyl trimethylammonium bromides (▼) as a function of the number of C-atoms in the linear alkyl chain which is varied in length. In particular, tetraalkylammonium bromides\(^2\). It is of interest to correlate these solution data with the kinetic data presented in this chapter, to investigate whether the pairwise interactions are specific for the hydration of alkylated ammonium compounds or whether they rather reflect specific interactions with BT.

However, partial molar volumes\(^{26,34}\), heat capacities\(^{35}\), compressibilities\(^{34,36}\) and expansibilities\(^{35}\) do not show total independence of the R substituent up to carbon atom three for the tetraalkylammonium salts. It may be that the intrinsic contributions to the partial molar properties are considerable in the case of these salts, *i.e.* that the hydration contribution does not dominate the partial molar property. The kinetics however, purely reflect the hydration characteristics of the salts.

A final remark should be made considering the effect of the counterion. Kinetic experiments with alkylated ammonium chlorides have been performed and did not give different results from those for the bromides. Therefore, it is concluded that there is no cation-anion pairing, because the anions are differently hydrated and an effect on the kinetics would be expected.

Moreover, the hydrated anions do not interact with BT, for similar reasons. Thus, the observed rate effects are caused by the cations only.

### 3.3 Conclusion

Analysis of G(c) parameters suggests that the ionic hydration shell of the ammonium headgroup in \(n\)-alkylated ammonium bromides is incompatible with the hydration shell of the alkyl groups attached to it. The water molecules in the ionic hydration shell will be oriented differently and have stronger (electrostatic) interactions with the solute than the water molecules in the hydrophobic hydration shell. The ionic hydration shell reduces the apparent hydrophobicity of methylene groups within a distance of 3 consecutive carbon atoms. Hydrophobic interactions are only observed for \(n\)-alkylated ammonium compounds with alkyl groups with more than two carbon atoms. For two or fewer carbon atoms, negative G(c) values are presumably caused by a reduction of the water (translational) mobility during the activation process, which requires the specific and precise orientation of two water molecules.
For those solutes containing methylene groups outside the ionic hydration sphere, additivity of methylene group interaction is observed.

3.4 Experimental procedures

Materials. 1-Benzoyl-1,2,4-triazole was available. Its synthesis has been described in the literature\textsuperscript{32a}. The \textit{n}-alkylamines, tetra-\textit{n}-alkylammonium bromides and methyl bromide were purchased from Janssen Chimica, Fluka and Sigma. The \textit{n}-alkylamines were distilled before use.

The \textit{n}-alkylammonium bromides and the dimethyl-\textit{n}-alkylammonium bromides were prepared in situ by acidifying the corresponding \textit{n}-alkylamines and dimethyl-\textit{n}-alkylamines, respectively, with aqueous hydrogen bromide to pH 4. The \textit{n}-alkyldimethylamines were synthesised by Esch-Weiler Clark methylation\textsuperscript{37} of the corresponding \textit{n}-alkylamine.

The \textit{n}-alkyldimethylammonium bromides were synthesised by methylation of the corresponding \textit{n}-alkyldimethylamine with methyl bromide at -20 °C in acetone. The acetone was carefully removed via a steel wire under moderate nitrogen pressure. The salts were dried in a drying pistol until no further loss in weight was observed. The purity of the tetra-\textit{n}-alkyl- and the \textit{n}-alkyl-trimethylammonium bromides was checked by \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectroscopy.

Kinetic measurements. The kinetic experiments have been carried out according to the procedures described in Section 2.7. Rate constants were reproducible within 2%. Reaction rate constants at each molality were measured in triplicate. Kinetic data for each set of solutions were determined at least 4 different molalities.

3.5 Acknowledgement

Peter Hol synthesised the alkylammonium bromides and performed the kinetic measurements reported in this chapter within the framework of the research project of his masters study. He is also acknowledged for the pleasant cooperation during this period.

3.6 References
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24. Chapter 2
32. Lensink, M.F., Mavri, J., Berendsen, H.J.C., submitted for publication