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Effect of different sodium halides on the self-association of tertiary butanol in water

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The molecular self-association of hydrophobic substances is an important process for many biological systems. Here, the authors study the effect of salt on the molecular self-association of *t*-butanol in water solution, using NMR techniques. They compare the effects of different sodium halides (NaCl, NaBr, and NaI) as a function of their concentration. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2714951]

I. INTRODUCTION

The self-organization of living matter into distinct phases of hydrophobic material (e.g., cell membranes) and hydrophilic phases (such as the cytoplasm) has its roots in interactions at the molecular level.[1] The relatively low solubility in water of many organic molecules, which leads to phase separation above a critical concentration, is called the hydrophobic effect.[1–8]

Thermodynamically, this effect manifests itself via the entropy of solution, even in completely miscible substances. The entropy of solution of simple alcohols, such as methanol, is lower than expected for ideal solutions. This implies that the hydrophobic units induce some order in the surrounding water. This effect has been assigned to the modification of the water structure, forming icelike or clathratelike structure around a solute molecule.[2,9,10] Experimental and theoretical evidence suggests that the hydrophobic portions of alcohol molecules in aqueous solution form aggregates even in homogeneous solutions.[11,12] At the molecular level, macroscopically homogeneous solutions of alcohol in water appear therefore not to be completely mixed.[13] X-ray emission spectroscopy indicates that water molecules bridge methanol chains to form ring structures containing six to eight methanol molecules.[14]

When considering hydrophobic effects in homogeneous solutions, the first step is often the identification of hydrophobic cavities, which may consist of individual molecules, clusters of molecules, or a combination of both. The interaction of these regions with the surrounding water depends also on the size of these units: for small hydrophobic cavities, the hydrogen bonded structure of water is maintained (four hydrogen bonds), although configured in a disordered manner. For large cavities, however, the hydrogen bond structure is modified more strongly and the number of hydrogen bonds can locally decrease to $\leqslant 3$.[8] Only if the length scale of the hydrophobic aggregates exceeds a few nanometers, the hydrogen bonding is strongly depleted and the apolar surfaces become dry.[15] The crossover between these two regions appears to be driven by collective effects.[6]

Tertiary butanol (TBA) is the largest monohydric alcohol that is fully miscible in water and is considered to be the most hydrophobic of the water-soluble alcohols.[16] The different types of interactions in a water-alcohol mixture (solute-solute, solute-solvent, and solvent-solvent interactions) have different dependencies on temperature and concentration. As a result, the hydrophobic association (or solute-solute interaction) increases with dilution of the alcohol concentration and reaches a maximum at a concentration of about 2–3 mol % alcohol.[17]

While most studies of hydrophobic effects use pure water as the solvent, biological systems always contain electrolytes in variable concentrations. Salts are known to affect the phase separation behavior,[18] as well as the molecular interactions in homogeneous solutions like aqueous solutions of alcohols.[19] This influence appears to correlate with the Hofmeister series of aqueous solutions.[20] Neutron scattering data indicate that the addition of salt influences the structure of the solute-solute interaction. According to Bowron and Finney,[21,22] the addition of NaCl leads to two coordination spheres. They attribute this effect to the anion (Cl^-), which appears to bridge a pair of TBA molecules. In contrast to their results, molecular dynamics simulations found no evidence of such structure.[23]

In this paper, we describe an experimental investigation of the effect of salt on the association of TBA molecules in water. The basis of our measurements is the dependence of the interaction between nuclear spins on their distance. Changes in the association between TBA molecules can be measured by their effect on the nuclear spin relaxation rate, which depends on d^6, where d is the distance between two nuclei. We therefore measured the relaxation rates of TBA-water mixtures for a range of different salts and different concentrations.

The paper is structured as follows: Section II gives the theoretical basis for our measurements. Then we describe the experimental scheme, present the results, and conclude with a brief summary.

II. THEORETICAL APPROACH

Our measurements of the molecular association are based on the dependence of the spin-lattice relaxation on the

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TABLE I. Dilution series of the samples 2:100:0 TBA:D_2O:NaCl used for the isotopic dilution experiment. The volumes are in microliters.

x_H	V_D	V_{TBA}	V_{d10}
1.00	490	51.0	0.0
0.75	490	38.3	12.8
0.50	490	25.5	25.5
0.25	490	12.8	38.3

internuclear distance.[24] For a pair of nuclear spins, the corresponding contribution to the nuclear spin relaxation rate T_1^{-1} in the extreme narrowing situation ($\omega\tau_c \ll 1$) is[24]

$$\frac{1}{T_1} = \frac{3}{2}\gamma^4\hbar^2\left(\frac{\mu_0}{4\pi}\right)^2\frac{1}{r^6}\tau_c, \tag{1}$$

where τ_c represents the correlation time of the molecular motion, r the internuclear distance, and γ the gyromagnetic ratio.

For a given molecular composition, the nuclear spin relaxation measurement yields a single number. To use this as a quantification of molecular self-association, we follow the approach of Hertz and co-workers.[25–28] Assuming that the only protons in the system are those in the TBA molecules, we may describe the molecular distribution by the proton-proton pair correlation function $g_{HH}(r)$. We then consider the weighted integral

$$A = \frac{1}{2}\frac{\gamma^4\hbar^2}{a^4}\left(\frac{\mu_0}{4\pi}\right)^2\int_0^\infty\left(\frac{a}{r}\right)^6 g_{HH}(r)4\pi r^2 dr, \tag{2}$$

where a represents the closest approach distance of the interacting nuclei. If the degree of self-association between TBA molecules increases, $g_{HH}(r)$ will increase at short distances. Since the weighting factor r^{-6} strongly favors short distances, this will lead to an increase in the association parameter A.

Comparing Eq. (2) with the expression (1) for the nuclear spin relaxation rate, we find that the association parameter is directly related to the relaxation rate by[28,29]

$$A = \frac{1}{T_{1,\mathrm{inter}}}\frac{D}{\rho_H}, \tag{3}$$

where D is the self-diffusion coefficient of the solute molecules and ρ_H is the number density of the ^1H nuclei in the system. The diffusion constant serves here as a measure of the correlation time $\tau_c = a^2/3D$ (Ref. 28) and can be measured independently, e.g., by pulsed field gradient measurements.

The observed spin relaxation rate depends on the sum of inter- and intramolecular interactions. To make this dependence explicit, we write the total relaxation rate as

$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + \frac{1}{T_{1,\mathrm{intra}}} + \frac{1}{T_{1,\mathrm{inter}}}. \tag{4}$$

Here, $1/T_{1,\mathrm{intra}}$ is the contribution due to intramolecular dipole-dipole interactions, $1/T_{1,\mathrm{inter}}$ is the corresponding intermolecular contribution, and $1/T_{1,0}$ includes external contributions, such as the interaction with water molecules. Since we are not interested in this term, we minimize it in the experiment by using deuterated water. The relaxation efficiency of deuterium, compared to protons, is reduced by a factor[24] $\alpha = 0.042$. To separate the relevant $T_{1,\mathrm{inter}}$ term from the others, we used the method of isotopic dilution.[23,30] Mixing the (at the methyl groups) fully protonated TBA molecules (TBA-d1) with fully deuterated molecules (TBA-d10) yields a variation of the intermolecular relaxation rate. If we parametrize the dilution via the mole fraction

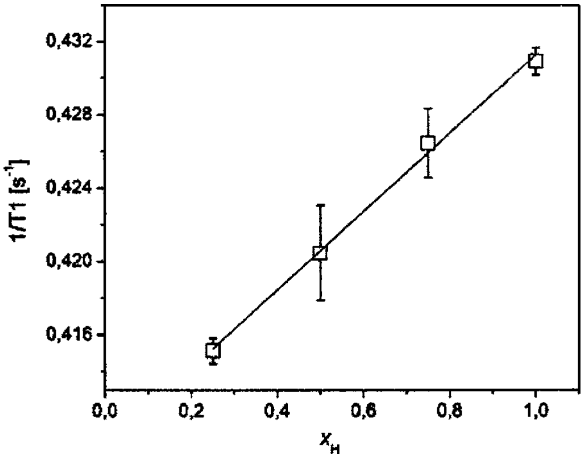

FIG. 1. Relaxation rate $1/T_1$ as a function of the isotopic dilution x_H.

$$x_H = \frac{[\text{TBA-d1}]}{[\text{TBA-d1}] + [\text{TBA-d10}]}, \tag{5}$$

we expect that the total relaxation rate should change as

$$\frac{1}{T_1} = \frac{1}{T_{1,0}} + \frac{1}{T_{1,\mathrm{intra}}} + \frac{1}{T_{1,\mathrm{inter}}}[(1-\alpha)x_H + \alpha]. \tag{6}$$

$1/T_{1,\mathrm{inter}}$ is thus the intermolecular relaxation rate for the fully protonated case ($x_H = 1$), i.e., it does not depend on the concentration.

III. EXPERIMENTAL DETAILS

A. Sample preparation

The TBA-d1 (99%) was purchased from Cambridge Isotope laboratories, TBA-d10 (99%) from Isotec. The solvent D_2O 99.96% was obtained from Merck KGaA. The solutions were prepared by measuring the appropriate amounts of each compound with a micropipette and by weighing corresponding amounts of NaCl, NaBr, and NaI. In order to eliminate spurious contributions to the relaxation by dissolved oxygen, the sample was put through multiple freeze-pump-thaw cycles until no gas bubbles developed from the solution. Then, the samples were flame sealed.

B. Relaxation measurements

Measurements of relaxation and diffusion were carried out by proton NMR on a 600 MHz Varian Infinity +spectrometer. All experiments were conducted under controlled temperature conditions at 25 °C.

The relaxation times were measured by the usual inversion recovery method. The free induction decay was Fourier

TABLE II. Measured relaxation times in seconds for the different samples. x_H is the proton mole fraction [see Eq. (5)].

x_H	1.0	0.75	0.5	0.25
		TBA:D2O:salt		
2:100:0	2.321	2.345	2.378	2.409
		TBA:D2O:NaCl		
2:100:2	2.267	⋯	2.334	2.369
2:100:4	2.230	2.321	2.348	2.373
		TBA:D2O:NaBr		
2:100:2	2.306	2.325	2.351	2.375
2:100:4	2.283	2.310	2.335	2.366
		TBA:D2O:NaI		
2:100:2	2.348	2.377	2.391	2.415
2:100:4	2.405	2.425	2.445	⋯

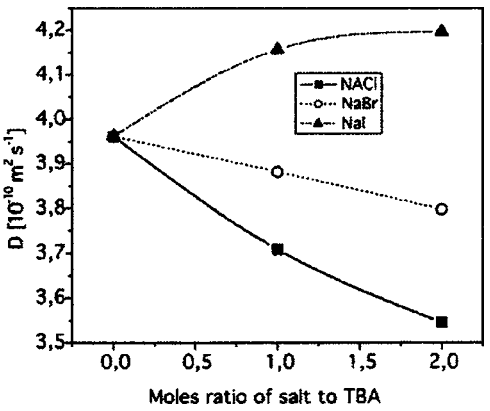

FIG. 2. Variation of the diffusion coefficient with the salt concentration.

transformed and the signal integrated over the TBA resonance line. The resulting signals were fitted to the function

$$I(\tau) = A + Be^{-\tau/T_1}, \tag{7}$$

which takes into account signal offset that may result, e.g., from imperfect inversion pulses. Each T_1 value reported is the average obtained from the analysis of three sets of relaxation data with two scans per spectrum.

To extract the intermolecular contribution, we used isotopic dilution series as the one shown in Table I.

Figure 1 shows a typical case, corresponding to the dilution series of Table I. The squares and error bars indicate the experimental data, while the straight line shows a least squares fit to Eq. (6). Since the first two terms in Eq. (6) do not depend on the concentration, their sum appears as the intercept of the straight line with the y axis, while the intermolecular term is given by the slope of the line.

C. Diffusion measurements

The diffusion coefficient of TBA-d1 was determined by pulsed gradient spin echo experiments.[31] For the gradient calibration, we used the diffusion coefficient of pure water $D_{H_2O} = 2.299 \times 10^{-9}$ m^2 s^{-1}.[32] The gradient pulse duration and separation were 3.0 and 75.01 ms, respectively. A delay of 20 s was made between subsequent experiments. To separate the signal of the TBA from the signal of the remaining water protons, we Fourier transformed the second half of the spin echo signal and integrated over the relevant range of the spectrum.

IV. RESULTS AND DISCUSSION

Table II gives an overview of the samples and the measured relaxation time in each of them. We fixed the mole ratio TBA:D_2O at 2:100 and varied the salt concentration from 0 to 2.0 (moles salt/moles TBA). For this study we fixed the cation and varied the anion of the salt (Cl, Br, and I). As expected, we observed an increase of the relaxation times as the proton content was reduced. Like in the case of the reference sample (Fig. 1), we extracted the intermolecular contribution to the relaxation time from each dilution series.

Table III and Fig. 2 summarize the observed dependence of the diffusion coefficients on the salt concentration for the three different salts. In the case of the smaller anions (Cl and Br), we find that the diffusion slows down significantly with increasing salt concentration, the effect being more pronounced for chloride. For NaI, however, we find an increase in the mobility of TBA.

TABLE III. Summary of the measurement results. The salt-free sample 2:100:0 is the reference. The relaxation times are in seconds. All experiments were carried out at a temperature $T = 25$ °C.

Sample	T_1	$T_{1,\text{intra}}$	$T_{1,\text{inter}}$	$D/10^{-10}$ m^2 s^{-1}	$A/10^{-39}$ m^5 s^{-2}
			TBA:D2O:salt		
2:100:0	2.321	2.445	44.889	3.962	1.628
			TBA:D2O:NaCl		
2:100:2	2.267	2.411	37.920	3.709	1.853
2:100:4	2.230	2.447	27.853	3.546	2.475
			TBA:D2O:NaBr		
2:100:2	2.306	2.403	56.002	3.882	1.319
2:100:4	2.283	2.398	47.506	3.798	1.569
			TBA:D2O:NaI		
2:100:2	2.348	2.441	63.727	4.157	1.254
2:100:4	2.405	2.491	69.646	4.196	1.202

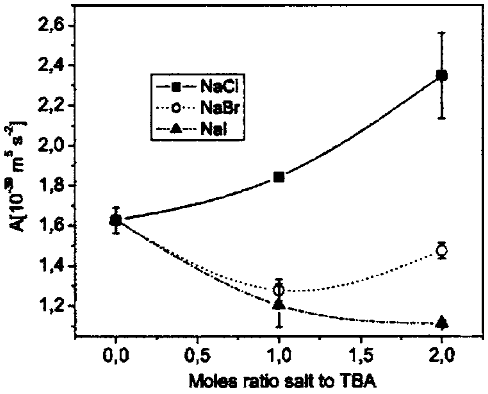

FIG. 3. Evolution of the *A* parameter. The curves are splines.

Combining the relaxation data with the diffusion coefficients, we used Eq. (3) to determine the association parameters. The quantitative results are shown in Table III and Fig. 3. The curves in Fig. 3 indicate that the relation between the association parameter and the mole ratio of salt to TBA is not linear, as described previously.[23]

For NaCl, we observe a strong increase in the association parameter, indicating that NaCl enhances the self-association of TBA at all concentrations. For NaBr, the effect appears to be a small decrease of the association. For NaI, the effect is definitely negative, indicating that the distribution of the TBA molecules becomes more uniform. These results agree with the effect observed in the system ethanol in water[19] where the addition of NaBr and NaI decreases the self-association tendency of the ethanol molecules.

The difference in the degree of involvement of the anion can be organized in the sequence $\mathrm{Cl}^- > \mathrm{Br}^- > \mathrm{I}^-$ which is a part of the Hofmeister series of stabilization of proteins. In the TBA-water system, the most electronegative anion (I^-) is found to be the most destabilizing upon increasing salt concentrations. Previous studies have highlighted the role of Cl^- as a determinant of the association behavior,[21] even though this role is still problematic.[21–23] It has been found that an attractive interaction exists between the Br^- and Xe in aqueous solution,[33] Xe being a small hydrophobic molecule. This result shows that Br^- does not promote the Xe–Xe hydrophobic interaction and might explain the smaller effect of Br^- on the self-association. To our knowledge, no similar results exist for I^-.

We have used nuclear magnetic resonance to quantify the modification of the hydrophobic effect of TBA molecules dissolved in water by the addition of different electrolytes to the solution. The data show a clear effect of the salts which varies with the anion used. Apart from the known effect of the salt on the solvent structure,[20,34] there also appears to be specific effects of the ions on the solute molecules as well as on the interaction between water and TBA molecules. At this stage, the interaction of the cation (Na^+) and the TBA molecules is hard to define. A study of systems with different cation (NaCl, LiCl, KCl, and RbCl) may be useful for this purpose. However, a study done by Holz and Patil[35] in a similar system indicates also that the cation sequence follows the Hofmeister series. These results might be a complement to our findings.

For the effects observed here, it appears that NaCl enhances the self-association of TBA, thereby lowering its mobility. NaI, on the other hand, appears to have the opposite effect, not only lowering the association parameter, but also increasing the diffusion coefficient. For both measures, NaBr is intermediate between the two. In the light of our results and of the references, we would mention that the salt effect on the self-association of relatively small hydrophobic species follows the Hofmeister series.

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[1] C. Tanford, *The Hydrophobic Effect: Formation of Micelles and Biological Membranes* (Krieger, Melbourne, 1991).
[2] W. Kauzmann, Adv. Protein Chem. **14**, 1 (1959).
[3] A. Ben-naim, *Hydrophobic Interactions* (Plenum, New York, 1980).
[4] J. N. Israelachvilli, *Intermolecular and Surface Forces: With Applications to Colloidal and Biological Systems* (Academic, New York, 1985).
[5] L. R. Pratt, Annu. Rev. Phys. Chem. **53**, 409 (2002).
[6] P. R. ten Wolde, J. Phys.: Condens. Matter **14**, 9445 (2002).
[7] B. Widom, P. Bhimalapuram, and K. Koga, Phys. Chem. Chem. Phys. **5**, 3085 (2003).
[8] D. Chandler, Nature (London) **437**, 640 (2005).
[9] H. S. Frank and M. W. Evans, J. Chem. Phys. **13**, 507 (1945).
[10] A. K. Soper and J. L. Finney, Phys. Rev. Lett. **71**, 4346 (1993).
[11] J. Tsai, M. Gerstein, and M. Levitt, J. Chem. Phys. **104**, 9417 (1996).
[12] S. Dixit, W. C. K. Poon, and J. Crain, J. Phys.: Condens. Matter **12**, L323 (2000).
[13] S. Dixit, J. Crain, W. C. K. Poon, J. L. Finney, and A. K. Soper, Nature (London) **416**, 829 (2002).
[14] J.-H. Guo, Y. Luo, A. Augustsson, S. Kashtanov, J.-E. Rubensson, D. K. Shuh, H. Agren, and J. Nordgren, Phys. Rev. Lett. **91**, 157401 (2003).
[15] K. Lum, D. Chandler, and J. D. Weeks, J. Phys. Chem. B **103**, 4570 (1999).
[16] D. T. Bowron, J. L. Finney, and A. K. Soper, J. Phys. Chem. B **102**, 3551 (1998).
[17] M. Mayele, M. Holz, and A. Sacco, Phys. Chem. Chem. Phys. **1**, 4615 (1999).
[18] A. F. Kostko, B. H. Cipriano, O. A. Pinchuk, L. Ziserman, M. A. Anisimov, D. Danino, and S. R. Raghavan, J. Phys. Chem. B **109**, 19126 (2005).
[19] A. Sacco, F. M. De Cillis, and M. Holz, J. Chem. Soc., Faraday Trans. **94**, 2089 (1998).
[20] M. G. Cacace, E. M. Landau, and J. J. Ramsden, Q. Rev. Biophys. **30**, 241 (1997).
[21] D. T. Bowron and J. L. Finney, Phys. Rev. Lett. **89**, 215508 (2002).
[22] D. T. Bowron and J. L. Finney, J. Chem. Phys. **118**, 8357 (2003).
[23] D. Paschek, A. Geiger, M. J. Hervé, and D. Suter, J. Chem. Phys. **124**, 154508 (2006).
[24] A. Abragam, *The Principles of Nuclear Magnetism* (Oxford University Press, New York, 1961).
[25] H. G. Hertz, Prog. Nucl. Magn. Reson. Spectrosc. **3**, 159 (1967).
[26] H. G. Hertz and R. Tutsch, Ber. Bunsenges. Phys. Chem. **80**, 1268 (1976).
[27] A. L. Capparelli, H. G. Hertz, and R. Tutsch, J. Phys. Chem. **82**, 2023 (1978).
[28] K. J. Muller and H. G. Hertz, J. Phys. Chem. **100**, 1256 (1996).

[29] U. Wandler and H. G. Hertz, Z. Phys. Chem. **178**, 217 (1992).
[30] G. Bonera and A. Rigamonti, J. Chem. Phys. **42**, 171 (1965).
[31] W. S. Price, Concepts Magn. Reson. **10**, 197 (1998).
[32] R. Mills, J. Chem. Phys. **77**, 685 (1973).
[33] M. Holz, J. Mol. Liq. **67**, 175 (1995).
[34] H. J. Bakker, M. F. Kropman, and A. W. Omta, J. Phys.: Condens. Matter **17**, S3215 (2005).
[35] M. Holz and K. J. Patil, Ber. Bunsenges. Phys. Chem. **2**, 107 (1991).