

# Pressure and Salt Effects in Simulated Water: Two Sides of the Same Coin?\*

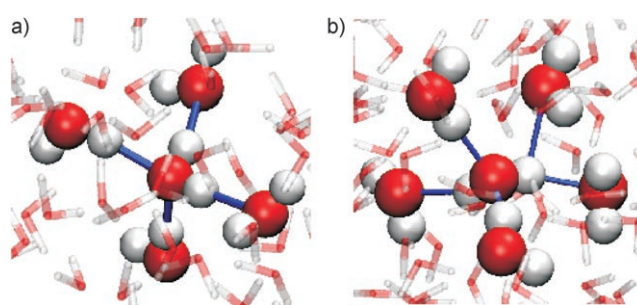
Jörg Holzmann, Ralf Ludwig,\* Alfons Geiger, and Dietmar Paschek\*

Water is certainly the most important liquid for life on earth. Moreover, it is also perhaps the liquid with the most puzzling physical properties. One of water's best known anomalies is the decrease of density upon cooling below 4 °C at atmospheric pressure. Other anomalous properties include the sharp increase of specific heat and compressibility upon cooling and supercooling. In addition to these thermodynamic features, the kinetic properties are also unusual, as the increase of diffusivity and decrease of viscosity upon compression indicate.<sup>[1,2]</sup> Adding solutes considerably broadens the spectrum of observed effects. For this reason the structure and dynamics of water in the vicinity of solutes have been studied for decades. The structure-making (kosmotrope) and structure-breaking (chaotrope) influence of ions on the hydration water has been understood as emerging from a balance between the water–water and ion–water interactions, which varies considerably with the charge density on the solute surface.<sup>[3–9]</sup>

Lebermann and Soper used neutron diffraction to compare the effects of applied pressure and high salt concentrations on the hydrogen-bonding network of water. They found that the ions induce a change in structure equivalent to the application of high pressures, and that the size of the effect is ion-specific.<sup>[10]</sup> Similar effects have been reported by Botti et al.,<sup>[11,12]</sup> who studied the solvation shells of H<sup>+</sup> and OH<sup>-</sup> ions in water. Mancinelli et al. could show that the structural perturbation due to monovalent ions (in aqueous solutions of NaCl and KCl) exists outside the first hydration shell of the ions.<sup>[13]</sup> Their study emphasized longer-ranged ion-induced perturbation and related shrinkages of the second and third coordination shells of water molecules, while the first hydration shell is largely unchanged. The O–O pair correlation function of water was modified by the ions in a manner closely analogous to what happens in pure water under pressure. In

contrast, recent molecular dynamics (MD) simulations of aqueous CaCl<sub>2</sub> solutions indicate unequivocally that the changes of the water structure caused by the presence of ions in solution cannot be emulated as a pressure effect owing to the local nature of such a structure perturbation.<sup>[14]</sup>

Growing evidence is emerging that the anomalous behavior of water and aqueous solutions is closely related to the existence of at least two major distinct local structural forms of water.<sup>[15,16]</sup> At low temperatures and at low to moderate pressures, water approaches a low-density liquid (LDL) state, which exhibits an almost perfectly interconnected random tetrahedral network. In the LDL state water has an average of four nearest neighbors, similar to the situation in ice I<sub>h</sub> (see Figure 1 a). Close to the low-density structure the mobility of



**Figure 1.** Configurations representing typical transient local environments of a water molecule in liquid water. a) “Low-density” configuration with four nearest neighbors, providing a well-ordered tetrahedral surrounding. b) “High-density” configuration with more than four nearest neighbors, showing a more distorted nearest neighbor environment. This configuration also indicates the presence of a bifurcated H-bond arrangement, providing a lower energy path for the reorientation of the central molecule.

water strongly slows down.<sup>[17–22]</sup> MD simulations suggest that defects in the random tetrahedral hydrogen-bonding network show fivefold water coordination.<sup>[18,22]</sup> With increasing pressure, these defects increase and provide low-energy pathways for reorientational motions and thus catalyze the restructuring of the network (Figure 1 b).<sup>[17,22]</sup> This interpretation has been further substantiated recently<sup>[23,24]</sup> and has also been proposed for aqueous electrolyte solutions.<sup>[25,26]</sup> The close link between anomalous thermodynamic and kinetic properties has been set into a broader perspective since supercooled liquid water has been shown to qualitatively obey the Adam–Gibbs relation, thus connecting the diffusion coefficient with the configurational entropy.<sup>[21]</sup>

In line with recent studies on solute-induced effects at supercooled conditions,<sup>[25,31–33]</sup> we have studied the aqueous

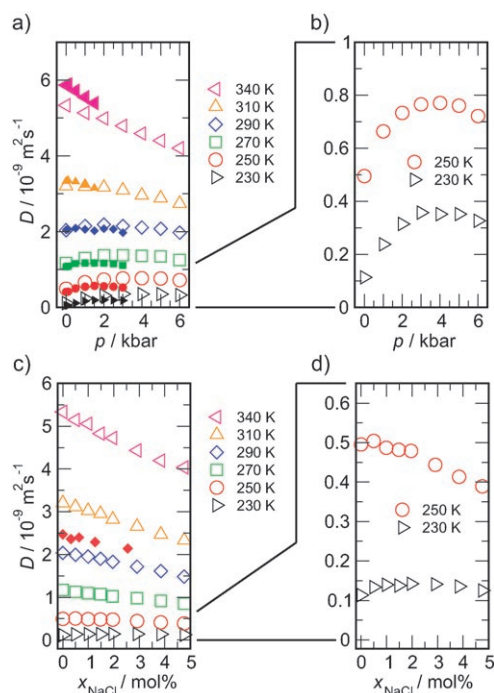
[\*] Dipl.-Chem. J. Holzmann, Prof. Dr. R. Ludwig  
Institut für Chemie, Abteilung Physikalische Chemie  
Universität Rostock, 18051 Rostock (Germany)  
Fax: (+49) 381-498-6524  
E-mail: ralf.ludwig@uni-rostock.de  
Prof. Dr. A. Geiger, Dr. D. Paschek  
Fachbereich Chemie, Physikalische Chemie  
Universität Dortmund, 44221 Dortmund (Germany)  
Fax: (+49) 231-755-3748  
E-mail: dietmar.paschek@udo.edu

[\*\*] This work was supported by the Deutsche Forschungsgemeinschaft (DFG, FOR 436) and the “Pact for Research and Innovation of the Federal Ministry of Education and Research/Leibniz Science Association”.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

salt solutions over a broad temperature range, extending deeply into the supercooled region. To dissect and test the proposed pressure analogy, we focussed particularly on the behavior of water beyond the second hydration shell, the so-called “free water”.<sup>[30]</sup> Here we report that the free water apparently exhibits structural, dynamic, and thermodynamic signatures, similar to those of water under pressure, suggesting that the effect of salt and pressure might be regarded as “two sides of the same coin”.

The mobility of water is quantified in terms of water’s self-diffusion coefficient  $D$ . Figure 2a shows  $D$  values for water over a broad temperature and pressure range along with the



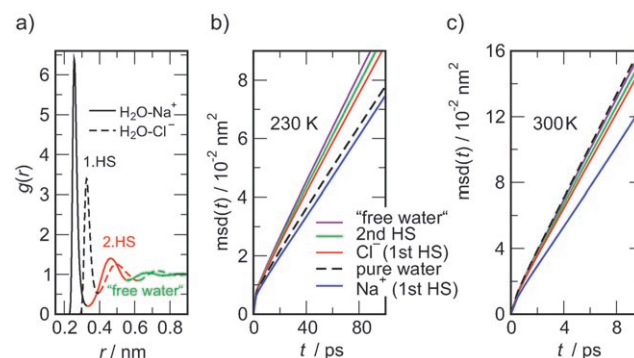
**Figure 2.** Self-diffusion coefficients  $D$  for TIP4P-Ew model water molecules (open symbols). a,b)  $D$  of pure water as a function of temperature  $T$  for pressures  $p$  between 1 bar and 6 kbar. Filled symbols indicate experimental data according to Prielmeier et al.<sup>[27,28]</sup> c,d)  $D$  of water in aqueous salt solutions ( $p=1$  bar) for NaCl concentrations between 0 and 4.76 mol%. The filled symbols represent the experimental data for 296 K according to McCall and Douglass.<sup>[29]</sup>

experimental data of Prielmeier et al.<sup>[27]</sup> The simulations are found to reproduce the experimental data almost quantitatively. Both simulation and experiment reveal that water’s mobility at high temperatures slows down with increasing pressure; below temperatures of about 290 K water displays an anomalous pressure dependence. In both simulation and experiment the diffusivity of water is found to go through a maximum. However, in the simulations the maximum is shifted to somewhat higher pressures (by about 1 kbar at 230 K).

A plot of the self-diffusion coefficients for water as a function of salt concentration is shown in Figure 2c. Note that for ambient pressure (and at higher temperatures) water’s mobility slows down with increasing salt concentration. The experimental salt effect reported by McCall and Douglass<sup>[29]</sup>

is found to be relatively well reproduced by our MD simulations. However, to our surprise, we find that with decreasing temperature, the effect of salt on the water dynamics becomes weaker and weaker, and is finally even anomalously inverted. At 230 K,  $D$  initially increases with increasing salt concentration and passes through a broad maximum at concentrations between 2 to 3 mol%. This behavior is similar to the effect observed for “structure-breaking” salts such as  $\text{KNO}_3$  at ambient temperature conditions,<sup>[6]</sup> using the “structure-breaking/-making” classification proposed by Samoilov.<sup>[4,5]</sup> Therefore we might conclude that the “structure-breaking” character even of ions, such as “ $\text{Na}^+$  and  $\text{Cl}^-$ ”, which are “structure making” at ambient temperatures becomes increasingly pronounced with decreasing temperature. Reexamination of the experimental data of Engel and Hertz<sup>[6]</sup> for different salt solutions between 0°C and 25°C seems to indicate a trend similar to that observed in our simulations.

Figure 3 focuses on the short-time mobility of the water molecules as a function of distance from the ions. Therefore we have divided the volume of the entire simulation cell into



**Figure 3.** a) The ion–water (center of mass) pair correlation functions indicating three different distance ranges.<sup>[30]</sup> b,c) Mean square displacement of water molecules as a function of time,  $\text{msd}(t) = \langle [r(t_0) - r(t_0 + t)]^2 \rangle$ , in 0.498 mol% aqueous salt solution at  $p=1$  bar and  $T=230$  K (b) and  $T=300$  K (c). Different colors indicate the water’s state at time  $t_0$ : 1st HS (of  $\text{Na}^+$  or  $\text{Cl}^-$ ), 2nd HS, or the “free water” phase.<sup>[30]</sup> For comparison the mean square displacement for pure water is also given.

subvolumes corresponding to “bound water”, as represented by the first and second hydration shells, and into a complementary “free water” phase.<sup>[30]</sup> The distance ranges were chosen according to the ion–water pair correlation functions given in Figure 3a. We would like to point out that even for the highest concentration (4.76 mol%), about one-third of the water molecules still belong to the “free water” phase. Figure 3b,c depict the mean square displacement of the water molecules (msd), depending on whether the water molecule was initially part of the first or second hydration shell of one of the ions or belonged to the “free water” fraction. The timespan shown in Figure 3 corresponds to the time for diffusion over the distance of roughly one molecular diameter. At high temperatures, the mobility of the water molecules in the hydration shell of the ions is found to be

significantly slowed down. This corresponds well to the observation of a reduced reorientational mobility of the water molecules in IR short-time experiments<sup>[34]</sup> and from NMR experiments.<sup>[6]</sup> Note that water in the first hydration shell of a sodium ion is significantly slower than the water in the first hydration shell of the chloride ion. This is in agreement with the tighter binding of water to the sodium ion, as revealed by the depth of the first minima of the water/ion pair correlation functions shown in Figure 3a. The water found in the second hydration shells of both ions is only marginally less mobile than in pure water, whereas “free water” has the same mobility as pure water. Quite interestingly, at 230 K the sequence of water mobilities is very much the same as at 300 K, with water in the first hydration shell of sodium being the slowest component (Figure 3b). However, surprisingly, now “free water” is significantly more mobile than pure water. Moreover, even the water in the first hydration shell of the chloride ion is found to be faster (typically “structure breaking”), and water in first hydration shell of the sodium ion is only marginally slower than in pure water. Apparently, the observed initial increase in the diffusion coefficient of water shown in Figure 2d must be attributed largely to a change of the properties of the “free water” phase in the aqueous solution, suggesting that also the ions are embedded in a more fluid matrix, at least at sufficiently low salt concentrations.

Selected thermodynamic properties for water and the aqueous solutions are discussed in Figure 4. The density of pure water as a function of temperature along several isobars is given in Figure 4a. The shown isobars indicate that the TIP4P-Ew model reproduces experimental data quite satisfactorily, although the density maximum is found to be slightly shifted to lower temperatures, and the thermal expansivity is somewhat too large at low pressures. Figure 4b shows how the presence of salt alters the location of the temperature of maximum density  $T_{\text{TMD}}$ . We would like to stress the fact that the relative shift with increasing salt

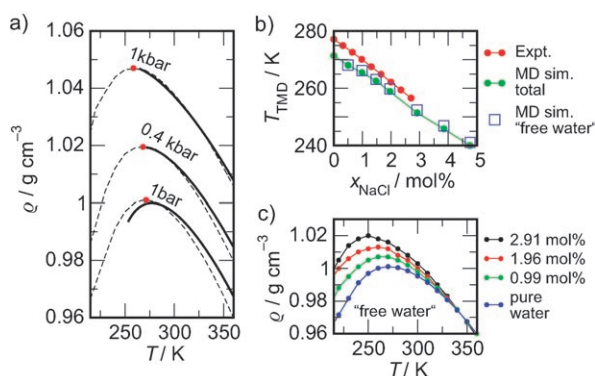
concentration is reproduced almost quantitatively. Below  $T_{\text{TMD}}$ , where the thermal expansivity  $\alpha$  is negative, entropy and volume fluctuations become anticorrelated  $\alpha \cong (\partial S \partial V)$ .<sup>[38]</sup> Therefore an equal shift of  $T_{\text{TMD}}$  simulation and experiment provides substantial evidence that structure and energetics are apparently altered in a similar way by the presence of the ions.

Figure 4c focuses on the temperature dependence of density of the “free water” phase. At high temperatures, the density matches exactly the values obtained for pure water. At low temperatures, however, a significant increase in density (about 2% at 250 K for 2.91 mol% NaCl) is observed. This density increase roughly corresponds to a pressure effect of about 0.4 kbar (compare with Figure 4a). Please note that the density of the “free water” phase also passes through a maximum, which shifts to lower temperatures with increasing salt concentration. As shown in Figure 4b,  $T_{\text{TMD}}$  of “free water” coincides almost exactly with  $T_{\text{TMD}}$  of the overall solutions. Hence we might conjecture that the experimentally measured shift in  $T_{\text{TMD}}$  of the aqueous salt solutions also very likely reflects the changing thermal expansion behavior of the “free water” phase in the real solution.

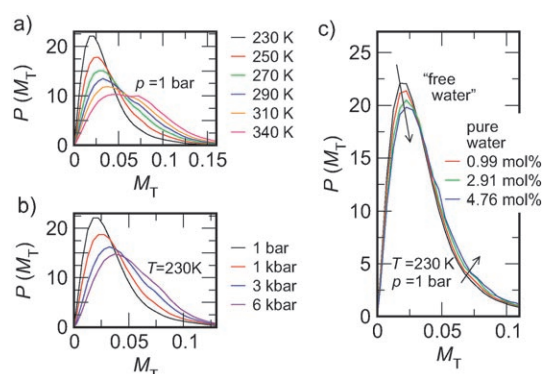
In this last section we discuss the structural changes of the local environment of water molecules induced by pressure and by salt. Medvedev and Naberukhin have proposed a “tetrahedrity parameter”  $M_T$ , characterizing the deviation from an ideal tetrahedron and defined by Equation (1), where  $l_i$  are the lengths of the six edges of a tetrahedron.<sup>[39]</sup>

$$M_T = \sum_{i < j} (l_i - l_j)^2 / (15 \langle l^2 \rangle) \quad (1)$$

$M_T = 0$  corresponds to ideal tetrahedral geometry. To characterize the symmetry of the local water environment, we consider the tetrahedron formed by the four nearest neighbor molecules around a central water molecule.<sup>[40]</sup> As shown in Figure 5a, the temperature dependence of  $P(M_T)$  indicates a bimodal distribution at high temperatures, suggesting the presence of two major local structural forms,<sup>[19,41,42]</sup> graphically illustrated in Figure 1. With decreasing temperature only the highly ordered structures prevail. Experimentally it has been shown for the amorphous forms of water that increasing pressure leads to an increasing number of nearest neighbors.<sup>[43]</sup> The enhanced local coordination number at elevated pressures is accordingly accompanied by an increasing population of distorted tetrahedral environments, given in Figure 5b. Figure 5c finally shows the  $M_T$  distributions for the “free water” fraction for different salt concentrations at 230 K. Similar to the effect of pressure, an increase of distorted tetrahedra is observed upon the addition of salt. In quantitative terms, the changes of the  $M_T$  distributions due to salt roughly compare with the changes induced by a pressure of about 0.4 kbar. The magnitude of the change corresponds well with the salt-induced density increase reported in Figure 4c. To complement the recent experimental studies by Mancinelli et al.,<sup>[13]</sup> we have also calculated O–O radial pair distribution functions including all water molecules (see the Supporting Information). Similar to the findings of Mancinelli et al., we observe a significant



**Figure 4.** a) Densities of pure water. Dashed lines: TIP4PEw model. Solid lines: experimental data.<sup>[35,36]</sup> The filled circles indicate the temperatures of maximum density for TIP4P-Ew water. b) Temperature of maximum density  $T_{\text{TMD}}$  as a function of salt concentration (experimental data were taken from Ref. [37]). The squares indicate  $T_{\text{TMD}}$  for water in the “free water” phase (as shown in c). c) Density of the water in the “free water” phase<sup>[30]</sup> as a function of temperature for different salt concentrations.



**Figure 5.** Distribution  $P(M_T)$  of water molecules in a tetrahedral environment as described by the tetrahedrity parameter  $M_T$  a)  $P(M_T)$  for pure water at various temperatures and  $p = 1$  bar. b)  $P(M_T)$  for pure water as a function of pressure at  $T = 230$  K. c)  $P(M_T)$  for aqueous salt solutions at  $T = 230$  K for different salt concentrations. Only water molecules belonging to the “free water” phase are considered.<sup>[30]</sup>

inward shift of the second peak with increasing salt concentration (and also with pressure), suggesting the presence of an increasingly distorted tetrahedral network.

We draw the following conclusions. The simulations reproduce the anomalous properties of water and salt solutions semiquantitatively. At low temperatures the simulations predict that the presence of salt enhances water’s mobility, in contrast to the behavior at ambient temperature. The effect is mainly attributed to the increased mobility of water in the “free water” phase, which serves as a more fluid matrix for the hydrated ions, similar to the fluidization of water observed upon application of moderate pressures below 1 kbar. In addition to the mobility enhancement at supercooled conditions, the “free water” phase also possesses structural and thermodynamical signatures of water under pressure, such as a density increase and a shift of the temperature of maximum density to lower temperatures. Also the structure of the water’s local environment changes in analogy to the changes due to pressure. This is in agreement with neutron diffraction data suggesting that the hydrogen-bonding network of water is modified well beyond the first hydration shell, in a manner similar to the application of external pressure to pure water.<sup>[10,13]</sup>

To summarize, the presence of sodium chloride seems to hamper water’s tendency to adopt a tetracoordinated low-density liquid form under supercooled conditions, not unlike the effect of solutes on water’s phase diagram proposed by Chatterjee et al.<sup>[32]</sup> As water becomes more structured at lower temperatures, even “structure-making” ions such as NaCl become finally “structure-breaking”. It should also be noted here that at least at low temperatures the structure and dynamics of the water beyond the first two hydration shells is significantly affected by the presence of the ions. In order to prevent misinterpretation, we would like to emphasize that the proposed pressure/salt equivalence should not be applied solely to explain the behavior of solvated biomolecules. In this case ion adsorption/desorption effects might play at least an equally important role.

## Methods

We conducted molecular dynamics simulations of aqueous salt solutions using system sizes of 1000 TIP4P-Ew model water molecules<sup>[44]</sup> plus additional NaCl ion pairs. Sodium chloride potential parameters reported by Heinzinger<sup>[45]</sup> were employed ( $\sigma_{\text{Na}} = 0.273$  nm,  $\epsilon_{\text{Na}}k_B^{-1} = 43.06$  K,  $\sigma_{\text{Cl}} = 0.486$  nm,  $\epsilon_{\text{Cl}}k_B^{-1} = 20.21$  K). Lorentz–Berthelot mixing rules were applied to determine Lennard–Jones cross interactions. A smooth particle-mesh Ewald method<sup>[46]</sup> was used to solve the electrostatics, using the same setup as in Ref. [47]. Long-range corrections for pressure and energy were taken into account. All simulations were carried out by the GROMACS 3.2 simulation program.<sup>[48]</sup> Bond-length constraints were solved by means of the SETTLE procedure.<sup>[49]</sup> The simulations were performed under isobar isothermal conditions using a Nosé–Hoover<sup>[50,51]</sup> thermostat and a Rahman–Parrinello barostat<sup>[52,53]</sup> with coupling times of  $\tau_T = 1.0$  ps and  $\tau_P = 2.0$  ps, using a MD timestep of  $\Delta t = 2.0$  fs. The self-diffusion coefficients  $D$  were obtained from the asymptotic slope from a plot of the mean-square displacement of the water molecules versus time. All properties were studied for the temperature range between 230 and 360 K in steps of 10 K. For all temperatures, pressures ranging from 1 bar to 6 kbar, and salt concentrations ranging from 0 to 50 ion pairs (4.76 mol%, at 1 bar) were considered. Each of the simulation runs (196 in total) was at least 12-ns long.

Received: June 21, 2007

Revised: July 30, 2007

Published online: October 17, 2007

**Keywords:** anomalies · molecular dynamics · salt effects · water

- [1] F. Franks, *Water: A Comprehensive Treatise*, Plenum, New York, **1972**.
- [2] D. Eisenberg, W. Kauzmann, *The Structure and Properties of Water*, Oxford University Press, London, **1969**.
- [3] R. W. Gurney, *Ionic Processes in Solution*, McGraw Hill, New York, **1953**.
- [4] O. Y. Samoilov, *Discuss. Faraday Soc.* **1957**, *24*, 141–145.
- [5] O. Y. Samoilov, *Structure of Aqueous Electrolyte Solutions and the Hydration of Ions*, Consultants Bureau Enterpr. Inc., New York, **1965**.
- [6] G. Engel, H. G. Hertz, *Ber. Bunsen-Ges.* **1968**, *72*, 808–818.
- [7] A. Geiger, *Ber. Bunsen-Ges.* **1981**, *85*, 52–63.
- [8] K. D. Collins, *Biophys. J.* **1998**, *72*, 65–76.
- [9] B. Hribar, N. T. Southall, V. Vlachy, K. A. Dill, *J. Am. Chem. Soc.* **2002**, *124*, 12302–12311.
- [10] R. Leberman, A. K. Soper, *Nature* **1995**, *378*, 364–366.
- [11] A. Botti, F. Bruni, S. Imberti, M. A. Ricci, A. K. Soper, *J. Mol. Phys.* **2005**, *117*, 77–79.
- [12] A. Botti, F. Bruni, S. Imberti, M. A. Ricci, A. K. Soper, *J. Mol. Phys.* **2005**, *117*, 81–84.
- [13] R. Mancinelli, A. Botti, F. Bruni, M. A. Ricci, A. K. Soper, *Phys. Chem. Chem. Phys.* **2007**, *9*, 2959–2967.
- [14] A. A. Chialvo, J. M. Simonson, *J. Mol. Liq.* **2004**, *112*, 99–105.
- [15] T. Loerting, N. Giovambattista, *J. Phys. Condens. Matter* **2006**, *18*, R919–R977.
- [16] P. G. Debenedetti, *J. Phys. Condens. Matter* **2003**, *15*, R1669–R1726.
- [17] F. Sciortino, A. Geiger, H. E. Stanley, *Nature* **1991**, *354*, 218–221.
- [18] F. Sciortino, A. Geiger, H. E. Stanley, *Phys. Rev. Lett.* **1990**, *65*, 3452–3455.
- [19] D. Paschek, A. Geiger, *J. Phys. Chem. B* **1999**, *103*, 4139–4146.
- [20] F. W. Starr, F. Sciortino, H. E. Stanley, *Phys. Rev. E* **1999**, *60*, 6757–6768.

- [21] A. Scala, F. W. Starr, E. L. Nave, F. Sciortino, H. E. Stanley, *Nature* **2000**, *406*, 166–169.
- [22] A. Geiger, P. Mausbach, J. Schnitker, in *Water and Aqueous Solutions* (Eds.: G. W. Neilson, J. E. Enderby), Adam Hilger, Bristol, **1986**, pp. 15–30.
- [23] D. Laage, J. T. Hynes, *Science* **2006**, *311*, 832–835.
- [24] D. Laage, J. T. Hynes, *Chem. Phys. Lett.* **2006**, *433*, 80–85.
- [25] A. Chandra, S. Chowdhuri, *J. Phys. Chem. B* **2002**, *106*, 6779–6783.
- [26] S. Chowdhuri, A. Chandra, *Phys. Rev. E* **2002**, *66*, 041203.
- [27] F. X. Prielmeier, E. W. Lang, R. J. Speedy, H. D. Lüdemann, *Phys. Rev. Lett.* **1987**, *59*, 1128–1131.
- [28] For better comparison the experimental diffusion coefficients of Ref. [27] were scaled by a factor of 1.1.
- [29] D. W. McCall, D. C. Douglass, *J. Phys. Chem.* **1965**, *69*, 2001–2011.
- [30] We distinguish three kinds of water molecules in aqueous salt solutions: First hydration shell (1st HS): any water molecule with a distance less than  $r_{\text{H}_2\text{O-Na}} < 0.33$  nm (Na), or  $r_{\text{H}_2\text{O-Cl}} < 0.4$  nm (Cl); “free water”: any water molecule with distances  $r_{\text{H}_2\text{O-Na}} > 0.55$  nm, and  $r_{\text{H}_2\text{O-Cl}} > 0.62$  nm to any ion in the system. Second hydration shell (2nd HS): any molecule not belonging to the two types above. “H<sub>2</sub>O” denotes water’s center of mass. The volume partitioning is achieved by identifying the corresponding sub-volumes via a cubic grid with a mesh size of around 0.02 nm.
- [31] D. Paschek, *Phys. Rev. Lett.* **2005**, *94*, 217802.
- [32] S. Chatterjee, H. S. Ashbaugh, P. G. Debenedetti, *J. Chem. Phys.* **2005**, *123*, 164503.
- [33] O. Mishima, *J. Chem. Phys.* **2005**, *123*, 154506.
- [34] M. F. Kropman, H. J. Bakker, *J. Am. Chem. Soc.* **2004**, *126*, 9135–9141.
- [35] G. S. Kell, *J. Chem. Eng. Data* **1967**, *12*, 66–69.
- [36] W. Wagner, A. Pruß, *J. Phys. Chem. Ref. Data* **1999**, *31*, 387–535.
- [37] *International Critical Tables of Numerical Data, Physics, Chemistry and Technology, Vol. III* (Eds.: E. W. Washburn), McGraw Hill, New York, **1928**.
- [38] H. E. Stanley, J. Teixeira, *J. Chem. Phys.* **1980**, *73*, 3404–3422.
- [39] N. N. Medvedev, Y. I. Naberukhin, *J. Non-Cryst. Solids* **1987**, *94*, 402–406.
- [40] Y. I. Naberukhin, V. A. Luchnikov, G. G. Malenkov, E. A. Zheligovskaya, *J. Struct. Chem.* **1997**, *98*, 593–600.
- [41] J. R. Errington, P. G. Debenedetti, *Nature* **2001**, *409*, 318–321.
- [42] A. Geiger, M. Klene, D. Paschek, A. Rehtanz, *J. Mol. Liq.* **2003**, *106*, 131–146.
- [43] J. L. Finney, D. T. Bowron, A. K. Soper, T. Loerting, E. Mayer, A. Hallbrucker, *Phys. Rev. Lett.* **2002**, *89*, 205503.
- [44] H. W. Horn, W. C. Swope, J. W. Pitera, J. D. Madura, T. J. Dick, G. L. Hura, T. Head-Gordon, *J. Chem. Phys.* **2004**, *120*, 9665–9678.
- [45] K. Heinzinger in *Computer Modelling of Fluids Polymers and Solids, Vol. C293 NATO ASI Series* (Eds.: C. R. A. Catlow, S. C. Parker, M. P. Allen), Kluwer Academic Publishers, Dordrecht, **1990**, pp. 357–369.
- [46] U. Essmann, L. Perera, M. L. Berkowitz, T. A. Darden, H. Lee, L. G. Pedersen, *J. Chem. Phys.* **1995**, *103*, 8577–8593.
- [47] D. Paschek, *J. Chem. Phys.* **2004**, *120*, 10605–10617.
- [48] E. Lindahl, B. Hess, D. van der Spoel, *J. Mol. Model.* **2001**, *7*, 306–317.
- [49] S. Miyamoto, P. A. Kollman, *J. Comput. Chem.* **1992**, *13*, 952–962.
- [50] S. Nosé, *Mol. Phys.* **1984**, *52*, 255–268.
- [51] W. G. Hoover, *Phys. Rev. A* **1985**, *31*, 1695–1697.
- [52] M. Parrinello, A. Rahman, *J. Appl. Phys.* **1981**, *52*, 7182–7190.
- [53] S. Nosé, M. L. Klein, *Mol. Phys.* **1983**, *50*, 1055–1076.