

HYDROGEN BONDING AND MOLECULAR MOBILITY IN AQUEOUS SYSTEMS

ALFONS GEIGER* and THOMAS KOWALL†

* *Physikalische Chemie, Universität Dortmund
D-44221 Dortmund, GERMANY*

† *Institut de chimie minérale et analytique
Place du Château 3, CH-1005 Lausanne, SWITZERLAND*

1. Introduction

Despite the extensive association of water molecules by a spanning hydrogen-bond network well above the percolation threshold [1, 2], the single particle mobility in pure water is comparable to that in simple non-associated liquids. This high translational and rotational mobility in pure water can be further increased by the application of hydrostatic pressure [3, 4] or decreased by the presence of nonpolar groups in solution [5-7].

Recent computer simulation studies explain the molecular mobility in pure water by the existence of defects in the random tetrahedral network of hydrogen-bonds [8, 9]. These defects provide lower energy pathways for reorientational motions and thus "catalyze" the restructuring of the infinitely connected network. They can be characterized in various ways: energetically, geometrically and topologically. In this contribution, we shortly summarize some results and subsequently apply the deduced principles to the hydration shell of a crown ether molecule, whose properties as an ionophoric molecule are determined by the simultaneous presence of polar (hydrophilic) and nonpolar (hydrophobic) molecular regions.

2. Molecular Mobility and Network Defects

The basic observations, leading to the network defect picture, have been made from simulations on stretched water [8, 9]. There it was observed that the mobility, i.e. the translational and rotational diffusion of model water molecules *decreases* when the density is decreased from 1.0 g/cm³ to 0.8 g/cm³ and below; and in parallel the structure of the liquid changes such that an approach to a more perfect tetrahedral hydrogen-bond network can be seen. This is in contrast to the expected behaviour of normal liquids: in this case the expansion of a sample *increases* the mobility due to the increase of the free volume and simultaneously the liquid becomes less structured, expressed for example by the decreasing peak height of pair distribution functions.

The emergence of a more perfect tetrahedral network with decreasing density can be established by the behaviour of various statistical features [8-10]:

- the average number of nearest neighbours decreases from about five at 1.0 g/cm³ to

four below 0.8 g/cm^3 , simultaneously the radial pair distribution functions become sharper, i.e. more 'icelike',

- for any reasonable definition of a hydrogen bond, the fraction of water molecules with more than four bonds decreases by about a factor of ten in the same density region,
- diminishing deviations from the local geometric arrangements of a perfectly tetrahedral random network (like the so called Polk-model [11, 12]), can be demonstrated by considering the characteristics of the Voronoi-polyhedra attributed to each water molecule,
- the occurrence probabilities for small clusters of connected water molecules as obtained from MD simulations deviate slightly from those predicted by lattice percolation theory. And again these deviations diminish in lower density water.

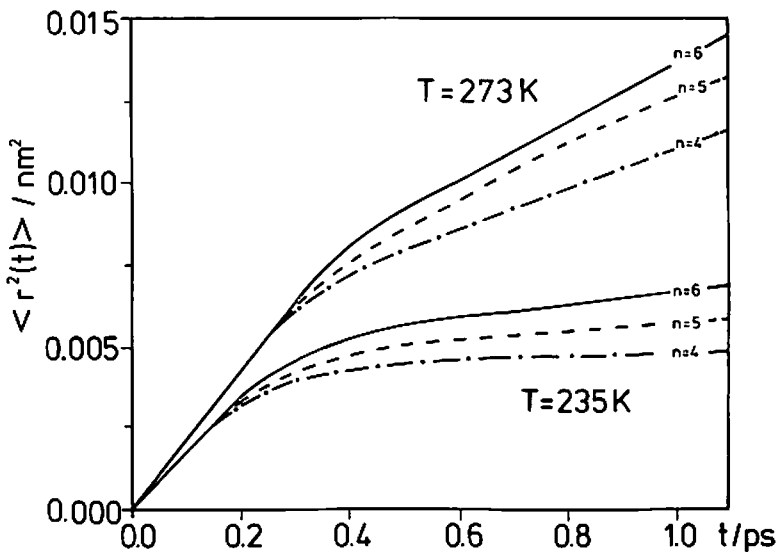


Figure 1: Mean square displacement $\langle r^2(t) \rangle_n$ of molecules with number of neighbours n equal to four, five and six for $T = 235$ and 273 K (from Ref. [9])

Simulation studies have demonstrated a direct relation between the local deviations from tetrahedrality, as discussed above, and the mobility of the individual molecules. For example, it has been shown that on average the mean square displacement of molecules with *more* than four neighbours is *increased* compared to those with exactly four neighbours (Fig. 1).

A possible mechanism for the accelerating effect of an additional neighbour has been found, when considering the pair interaction energy V_{ij} between neighbouring molecules. In Fig. 2 the corresponding distributions are given separately for two kinds of neighbouring pairs: for pairs that are connected by a linear (although possibly strongly distorted)

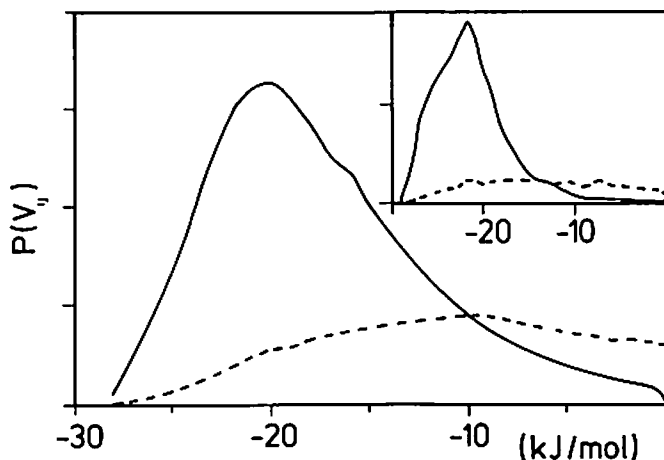


Figure 2: Distribution functions for the pair interaction energy V_{ij} for linear bonded pairs (solid line) and for pairs that are connected via a bifurcated bond (dashed line). Insert: The analogous plot for the quenched configurations [17] (from Ref. [18])

hydrogen bond and for pairs that are connected via a bifurcated hydrogen bond. Here, bifurcated H-bonds are identified in the following way: for a given pair of water molecules with oxygen-oxygen distance less than 3.4 \AA and negative interaction energy the proton closest to the oxygen-oxygen connecting line is marked as the proton associated with that hydrogen bond. If the same proton is marked twice, it is "bonded" to two accepting oxygen atoms and therefore engaged in a bifurcated bond. Clearly, a bifurcated bond is a network defect in the above given sense.

It is interesting to note that the distributions in Fig. 2 peak at roughly -20 and -10 kJ/mol, suggesting that the sum of the *two* interaction energies of a 'bifurcated bond arrangement' is roughly the energy of *one* linear bond. Thus the comparatively small energy kT can be sufficient to transfer one strong linear hydrogen-bond to another strong linear H-bond via an intermediate bifurcated bond, if the presence of an extra neighbour allows this. In other words: the presence of a fifth molecule allows the formation of bifurcated bonds and thus "catalyzes" the local reorganization of the H-bond network.

The existence of bifurcated H-bonds, which are about half as strong as the linear H-bonds, has already been suggested from spectroscopic observations [13, 14]. Also, a switching mechanism comparable to the one discussed above has been postulated to understand the concentration and temperature dependence of dielectric relaxation times in alcohol mixtures [15].

In a detailed simulation study of the local energy fluctuations in water, Ohmine et al. [16] detected 'flip-flop-type' energy exchanges between neighbours, leading to a negative potential energy correlation

$$\left. \frac{\langle \Delta V_i \Delta V_j \rangle}{\langle (\Delta V_i)^2 \rangle} \right|_{R < R_c, < R_c + \delta R} \approx -0.5,$$

where ΔV_i is the potential energy change of water molecule i between two successive quenched structures [17] separated by 10 fs (center of mass distance R_{ij} between 2.8 and 3.2 Å).

This value can be related to a switching mechanism via bifurcated bonds by a rough estimate, which uses the position of the maxima in Fig. 2; we start from an arrangement with a linear bond between two molecules i and j and no bond between i and another neighbour k (assuming interaction energies $V_{ij} = -20$ kJ/mol, $V_{ik} = 0$) and consider a switch to a bifurcated bond arrangement between molecules i , j and k ($V_{ij} = V_{ik} = -10$ kJ/mol). Neglecting all other changes in the systems, this leads to the above given negative potential energy correlation factor of -0.5 (with $\Delta V_i = 0$, $\Delta V_j = +10$ kJ/mol, $\Delta V_k = -10$ kJ/mol).

The observed structure/mobility relations can be generalized to one simple principle: a moderate *decrease* of the local concentration of 'hydrogen bonding possibilities' decreases the mobility of the molecules due to a reduction of H-bond switching possibilities. Correspondingly, a concentration *increase* raises the molecular mobility.

These local concentration changes can not only be produced by global density changes (applying positive or negative pressures), but also locally, by dissolving other molecules. In the case of hydrophobic particles, the water molecules in the first hydration shell experience less water neighbours than in the bulk and are therefore less mobile [19] (the inert particle prevents the hydration shell water molecules from an approach of a fifth water neighbour). The opposite effect, where a dissolved molecule offers *extra* H-bond possibilities and thus increases the water mobility is discussed in the following part of the contribution.

Also, in accord with this principle, recently Kaatze and Pottel demonstrated a 'universal' proportionality between the dielectric relaxation rates of mixtures of hydrogen bonded liquids and the spatial density of H-bond forming molecular groups [7].

3. Hydration Shell of a Crown Ether Molecule

The most prominent feature of the crown ether molecule 18-crown-6 (18C6) is its capability to complex alkalimetal ions in its polar cage of oxygens and to transport them eventually into lipophilic phases. The crown is also able to bind neutral polar guest molecules by H-bonds and dipolar forces.

The potential energy of different 18C6-conformers and the potential complexation energy for various ions and neutral guests have been the target of numerous molecular mechanics studies (e.g. Refs. [20-24]). Most interesting for MC- and MD-simulations are surely aqueous solutions. Water has a particular impact on the solvent-dependent conformational equilibrium and on the stability of 18C6-complexes. A MC-study [25] for different rigid 18C6 conformers revealed considerable differences concerning the accessibility for water molecules and concerning the H-bond pattern in the first hydration shell. By conformational and hydration energy the D_{3d} -geometry as given in Fig. 3 proved to be most favourable.

In the following, a detailed analysis of the structural and dynamical properties of the hydration shell of this conformer is presented.

3.1. POTENTIAL ENERGY FUNCTION AND SIMULATION OUTLINE

Our MD-simulations were performed with the program package GROMOS86 [27]. For the Lennard-Jones part of non-bonded interactions the corresponding GROMOS-parameters were employed. CH_2 -groups were handled within the 'united atom approximation'. Since

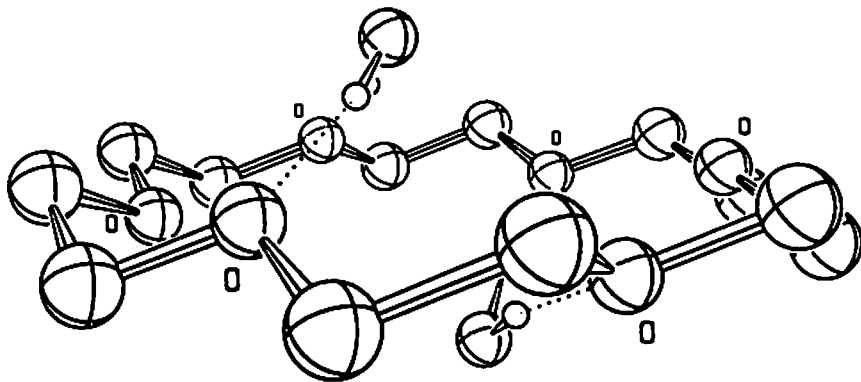


Figure 3: Crown ether molecule 18C6 in D_{3d} conformation (with CH_2 -groups as pseudoatoms) and two SPC water molecules in energy optimized positions

ether oxygens are not incorporated in GROMOS86, the parameters for ester oxygens were selected, which e.g. in AMBER [26] are also among the same class as ether oxygens. The used point charges were transferred from an *ab initio*-calculation [28] and amount to $-0.4e$ for the ether oxygens.

For the torsion potential we use a Fourier series representation *without* nonbonded 1,4-terms [20]. For water the SPC-model from Berendsen et al. [29] was used, that best conforms the nonbonded parameters from GROMOS.

Fig. 4 shows the isoenergy-contour-diagram for a single SPC-water molecule in the field of a fixed, energetically minimized D_{3d} -crown after optimizing the water molecule orientation at each grid point. Due to the ether's threefold symmetry there are three equivalent oxygen positions of minimum energy ($E_{\min} = -51.1$ kJ/mol) on each side, with a separating barrier of 8.9 kJ/mol.

A MD simulation run of 260 ps duration was preceded by an equilibration period of 60 ps. A cutoff is applied to neutral charge groups consisting of COC-units in the case of the solute. The algorithm of Berendsen et al. [30] is applied to keep the system at ambient temperature and pressure. Bond lengths of the 18C6 molecule and the geometry of the water molecules are fixed by the procedure SHAKE [31]. D_{3d} -symmetry was selected as starting conformation and preserved with little deviations throughout the run.

3.2. STRUCTURE OF THE HYDRATION SHELL

3.2.1. Molecular Distributions. For molecular solutes like 18C6 the pair distribution function solute-water is more difficult to interpret than e.g. for spherical solutes. To provide an illustrative insight into the structure of the hydration shell a graphical representation is used which in a certain way is more instructive than the more quantitative pair distribution approach. In Fig. 5 for 400 configurations the positions of the water oxygens and of the crown atoms have been accumulated for two perpendicular slices through the MD-box. The mean plane of the first crown has been rotated into the exterior xy-plane and all further configurations have been shifted and rotated in such a way that the crown molecules get

Figure 4: Isoenergy-contour-diagram (kJ/mol) for SPC-water in the field of the D_{3d} -crown (orientation of water molecule optimized at each grid point)

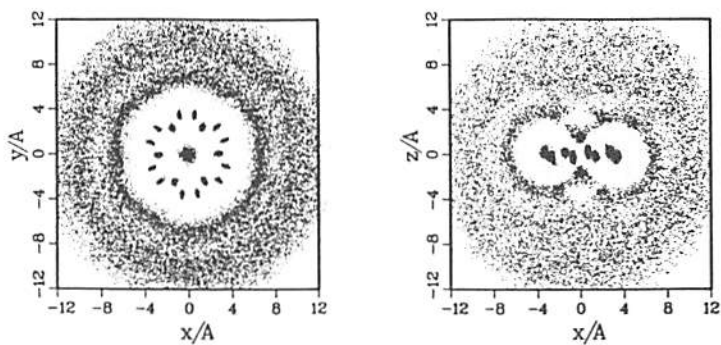
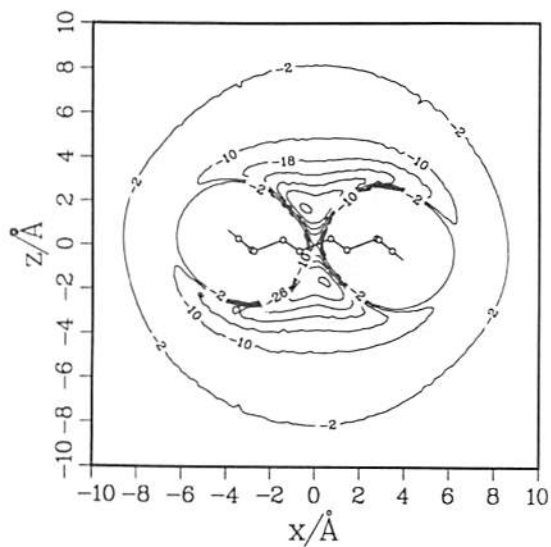


Figure 5: Structure of the hydration shell: 'dot plot' of water oxygens and crown (pseudo) atoms

superimposed to a maximum degree [32].

By this procedure a first density maximum, the following minimum and a hint for a second maximum is perceivable in the hydration shell. The most conspicuous feature in Fig. 5 are the two dark patches above and below the crown centre close to the energy minima of the pair interaction 18C6-SPC-water. Here, in the concave part of the hydration shell, two outstanding 'complexed' water molecules are staying with high probability.

Whereas for guest molecules with threefold symmetry like acetonitril, nitromethane or organic ammonia ions 2:1-complexes with 18C6 have been characterized by X-ray studies [24], this has not been accomplished yet for water, except for the H_3O^+ -cation [33] or in presence of activating transition metal ions [34]. Apparently because water offers solely two H-bonds, water is not an ideal guest molecule. Nevertheless, the two strongly complexed water molecules are regarded as playing a crucial role in keeping the crown cavity open and in stabilizing the D_{3d} -geometry.

3.2.2. Orientational Distributions. The analysis relies on a geometrical classification of all water molecules into four categories in order to allow a separate determination of their properties:

type c ('complexed'): comprises the two complexed water molecules that are closest to the crown's centre

type i ('intermediate'): constituted by the rest of the concave part of the first hydration shell, that is those water molecules that do not exceed a distance of 3.5 Å to at least one crown oxygen

type h ('hydrophobic'): the outer convex part of the shell; here those water molecules are grouped that are closer than 4.5 Å to at least one crown atom (without type c and i)

type b ('bulk'): the remaining water molecules are denoted as bulk.

In the following we concentrate on categories c, h and b. To show the orientating influence of the crown solute on the solvent, orientational distribution functions are shown for three molecule fixed vectors, namely the dipole vector $\vec{\mu}_{\text{Dip}}$ and the HH- and OH-connecting vectors $\vec{\mu}_{\text{HH}}$ and $\vec{\mu}_{\text{OH}}$. The corresponding distribution functions $p(\cos\phi)$ are displayed in Fig. 6. The angle ϕ is the angle between one of the vectors $\vec{\mu}_{\text{Dip}}$, $\vec{\mu}_{\text{HH}}$, $\vec{\mu}_{\text{OH}}$ and a vector connecting the water oxygen to a reference site in the crown molecule. For type c this reference site is the crown's geometric centre, whereas for h and b the crown atom next to the water oxygen was chosen.

The complexed molecules c prefer an orientation where the dipole vector resides perpendicular on the crown's plane. Accordingly the distribution for the intramolecular HH-vector yields a maximum for parallel alignment with respect to the crown's plane. The OH-distribution function for type h is especially indicative for the hydrophobic character in the convex part of the shell. Maxima at $\phi \cong 60^\circ$ and $\phi \cong 180^\circ$ correspond to the picture of the solvation of apolar solutes in water [6]: an orientation of the hydration shell water molecules such that three of its favourable hydrogen bonding directions are straddling the hydrophobic solute and one is pointing outward results in optimized water-water interaction (also refer to Sect. 3.3.2).

3.3. INTERACTION ENERGIES

3.3.1. H-bonding between 18C6 and Water. A closer inspection of the 18C6/water-interaction for the different groups of water molecules supports the previous sub-division.

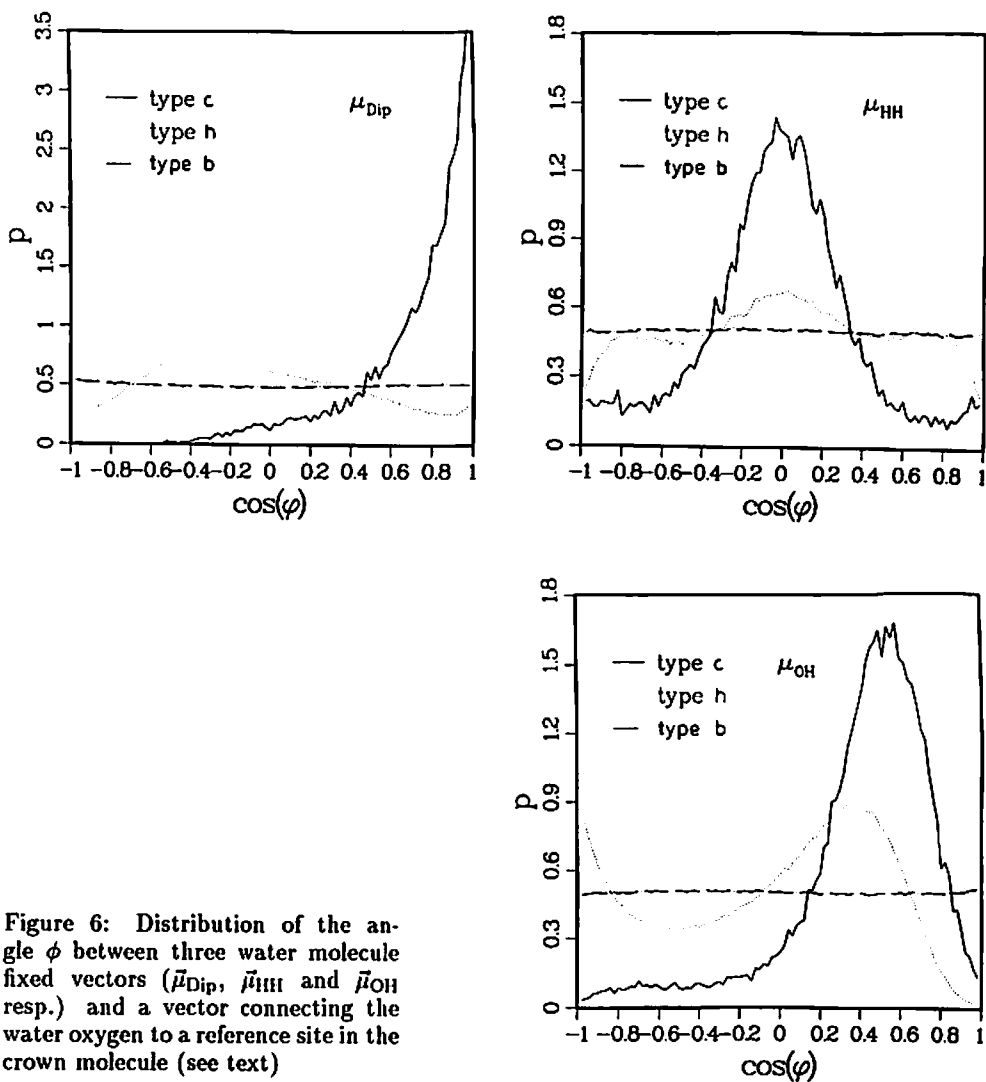


Figure 6: Distribution of the angle ϕ between three water molecule fixed vectors ($\vec{\mu}_{\text{Dip}}$, $\vec{\mu}_{\text{HH}}$ and $\vec{\mu}_{\text{OH}}$ resp.) and a vector connecting the water oxygen to a reference site in the crown molecule (see text)

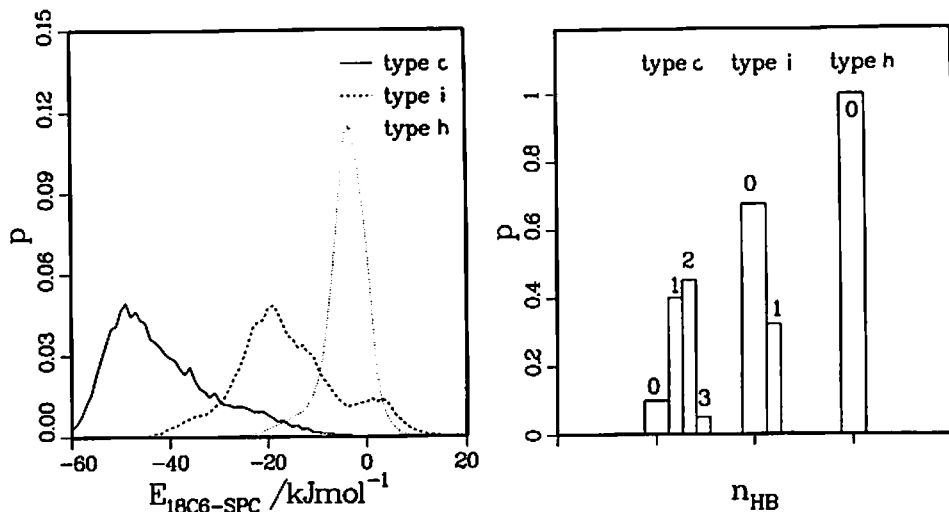


Figure 7: a) Distribution of water-solute interaction energies and b) number of H-bonds between 18C6 and a water molecule of type c, i and h

Table 1: Interaction between water molecules and 18C6 (see text)

type	18C6-water		water-water			
	N	$\bar{n}_{HB,SW}$	\bar{n}	\bar{n}_{HB}	\bar{n}_{HB}/\bar{n}	$E_{HB}/\text{kJ mol}^{-1}$
c	2.0	1.47	3.17	1.97	0.622	-16.9
h	38.6	0.00	4.80	3.33	0.693	-17.7
b	209.8	0.00	5.16	3.34	0.647	-17.4

In Fig. 7a the distribution of the pair interaction energies between the water molecules of a given type and the crown ether is depicted. Besides the mean number N of water molecules, which belong to the different classes, Tab. 1 gives the average number of hydrogen bonds $\bar{n}_{HB,SW}$ between 18C6 and those water molecules. The geometric definition of a H-bond was adopted from Ref. [35] and demands a $OW \cdots O$ -distance shorter than 3.3 \AA and a $OW-HW \cdots O$ -angle larger than 145° . In Fig. 7b the mean number of H-bonds is expanded into the distribution functions. As the histograms show, type h water molecules constitute a truly 'hydrophobic' part of the total hydration shell, avoiding any hydrogen bonds to the solute, whereas type c molecules interact with 18C6 preferentially with two, sometimes even with three hydrogen bonds. Inevitably, in the latter case bifurcated H-bonds must be present.

3.3.2. Water-Water-Interaction. The hydrophobic character of the convex part of the hydration shell can also be seen from the water connectivity and the water-water interaction. For each water molecule we determine the number of geometric nearest neighbours \bar{n} up to a distance of $r = 3.5 \text{ \AA}$, the average number of H-bonds \bar{n}_{HB} , and the average pair energy of hydrogen-bonded neighbours E_{HB} (Tab. 1). All this refers only to water neighbours, excluding interactions with 18C6.

Table 2: Reorientation times of water in ps

type	dipole vector		HH-vector		OH-vector	
	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2
c	80	23	2.3	1.4	2.2	1.3
h	7.8	4.0	4.4	3.8	6.1	3.6
b	4.1	2.3	3.2	2.3	3.2	1.5
SPC-water[36]	3.2	1.3	3.0	1.6		

Due to the presence of the neighbouring hydrophobic regions of 18C6, type h water molecules experience a reduced local water density compared to the bulk (less neighbours \bar{n} , less bonding possibilities). As in the case of the global density decrease in stretched water, this leads to an increased water structure: on average the H-bonds are stronger (\bar{E}_{HB}) and there are more bonds per neighbour (\bar{n}_{HB}/\bar{n}). This is a clear indication of the so called 'structure making' effect of hydrophobic solutes, which will also show up in a reduced dynamics.

As to the two complexed water molecules, one has to keep in mind that due to the presence of the three oxygens of 18C6, which are closely neighboured, these molecules have a total of $\bar{n}_{tot} = 3.17 + 3 = 6.17$ bonding possibilities, resulting in a total number of hydrogen bonds $\bar{n}_{HB,tot} = \bar{n}_{HB} + \bar{n}_{HB,sw} = 3.44$. Both of these values are higher than in the bulk, which should—in accord with the previously discussed ideas—lead to an increased mobility of these water molecules.

3.4. REORIENTATIONAL DYNAMICS OF WATER MOLECULES

Reorientational time correlation functions for three vectors $\vec{\mu}_{Dip}$, $\vec{\mu}_{OH}$ and $\vec{\mu}_{HH}$ —fixed in the water molecule—are defined as

$$C_l(\tau) = \langle P_l(\vec{\mu}_i(0) \cdot \vec{\mu}_i(\tau)) \rangle \quad l = 1, 2 \quad ,$$

where P_l are Legendre-polynomials.

$C_1(\tau)$ is shown in Fig. 8. Characteristic reorientational time constants from an exponential fit are summarized in Tab. 2. Somewhat larger reorientational times for the bulk part compared to pure water [36] are due to the demobilizing influence of the solute that still extends beyond the first hydration shell. In the hydrophobic shell, water for all three vectors exhibits lowered mobility compared to bulk water, as anticipated from the local density reduction.

A comparison between the two complexed water molecules (type c) and bulk water reveals a distinct behaviour. For type c the mobility of its dipole vector is strongly reduced, since a complexed water molecule simply tends to preserve its perpendicular orientation with respect to the crown's plane. In sharp contrast, however, the correlation times for the OH-vector and particularly the HH-vector are smaller than in bulk water. Thus a certain translational fixing of a complexed water molecule may not be simply transferred to the picture of the rotational behaviour. The presence of three closely spaced 18C6-oxygens, which can act as H-bond acceptors, facilitates the formation of bifurcated bonds (see Fig. 7b), and by this induce an enhanced rotational mobility. Due to the spatial anisotropy of the local surrounding of the two complexed water molecules, their rotational motion becomes also very anisotropic. In another graphical picture, the selectively enhanced rotatory motion around its dipole axis enables a type c-water molecule with solely two H-bond donor sites to coordinate all three crown oxygens on each side of the molecule efficiently and evenly.

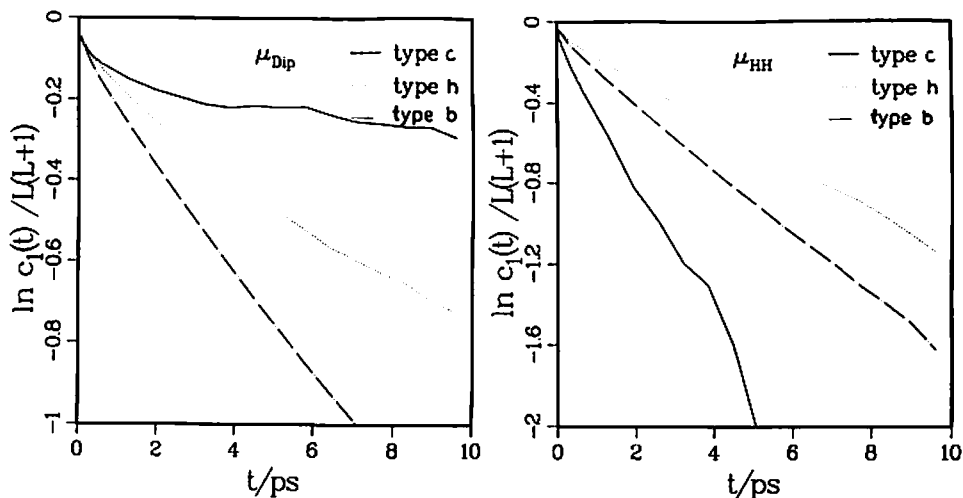


Figure 8: Reorientation-auto-correlation function $C_1(t)$ for water fixed vectors $\vec{\mu}_{\text{Dip}}$ and $\vec{\mu}_{\text{HH}}$

In a more general sense a relation to the mechanism of enzymetically catalyzed biochemical reactions might be constructed. Basically the reactive species must be strongly bound together. Beyond that, the reaction demands a definite relative orientation of host and guest, so that a certain rotational mobility within the complex bears some advantages.

4. Conclusions

We have shown that it is possible to explain different observations, concerning the mobility of water molecules in aqueous systems by one simple principle: the mobility of water molecules (primarily the rotational, but because of a strong translation/rotation coupling in pure water also the translational one) is a function of the local density of H-bonding possibilities. The underlying mechanism is the formation of bifurcated bonds that 'catalyze' the local restructuring of the H-bond network. From this, we understand the reduction of the mobility in stretched water and in hydrophobic hydration shells, as well as the increased mobility in compressed water and in certain hydrophilic associations. For the future, the range of validity of this principle (concerning density, temperature, chemical composition etc.) has to be examined by new simulations as well as by experimental studies like the dielectric relaxation measurements of Pottel and Kaatz [7].

Acknowledgement

Collaboration and valuable discussions with F. Sciortino and H.E. Stanley are acknowledged. For assistance in preparing the manuscript we thank Ms. A. Ahlke. The work was supported by grants of Deutsche Forschungsgemeinschaft und Fonds der Chemischen Industrie.

References

- [1] F.H. Stillinger, *Science* **209**, 451 (1980)
- [2] A. Geiger, F.H. Stillinger, and A. Rahman, *J. Chem. Phys.* **70**, 4185(1979)
- [3] E.W. Lang and H.D. Lüdemann, in 'High Pressure NMR', edited by J. Jonas (Springer, Berlin 1991)
- [4] R. Pottel, E. Asselborn, R. Eck, and U. Tresp, *Ber. Bunsenges. Phys. Chem.* **93**, 676 (1989)
- [5] F. Franks, in 'Water — A Comprehensive Treatise', edited by F. Franks (Plenum, New York 1975), Vol. 4, Chap. 1
- [6] A. Geiger, A. Rahman, and F.H. Stillinger, *J. Chem. Phys.* **70**, 263–276 (1979)
- [7] U. Kaatze and R. Pottel, *J. Molec. Liquids* **52**, 181 (1992)
- [8] A. Geiger, P. Mausbach, and J. Schnitker, in 'Water and Aqueous Solutions', edited by G.W. Neilson and J.E. Enderby (Adam Hilger, Bristol 1986)
- [9] F. Sciortino, A. Geiger, and H.E. Stanley, *J. Chem. Phys.* **96**, 3857 (1992); *Nature* **354**, 218 (1991)
- [10] A. Geiger, N.N. Medvedev, and Yu.I. Naberukhin, *J. Struct. Chem.* **33**, 226 (1992)
- [11] D.E. Polk, *J. Noncryst. Solids* **5**, 365 (1971)
- [12] P. Steinhardt, R. Alben, and D.J. Weaire, *J. Noncryst. Solids* **15**, 199 (1974)
- [13] P.A. Giguère, *J. Chem. Phys.* **87**, 4835 (1987)
- [14] G.E. Walrafen, M.S. Hokmabadi, and W. H. Yang, *J. Phys. Chem.* **92**, 2433 (1988)
- [15] M.W. Sagal, *J. Chem. Phys.* **36**, 2437 (1962)
- [16] I. Ohmine, H. Tanaka, and P.G. Wolynes, *J. Chem. Phys.* **89**, 5852 (1988)
- [17] A 'quenched' or 'inherent' configuration is obtained from an MD configuration by applying a two-stage procedure: First, kinetic energy is removed rapidly by applying a strong damping to the equations of motion. Then a steepest decent follows, to move the molecules along the potential energy surface to the local minimum.
- [18] F. Sciortino, A. Geiger, and H.E. Stanley, *Phys. Rev. Lett.* **65**, 3452 (1990)
- [19] A. Geiger, *Ber. Bunsenges. Physik. Chemie* **85**, 52 (1981)
- [20] M. Billeter, A.E. Howard, I.D. Kuntz, and P.A. Kollmann, *J. Am. Chem. Soc.* **110**, 8385–8391 (1988)
- [21] G. Wipf, P. Weiner, and P. Kollmann, *J. Am. Chem. Soc.* **104**, 3249–3258 (1982)
- [22] M.J. Bovill, D.J. Chadwick, and I.O. Sutherland, *J. Chem. Soc. Perkin Trans. II*, 1529–1543 (1980)

- [23] J.W.H.M. Uiterwijk, S. Harkema, and D. Feil, *J. Chem. Soc. Perkin Trans. II*, 721-731 (1987)
- [24] J.R. Damewood, W.P. Anderson, and J.J. Urban, *J. Comp. Chem.* **9**, 111-124 (1988)
- [25] G. Ranghino, S. Romano, J.M. Lehn, and G. Wipf, *J. Am. Chem. Soc.* **107**, 7873 (1985)
- [26] S.J. Weiner, P.A. Kollmann, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, S. Profeta, and P. Weiner, *J. Am. Chem. Soc.* **106**, 765-784 (1984)
- [27] W.F. van Gunsteren and H.J.C. Berendsen; BIOMOS b.v., Biomolecular Software, Laboratory of Physical Chemistry, University of Groningen
- [28] M. Welti, Doctoral Thesis, ETH Zürich (1987)
- [29] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, and J. Hermans, in 'Intermolecular Forces', ed. by B. Pullmann (Reidel, Dordrecht 1981), pp. 331-342
- [30] H.J.C. Berendsen, J.P.M. Postma, W.F. van Gunsteren, A. DiNola, and J.R. Haak, *J. Chem. Phys.* **81**, 3684-3690 (1984)
- [31] J.P. Ryckaert, G. Ciccotti, and H.J.C. Berendsen, *J. Comp. Phys.* **23**, 327-341 (1977)
- [32] G.R. Kneller, *Mol. Sim.* **7**, 113 (1991)
- [33] J.L. Atwood, S.G. Bott, A.W. Coleman, K.D. Robinson, S.B. Whetstone, and C. Mitchell Means, *J. Am. Chem. Soc.* **109**, 8101-8102 (1987)
- [34] A. Elbasyouny, H.J. Brüggel, K. von Deuten, M. Dickel, A. Knöchel, K.U. Koch, J. Kopf, D. Meizner, and G. Rudolph, *J. Am. Chem. Soc.* **105**, 6568-6577 (1983)
- [35] P. Krüger, W. Strassburger, A. Wollmer, and W.F. van Gunsteren, *Eur. Biophys. J.* **13**, 77-88 (1985)
- [36] E. Guardia and J.A. Padro, *J. Phys. Chem.* **94**, 6049-6055 (1990)