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[22] At this point, removal of the solvent under reduced pressure affords the potassium salt of the dtc ligand [K_4] [**1**]: ^{1}H NMR (300 MHz, [D_6]DMSO): $\delta = 7.47$ (4H, s, ArH), 5.95 (4H, d, OCH_2O outer), 5.18 (8H, s, $ArCH_2$), 4.67 (4H, t, $ArCHC_5H_{11}$), 4.15 (4H, d, OCH_2O inner), 2.2–2.4 (8H, br. m, CH_2), 1.05–1.25 (40H, br. m, CH_2), 0.81 (12H, t, CH_3), 0.55 (12H, t, CH_3); ES-MS (positive-ion): *m/z* calcd for $[C_{72}H_{96}N_4O_8S_8K_5]^+$: 1595.23; found: 1595.51.

Carbohydrates Exhibit a Distinct Preferential Solvation Pattern in Binary Aqueous Solvent Mixtures**

Aleksey Vishnyakov, Göran Widmalm, and
Aatto Laaksonen*

Many substances are readily soluble in solvent mixtures but not in the pure components and vice versa.[1] Some examples of such solvents are binary mixtures of water, alcohols, acetonitrile, and dimethyl sulfoxide (DMSO), including both aqueous and nonaqueous mixtures of them. Selective solvation of ions from salts in mixed solvents is another, early discovered, property. The classic example is the heteroselective solvation of the ions of silver nitrate in a water–acetonitrile mixture, as demonstrated in 1958 by Strehlow and Koepp in a Hittorf experiment.[2] They found that in an equimolar solvent mixture, the nitrate anions were mainly solvated by the water molecules, while the silver cations were approximately four times more solvated by acetonitrile than by water molecules, although acetonitrile is generally known to solvate cations poorly. The unusual solvation properties of some binary liquid mixtures can, to a large extent, be related to a strong deviation from the ideality of Raoult's law. For example, the guide "like dissolves like" is challenged in the mixture of the highly polar molecules water and acetonitrile. This particular mixture exhibits a liquid–liquid separation, with an upper critical point at $-1\,^\circ C$ at 38 mol% of acetonitrile. Both IR measurements[3, 4] and computer simulations[5, 6] have confirmed the existence of "micro-heterogeneities" and conglomerate water structures at higher acetonitrile concentrations. The often peculiar properties of liquid mixtures have fascinated many, including Mendeleev, who studied the nonideal behavior of water–alcohol mixtures some 130 years ago.[7] The ions of salts are not the only examples of selectively solvated species in mixed solvents. Many amphiphilic[8] and biomolecular systems[1] are better dissolved in mixtures, as a result of preferential solvation.

We have studied a model disaccharide molecule (α-D-Man*p*-(1→3)-β-D-Glc*p*-OMe, **1**) in a mixture of DMSO and water. The solvent mixture is not needed for the purpose of increasing solubility, since disaccharides easily dissolve in both water and DMSO. Our emphasis is to study the resulting preferential solvation of the disaccharide and to learn about the behavior of the 1:3 DMSO–water molar mixture used. We would stress that the characteristic properties of the solvent mixture itself are very different from those of either water or DMSO. Based on neutron diffraction[9] and computer simulation studies,[10, 11] it has been suggested that DMSO–water mixtures contain complexes with either two or three water molecules attached to one DMSO molecule, held together by hydrogen bonds, as shown schematically in Figure 1. Near to its astonishingly low freezing point of $-62\,^\circ C$ (roughly $80\,^\circ C$ below the freezing point of pure DMSO), the 1:3 mixture of DMSO and water behaves essentially like a one-component system.[12] Our own molecular dynamics (MD) simulations of this 1:3 DMSO–water, both at +15 and $-50\,^\circ C$, confirm that hydrogen-bonded associates (Figure 1) are formed. Besides being a popular cryosolvent, DMSO–water mixtures have been used in applications ranging from antibacterial activity to membrane permeability.[13] Most of these effects are, however, still not well understood. The solvation of carbohydrates in the DMSO–water mixture should be of some broader interest, not least because this group of biomolecules is associated with cell membranes and is involved in processes such as cell–cell recognition.[14]

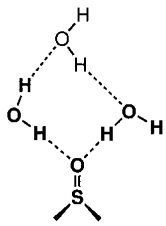

Figure 1. Schematic representation of a 1:3 DMSO–water complex in the binary mixture, observed in MD simulations of the mixture.

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[*] A. Laaksonen
Division of Physical Chemistry
Arrhenius Laboratory, Stockholm University
10691 Stockholm (Sweden)
Fax: (+46) 8 15 21 87
E-mail: aato@tom.fos.su.se

A. Vishnyakov
Department of Chemistry
St. Petersburg State University
Universitetski pr. 2, 198904
St. Petersburg (Russia)

G. Widmalm
Department of Organic Chemistry
Arrhenius Laboratory, Stockholm University
10691 Stockholm (Sweden)

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MD simulations have been very helpful in the investigation of water structures around carbohydrates.[15] From these studies, a complex and highly anisotropic hydration structure has been reported. We have recently studied **1** solvated in water and in a 1:3 DMSO–water mixture[16] using MD and compared the simulation results to data from NMR measurements.[17] One important purpose of the previous study was to critically evaluate several sets of force-field models for the disaccharide–DMSO–water system, which involves many different types of competing intermolecular interactions.[16] In the present work we have carried out a new simulation with a larger system and used the force fields previously found to agree best with the experiment regarding the overall reorientational motion, proton–proton distances, and the conformation of the disaccharide. Simulations were carried out in an NPT ensemble at 1 atm pressure and at 288 K. The total simulated time was 1.3 ns, and reported properties were averaged over the last 1.0 ns.

In the present study, throughout the 1 ns simulation, the *trans*-glycosidic torsional angles φ (H1$_m$-C1$_m$-O3$_g$-C3$_g$) and ψ (H3$_g$-C3$_g$-O3$_g$-C1$_m$), where m and g denote mannose and glucose residues, respectively, stayed in a stable conformation with their librational motion close to −33 and +56°, respectively. The resulting *trans*-glycosidic H1$_m$–H3$_g$ proton–proton distance of 2.41 Å agrees very well with the experimental value of 2.45 Å by Mäler and coworkers.[17] In this conformation, an intramolecular inter-residue hydrogen bond is formed between the hydroxymethyl (CH$_2$OH) group in the mannosyl residue and a hydroxyl group in the glucosyl residue, namely, from HO6$_m$ as a donor to O2$_g$ as an acceptor (Figure 2).

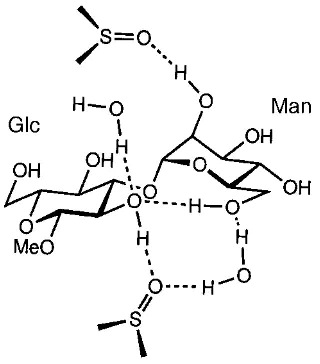

Figure 2. Schematic representation of the disaccharide **1**. Preferential solvation by the binary DMSO–water mixture, identified from MD simulations, is shown with a hydrogen bonded associate of solvent molecules together with an intramolecular hydrogen bond. In addition, a water molecule acting as a hydrogen bond donor and a DMSO molecule preferentially solvate the hydroxyl groups of the solute molecule.

The characteristic features of the solvation structure around the disaccharide stem from the rich variety of solute–solvent hydrogen bonds. Due to the large number of hydroxyl groups, able to serve both as hydrogen bond donors and acceptors, carbohydrates generally impose a strong anisotropic structuring on the surrounding associated solvent. Our disaccharide is no exception. In addition to a well-defined first solvation shell, we can even observe the second shell around it. Water and DMSO both compete as hydrogen bond acceptors, but only water can serve as a hydrogen bond donor to the oxygen atoms of the hydroxyl groups. This gives a clear preference for water to enter the first solvation shell. The DMSO:water molar ratio in the first shell was estimated to 1:5, which is considerably lower than the overall molar ratio of 1:3 in the bulk solvent. The composition of the second shell is close to that of the surrounding bulk solvent.

Details on the structure of the first solvation shell can be obtained from the radial distribution functions (RDFs), calculated between the solvent molecules and each oxygen atom of **1**. The oxygen–oxygen RDFs for O4$_m$ and O2$_g$ and the oxygen atom of the solvent (both water and DMSO) are shown in Figure 3. All RDFs between the hydroxyl groups and the oxygen atoms of the solvents exhibit a pronounced first peak due to hydrogen bonding. There is, however, a clear competition between water and DMSO as proton acceptors to the hydroxyl groups. We can see that the O4$_m$ oxygen atom prefers water molecules, while O2$_g$ dominantly selects DMSO as a proton acceptor.

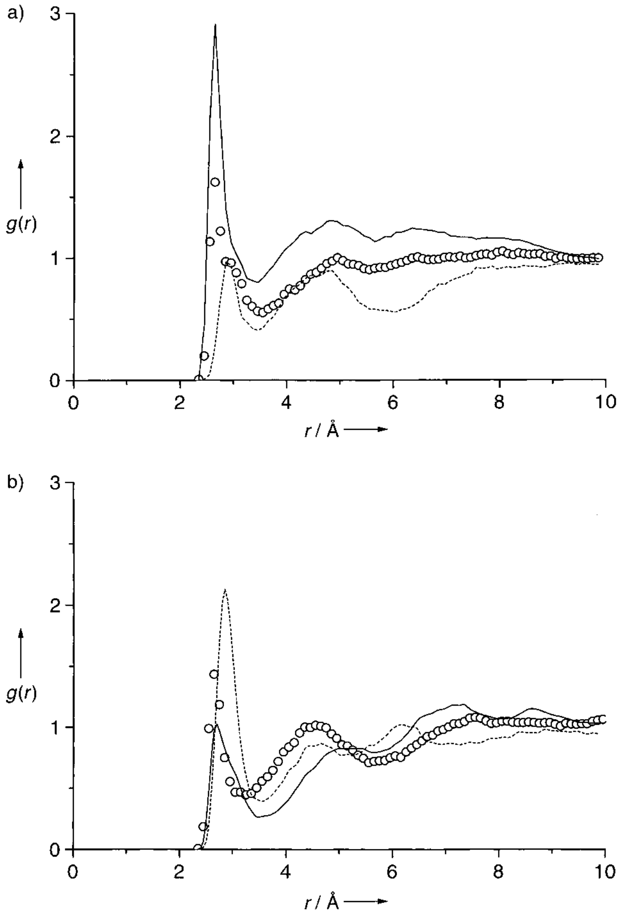

Figure 3. Oxygen–oxygen RDFs for two different oxygen atoms of **1** (O4$_m$ (a), O2$_g$ (b)) and the oxygen atom of the solvent (water (——), DMSO (----)) in the water–DMSO solution. In addition the RDFs for O$_{sugar}$-O$_{water}$ in the α-D-Man*p*-(1→3)-β-D-Glc*p*-OMe–water system are represented by circles.[16]

The traditional analysis of solvation structure using the RDF method can be extended by the use of the three-dimensional spatial distribution function (SDF).[18] This has been done for the two-component solvent DMSO–water around **1** (Figure 4). Although the resulting first solvation shell has the same characteristic structure as that formed by water molecules in a pure aqueous solution,[16] a distinct preferential solvation pattern can be identified close to the

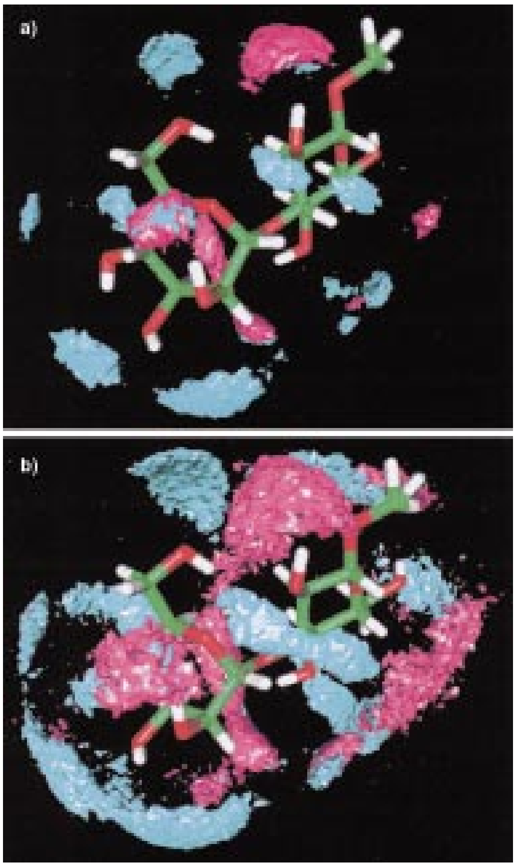

Figure 4. Time-averaged positions of each atom of **1** in a reference coordinate system, and contoured surfaces showing high, positive deviation of the solvent oxygen atom density from the average values. The colour intensity is a function of the probability of finding a certain atom in a certain place related to the average number density. In (a) the intensity is 12.0 and in (b) the intensity is 6.0. Atomic coloring is green for carbon, red for oxygen, and white for hydrogen. Isointensity contours colors are blue for water oxygen atoms and pink for DMSO oxygen atoms. The figures are produced with the "gOpenMol" package.[19]

different hydroxyl groups. For example, DMSO acts as a hydrogen bond acceptor and solvates predominantly the regions close to $HO2_g$ and $HO2_m$ (see also Figure 2). Water, acting as a hydrogen bond donor, hydrates selectively the regions around $O6_m$ and $O2_g$. The SDFs obviously provide a very detailed picture of solvation. Various graphical representations and techniques to analyze them are given by Bergman and co-workers.[20]

Another interesting feature is that DMSO, while acting as a hydrogen bond acceptor to the $HO2_g$ hydroxyl group, can simultaneously act as an acceptor for a specific water molecule, which is in turn hydrogen bonded to $O6_m$. This leads to a remarkable hydrogen bonded associate, involving two hydroxyl groups of the disaccharide and one molecule each of water and DMSO (see Figure 2). To investigate the relative stability of these associates, we can compare association times[21] for the oxygen atoms of the solvent attached to the hydroxyl groups. In most cases these were found to be slightly below 10 ps for both water and DMSO. The association time for the $O2_g{-}O_{DMSO}$ pair, however, was found to be between 20 and 30 ps. For the $O6_m{-}O_{water}$ pair it was between 10 and 20 ps. For a comparison, the rotational correlation times for water and DMSO in the binary solvent mixture are 2 ps and 3 ps, respectively. Thus, these hydrogen-bonded associates survive several rotational correlation time periods. Furthermore, similar associates with water molecules are present in the bulk solvent.

To summarize, we have shown that MD simulations can be used further to obtain detailed information about important solution properties. By combining the information obtained from using the traditional RDFs and the three-dimensional SDFs with the association times for the individual hydrogen bonds, we can see the different parts of disaccharide **1** preferentially solvated by either water or DMSO. We can also see that in some parts there is a clear competition between the components.

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