Intramolecular versus intermolecular hydrogen bonding in solution[1]

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Abstract

The balance between intra- and intermolecular hydrogen bonding is studied for a solution of methyl β-cellobioside in water and dimethylsulfoxide by ^{1}H NMR and molecular dynamics simulations. In water O(3) predominantly interacts with water molecules, whereas in dimethylsulfoxide it is intramolecularly hydrogen bonded to O(5'). The temperature coefficient of the chemical shift of the hydroxy groups appears to be a reliable indicator of intermolecular hydrogen-bond formation, whereas the exchange rate is not.

1. Introduction

The balance between intra- and intermolecular hydrogen bonding between solute and solvent molecules is an important issue since it can influence the molecular conformation. A good example of a solvent effect on molecular conformation mediated by such an equilibrium is the case of methyl β-D-glucoside, where it is found that the conformation of the hydroxymethyl group strongly depends on the polarity of the solvent [1].

In this paper we shall focus on the accessibility of hydroxy groups to solvent molecules as a decisive factor that determines whether intra- or intermolecular hydrogen bonding will take place. The compound under study is methyl β-cellobioside. The degree and nature of the hydrogen-bond formation is studied by ^{1}H NMR spectroscopy and molecular dynamics (MD) simulations.

^{1}H NMR spectroscopy provides a wealth of information about hydrogen bonding. The chemical shift, δ, of hydroxy protons tends to increase upon hydrogen bonding. This is because of the accompanying deshielding effect that causes the resonances to shift downfield. In crystals a good correlation between hydrogen-bond lengths and proton chemical shifts is found in the cases of inorganic salts, hydrated salts and carboxylic acids [2]. However, in saccharides the chemical shifts of the hydroxy groups are rather different, because of their different chemical environments. Furthermore, by a change in chemical shift alone it is not possible to discriminate between inter- and intramolecular hydrogen bonding.

In contrast, the temperature coefficient of the chemical shift provides useful information for the existence of intramolecular hydrogen bonding. The chemical shifts of hydroxy protons that are
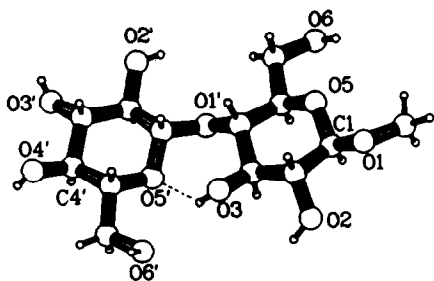

Fig. 1. Perspective view of the methyl β-cellobioside molecule with atomic numbering.

hydrogen bonded to the solvent have a marked temperature dependence due to changes in mobility of the solvent molecules. However, these changes hardly influence the chemical shifts of protons involved in intramolecular hydrogen bonds, since they have weaker interactions with the solvent molecules.

A third parameter that is of use is the $^3J_{HO,CH}$ vicinal coupling constant that is related to the H–O–C–H torsion angle. Knowledge of that torsion angle should show whether a hydroxy group proton is directed towards an oxygen in the same molecule. Unfortunately, it is generally not possible to derive the torsion angle from the observed coupling constants because they are often time averages for several conformations.

Lastly, the exchange rate, k_{ex}, can be studied for the exchangeable protons. It seems plausible that this value will be lower for protons involved in intramolecular hydrogen bonds than for those interacting with solvent molecules.

In the present paper attention will only be paid to the chemical shift temperature coefficient and the exchange rate as possible indicators of intramolecular hydrogen bonding. We have studied these NMR parameters in context with MD simulations of methyl β-cellobioside in water. With the data obtained from these simulations it is possible to assess the significance of the experimental data. We consider in this paper the donor/acceptor (DTA) capacity of a hydroxy group and the number of times (N_{occur}) that water molecules pass the boundary of the first shell of the primary solvation of a particular hydroxy group. In the next section on the computational details the definition of D + A and the concept of primary solvation are given.

2. Experimental and computational details

For a detailed description of the ^{1}H NMR experiments and MD computations we refer readers to a previous paper of Leeflang et al. [3]. Measurements were carried out in an aqueous solution and in a solution of dimethylsulfoxide. To prevent proton exchange that is too fast in the protic solution the measurements were done at sub-zero temperatures. For that reason 20% (on a weight basis) fully deuterated CD_3OD was added to water. All measurements were carried out at 500 MHz on a Bruker AM-500 NMR spectrometer.

The MD simulations in water were performed using the program GROMOS [4] and its standard force field for carbohydrates [5]. For water the SPC model [6] was used. The atomic numbering of the methyl cellobioside molecule is shown in Fig. 1 with the possible intramolecular hydrogen bond $O(3)\cdots O(5')$ indicated by a broken line. The solute molecule was placed in a periodic computational box containing 358 water molecules. Three separate runs of 100 ps each were performed starting with different configurations. Data were stored every 20 fs and averaged over 300 ps. For further details see Ref. 3.

The fraction of time a hydrogen bond exists was evaluated by counting the number of time steps the $H\cdots O$ distance was smaller than 2.4 Å. The donor/acceptor capacity of the hydroxy groups are established by the fraction of time that this criterion holds for intermolecular hydrogen bonding of the solute donor or acceptor oxygen atoms concerned with the water molecules. Also the following operational definition is of importance. It concerns the primary solvation of a solute atom X [7]. It is the volume occupied by the set of solvent atoms Y that is closer to X than to any other solute atom. The primary solvation should not be confused with the first solvation shell that ends at the first minimum in the radial distribution function $X\cdots Y$.

3. Results and discussion

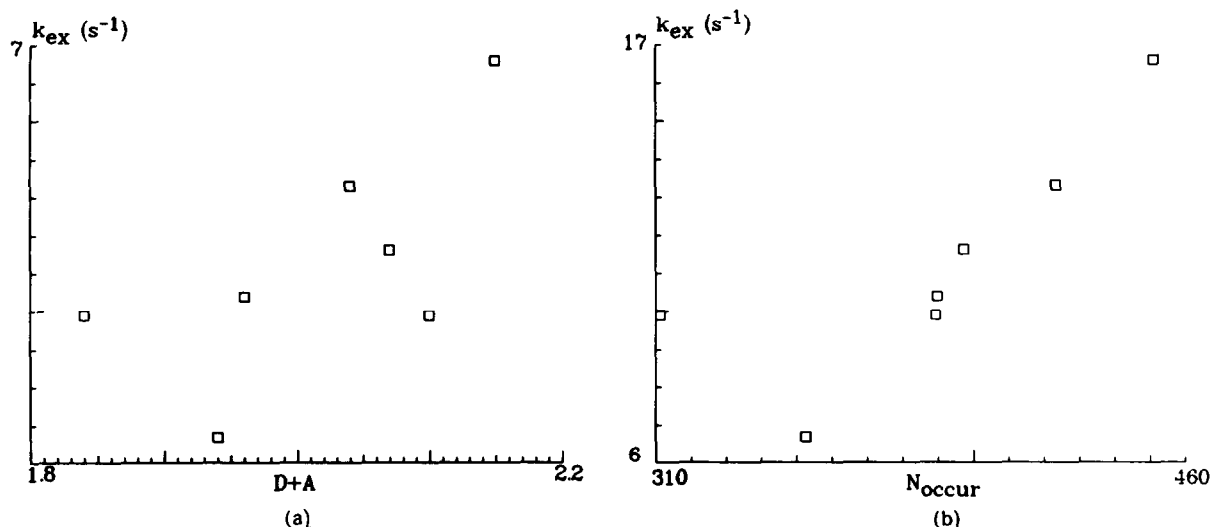From Table 1 it is seen that the temperature

Fig. 2. Plots of exchange rates (s^{-1}) against (a) donor/acceptor capacities, and (b) numbers of water molecules that pass the boundary of the first shell of the primary solvation in 300 ps.

coefficient of the chemical shift of the O(3) hydroxy proton in water does not deviate from those of the other hydroxyl groups. However, the temperature coefficient of O(3) is drastically diminished with respect to the others when measurements take place in a solution of dimethylsulfoxide. This points to the formation of an intramolecular hydrogen bond in which O(3) is involved when Me_2SO-d_6 is the solvent. The fact that in an aqueous medium intermolecular hydrogen bonding prevails also for O(3) is not corroborated, however, by the exchange rates, since a relatively low exchange rate for O(3) is found. In

Table 1
dδ/dT values and exchange rates for hydroxy protons of methyl β-cellobioside. Solvents were 4 : 1 (w/w) H_2O–CD_3OD (1) and Me_2SO-d_6 (2). Standard deviations of the mean are given in parentheses

	1	2
Chemical shift temperature coefficient (ppb deg^{-1})		
O(3)	11.1	2.6
Average O[a]	11.7(3)	7.0(3)
Exchange rate (s^{-1})		
O(3)	6.7	
Average O[a]	12.0(10)	

[a] O(3) excluded in the averaging.

this respect the MD simulations in water are expected to give additional information.

In Fig. 2 plots are shown correlating parameters obtained for the seven hydroxy groups present in the solute molecule as obtained by the MD simulations in water. First of all the donor/acceptor capacity is plotted as a function of the exchange rate (Fig. 2(a)). No good correlation can be ascribed to these two parameters, so it appears that this exchange rate is an unreliable indicator of the existence of intermolecular hydrogen bonds and consequently also for the occurrence of possible competitive intramolecular hydrogen bonding. In contrast a good correlation, as shown in Fig. 2(b), is found between the exchange rate and the number of water molecules that enter the first shell (at 2.4 Å) of the primary solvation in a certain time.

In Fig. 3 an illustrative picture is shown of the first solvations of the different solute atoms at different distances. The plots are simply made by drawing spheres around the atoms with radii of 1.8, 2.4 and 4.0 Å respectively (hydroxy groups were considered as united atoms with their centers at the oxygen atom positions). It is seen that the primary solvation of O(3) becomes less important at larger distances compared with those of the other atoms. It is also found as the result of the

(a)

(b)

(c)
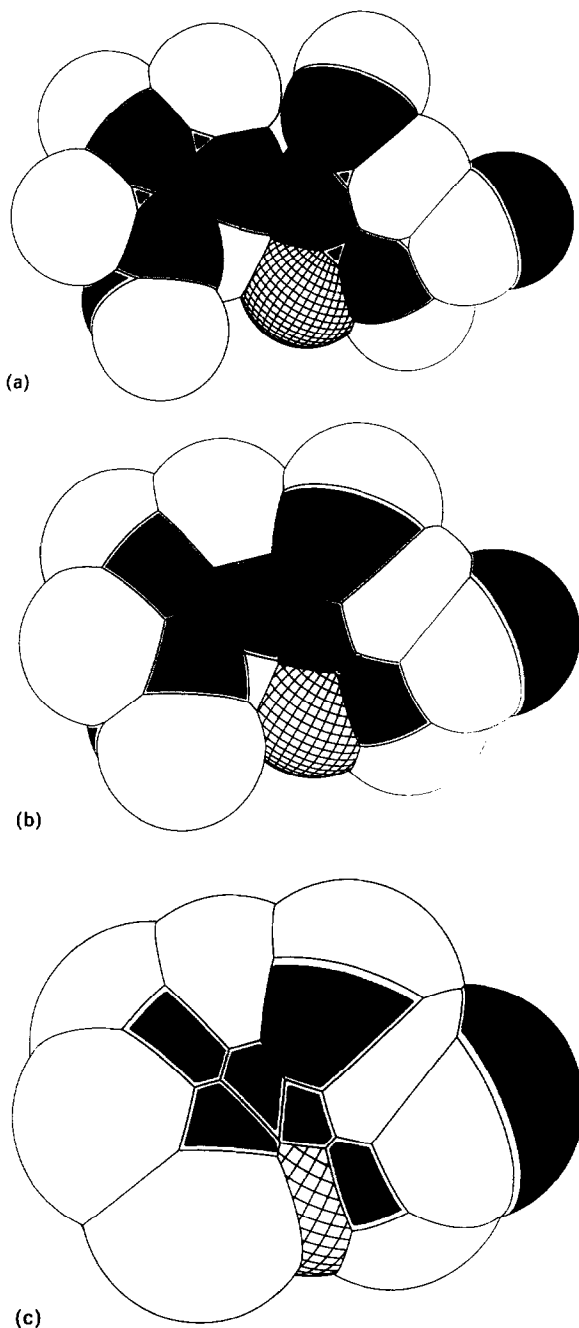
Fig. 3. Representation of the first solvations of the atoms in methyl β-cellobioside extending to (a) 1.8, (b) 2.4, and (c) 4.0Å.
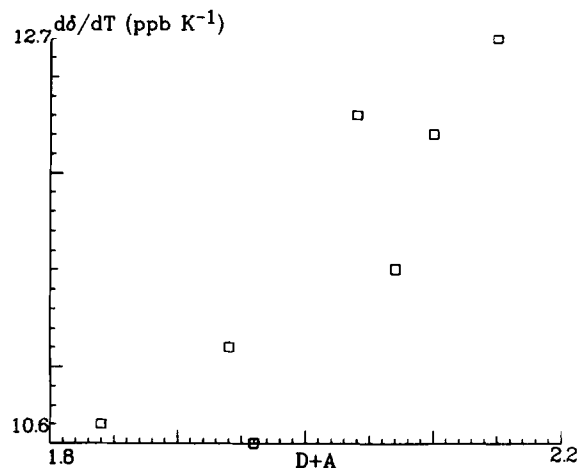

Fig. 4. Plot of the chemical shift temperature coefficients ($ppb\,K^{-1}$) against donor/acceptor capacities.

MD simulations that at a distance of 10 Å the coordination number of O(3) is about 8, compared with 22 for the other oxygen atoms. So the amount of available volume in the primary solvation is an important factor in determining that coordination number.

Now two alternative explanations can be given for the relatively low exchange rate of O(3) in aqueous solution, where for the major part it is intermolecularly hydrogen bonded. First we can imagine that the exchange mechanism is governed by a cooperative action in a chain of hydrogen-bonded water molecules. Then it is clear that O(3), by its relatively small primary solvation, is "in command" of only relatively few water molecules. That may hamper the cooperative proton transfer necessary for the exchange. Alternatively and more attractively, we may think of a more dynamic process. This is suggested by the good correlation that exists between the exchange rate and the number of water molecules that enter the primary solvation of a particular atom in a given time. Of course, that number is also determined by the shell surface in the primary solvation.

From the above considerations it should be clear that $d\delta/dT$ and k_{ex} reflect essentially different phenomena and that the use of k_{ex} as a measure of inter- or competitive intramolecular hydrogen bonding is very hazardous indeed.

In contrast with that, as Fig. 4 shows, a very

good correlation is apparent between the chemi-cal shift temperature coefficient and the donor/acceptor capacity. Thus $d\delta/dT$ should indeed be considered as a reliable parameter for studying the nature of hydrogen bonding (intra- versus inter-).

Finally, it is easy to understand that O(3) resorts to intramolecular hydrogen bonding when dimethylsulfoxide is used as a solvent. This effect can undoubtedly be ascribed to the low degree of accessibility of O(3) in connection with the bulky dimensions of the carrier of the potential acceptor oxygen atom in the solvent molecule.

4. Acknowledgment

5. References

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