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The effect of stereochemistry upon carbohydrate hydration. A molecular dynamics simulation of β-D-galactopyranose and (α,β)-D-talopyranose

Saskia A. Galema [a,1], Eduardo Howard [b], Jan B.F.N. Engberts [a,*], J. Raul Grigera [b]

[a] *Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, Netherlands*

[b] *Instituto de Fisica de Liquidos y Sistemas Biologicos (IFLYSIB), University of La Plata, 59-789 C.C. 565, 1900 La Plata, Argentina*

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Abstract

This paper reports a molecular dynamics simulation study of β-D-galactopyranose and (α,β)-D-talopyranose in aqueous solution. Special emphasis was placed on the intramolecular next-nearest neighbour oxygen distances in the carbohydrate molecule and the hydrogen bonding of the hydroxy functionalities of the carbohydrates with water. The average number of hydrogen bonds of the hydroxy groups of the carbohydrates depends on the stereochemistry of the molecule. In contrast to the HO-2 and HO-4 of D-galactopyranose, those of D-talopyranose are shielded. This is a consequence of an intramolecular hydrogen bond between the HO-2 and HO-4 in D-talopyranose, which also explains why the apparent hydrophobicity of D-talose is found to be greater than that of D-galactose.

Keywords: Molecular dynamics simulation; Hydrogen-bonding; Fit into hydrogen bond network of water; Stereochemistry of monosaccharides

1. Introduction

Polyhydroxy compounds such as carbohydrates possess such small differences in their hydration characteristics that only very few experimental methods have sufficient sensitivity to permit those differences to be measured satisfactorily. The hydration of a carbohydrate depends on its stereochemistry [1], but how the hydration of a carbohydrate depends on

* Corresponding author.

[1] Present address: Unilever Research Laboratory, P.O. Box 114, 3130 AC Vlaardingen, Netherlands.

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its hydroxy topology is a matter of debate and controversy. Generally there are three points of view. It has been proposed that the anomeric effect of a carbohydrate governs its hydration [2,3]. In addition, Franks [1,4] postulated the stereospecific hydration model, which assumes that an equatorial hydroxy group is better hydrated than an axial hydroxy group; hence, the hydration of a carbohydrate was proposed to depend on the ratio of equatorial versus axial hydroxy groups. Although this theory has found considerable support [5–10], doubts have arisen concerning its general applicability [11]. Recently a modified stereospecific hydration model has been proposed [12–14], emphasizing that the hydration of a carbohydrate depends predominantly on the relative distance of the next-nearest neighbour oxygens of a carbohydrate compared to the oxygen–oxygen distances of water. The relative position of the hydroxy groups at C-2 and C-4 appears to be a key factor. This theory is fully consistent with quantitative studies of kinetic medium effects [12,13] and relevant thermodynamic measurements [14]. A recent study was focused on which of the many thermodynamic parameters for aqueous carbohydrate solutions are sensitive to differences in the stereochemistry of the solute [15].

In this paper, it is shown that a molecular dynamics (MD) study of carbohydrates in aqueous solutions provides important insights into their hydration characteristics. Two carbohydrates were chosen: β-D-galactopyranose and both α- and β-D-talopyranose. These two carbohydrates exhibit the most different hydration characteristics according to previous investigations [12–14]. For both carbohydrates, the dominant conformers in solution were chosen for the simulations. Since for D-talose both anomers are present in almost the same quantities, both anomers were studied.

Molecular dynamics simulations [16,17] as well as quantum chemical conformational analysis [18] provide tools for the study of the hydration of a carbohydrate at a molecular level. Information on how a carbohydrate fits into the three-dimensional hydrogen-bond network of water can be provided either by the use of structures of carbohydrates from X-ray data when they are the dominant ones in aqueous solutions, or structures which originate from a molecular dynamics simulation in water. Because solutes in aqueous solution are inherently dynamic in character, the use of molecular dynamics simulations [19,20] has definite advantages. There has been, and still is, a lively discussion as to the way in which molecular dynamics simulations should be performed for carbohydrates in aqueous solution, because most carbohydrates have a hemiacetal functionality that is subject to mutarotation. In addition, the question arises as to which force field and point charges should be used for carbohydrates in aqueous solution and how to account for the anomeric effect [16].

For the simulations, potential energy functions have been devised which are semi-empirical. It is notoriously difficult to describe a potential energy function for carbohydrates because of the presence of the hemiacetal function. The many forms of a carbohydrate in solution (due to either simple or complex mutarotation) pose a severe problem for developing a force field for calculations. For example, the question arises whether the anomeric effect should be introduced into the force field or whether it should automatically be taken into account by the calculations, without the simulation being prejudiced.

Fortunately, several carbohydrate potential energy functions are now available [21–26], sometimes especially developed for small molecule analogues of carbohydrates. However, most force fields developed for carbohydrates are incompatible with those developed for other solutes, for example, glycoproteins.

Since 1987, simulations of carbohydrates in vacuum and in aqueous solution have been published [27–37]. In the case of cyclodextrins, simulations have also been reported for the crystalline state and for cyclodextrins in aqueous solution [38–41]. In addition, polyols and other small organic solutes have been subjected to a simulation in aqueous solution [42–44]. Monte Carlo simulations have also been performed for carbohydrates [23,45,46].

The molecular dynamics simulations of both α- and β-D-glucopyranose, published by Brady [28], are of special interest. Those studies reproduce the energy difference between α- and β-glucose in water satisfactorily. Brady has also studied maltose in water through an MD simulation. [30] The simulations described in this paper have been performed with the GROMOS [20] force field applying the charges used by Brady [31].

2. Experimental

Crystal data.—The crystal data were obtained from the Cambridge Crystallographic Data Centre for those carbohydrates for which the conformation in the crystal was similar to the dominant conformation in water. The next-nearest neighbour oxygen distances of the carbohydrates in the crystalline state were calculated using the CHEMX program [47].

Procedure.—MD simulations were performed for β-D-galactopyranose, α-D-talopyranose and β-D-talopyranose. For all the simulations, the same procedures and conditions were taken into account. The carbohydrates were placed in a cubic box of 1.8662 nm average length with periodic boundary conditions. The box was filled with SPC/E water [48]. This led to 216 water molecules in the box. The systems were energy-minimized (steepest descent method); 50 steps were performed keeping the carbohydrates harmonically constrained to their original positions enabling the water molecules to equilibrate, followed by 200 steps without constraints. The configurational energies and forces were computed with GROMOS87 [20] parameters. For the partial charges in the carbohydrate molecules, we have used the values obtained by Brady and co-workers [31] using ab initio calculations. Previously, the GROMOS force field was shown to reproduce experimental NMR coupling constants remarkably well [43]. The polar hydrogen atoms were explicitly included; they have only partial charges. In this way all the charges were fully compatible with those of Brady and co-workers [31]. The energy of a molecular system is described by simple potential energy functions comprising stretching, bending, Lennard–Jones, and electrostatic interactions. The molecular model that was used treats all atoms explicitly and no special hydrogen-bond potential has been included. The simulations, under periodic boundary conditions, were performed with a rigid backbone of the carbohydrate molecules by constraining the improper dihedral/torsional angles. Vibrations of the C–C and C–O bonds as well as rotational freedom around the C–O bond were allowed.

No ring flip was possible, which seems justified because ring flip was not observed during the 32-ps simulation of D-glucose in water [28]. The molecular dynamics phase of the calculations involved a period of 10-ps equilibration with simultaneous heating of the system to 298 K by coupling to an external heat and pressure bath [49] at 298 K and 1 atm, with time constraints of 0.01 and 0.05 ps, respectively. Temperature fluctuations during the complete run were less than 7 K.

After the equilibration, an MD simulation of 100 ps was performed. Intermediate structures generated during these MD runs were saved every 10 steps (0.01 ps). The temperature and pressure were controlled by coupling to an external bath at 298 K and 1 atm. Time constraints were chosen as 0.1 and 0.5 ps for coupling to the heat and pressure baths, respectively. All HO covalent bond lengths as well as the water bond angle were constrained by the procedure SHAKE [50], and a 1-fs time step was used. Except for O–H bonds, a harmonic potential was used for stretching interatomic bonds. All non-bonded forces were cut off at 0.9 nm.

All simulations were run on a VAX 2000 or IBM RS/6000 32H computer of the IFLYSIB. Criteria for hydrogen bond formation were (*a*) the O···H distance had to be less than 2.4 Å, and (*b*) the angle of O-H···O had to be equal to or greater than 145°. The reference temperature was 298 K and the pressure was 1 atm.

3. Results and discussion

In the modified stereospecific hydration model, it was proposed that the compatibility of a carbohydrate with water depends predominantly on the relative positions of HO-2 and HO-4 [12–14]. Why these two hydroxy groups in particular are so important and what the molecular picture is behind the fit of a carbohydrate molecule into water has, so far, remained rather unclear. What does it mean if a carbohydrate fits very well into water? In addition, why do the aldohexoses appear to be divided into three groups with different fits in water? It will also be interesting to find out why HO-2 and HO-4, rather than HO-1 and HO-3 [5–7], are so important for the fit of an aldohexose in water. Since HO-2 and HO-4 are next-nearest neighbour oxygens in a carbohydrate molecule, all next-nearest neighbour oxygen distances within a carbohydrate molecule were studied, and compared to the oxygen–oxygen distances in liquid water. This approach has previously been suggested by Danford [51] and Warner [52].

Initially only the data for the crystalline carbohydrates as obtained from the Cambridge Crystallographic Data Centre were available. The through-space oxygen distances of the dominant conformers of hexoses in the crystalline state could be calculated with aid of the CHEMX program [47]. In Table 1, the next-nearest neighbour oxygen distances for β-D-galactose, β-D-glucose, and α-D-talose are given.

For a carbohydrate which fits very well into water (D-talose), it is seen that the through-space next-nearest neighbour oxygen distances O-2–O-4, O-2–O-5, and O-4–O-5 are at a distance from each other which is comparable to the nearest neighbour oxygen distance in water. The O-1–O-3 distance in the α-D-talose molecule is much longer but is too small to fit with the next-nearest neighbour oxygen distances in water. For a carbohydrate, which has no good compatibility with the hydrogen-bond network of water, as exemplified by D-galactose, the O-1–O-3 distance matches the next-nearest neighbour oxygen distances of water, but the oxygen distances between HO-2, HO-4 and O-5 show great differences. For D-glucose, an intermediate behaviour (intermediate fit) was suggested [13,14]. This might be caused by the fact that both the O-2–O-4 and the O-1–O-3 distance are compatible with the next-nearest neighbour oxygens in water (O-2–O-4 is 4.874 and O-1–O-3 is 4.754 Å, respectively).

Table 1
Next-nearest neighbour oxygen distances of carbohydrates in the crystalline state and in aqueous solution [a]

Carbohydrate	O-2–O-4	O-2–O-5	O-4–O-5	O-1–O-3	O-1–O-6	O-3–O-6
Crystalline state [b]						
β-D-Galactopyranose	4.28	3.66	2.83	4.82	4.70	6.14
α-D-Talopyranose	2.66	2.93	2.87	4.17	4.44	6.19
β-D-Glucopyranose	4.87	3.67	3.66	4.75	5.22	5.33
Aqueous solution [c]						
β-D-Galactopyranose	4.3	3.7	3.0	4.9	5.7	5.5
β-D-Glucopyranose [d]	4.9	3.7	3.7	4.9	5.7	5.3
α-D-Talopyranose	2.7	3.1	3.0	4.2	5.1	5.5
β-D-Talopyranose	2.7	3.0	3.0	4.9	5.7	5.6

[a] Distances in Ångstroms.
[b] These distances have been calculated using the CHEMX program as described in ref. 13.
[c] As determined in the MD simulation.
[d] E. Howard and J.R. Grigera, unpublished results.

Three hexoses were selected for a molecular dynamics simulation. When the results of refs 13 and 14 are summarized (Table 2) for D-galactose and D-talose, it is concluded that D-galactose has a poorer fit into water than D-talose. This is shown by a more negative partial molar compressibility ($K_{2,S}$) for D-galactose, and a higher hydration number (n_h) indicative of a small apparent hydrophobicity (*vide infra*). By contrast, D-talose has a substantial apparent hydrophobicity as shown by its G(C) value. Therefore, these aldohexoses were selected for a simulation. For galactose, it was logical that only the β anomer was subjected to the simulation exercise as this anomer predominates in aqueous solution. For D-talose, both the α and β anomer are present in aqueous solution in comparable amounts [53,54]; hence the simulation was performed for both anomers. The structures of the aldohexoses are drawn in Scheme 1.

The results of the simulations are depicted in Tables 1 and 3 and Figs. 1 and 2. The oxygen distances of a carbohydrate in water refer to the oxygen distances of the carbohydrate molecule as obtained by means of a simulation in water.

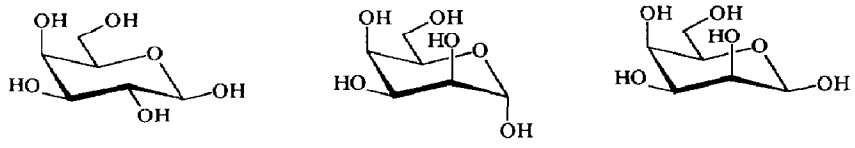
In Table 1, the oxygen–oxygen distances of the carbohydrates are given in both the crystalline state and in aqueous solution (after the simulation) for talose, galactose, and, for comparison, glucose. The results for β-glucose in water are presented as well.

Generally it is observed that the trends found in the crystal data are reproduced in the simulation for the through-space intramolecular oxygen–oxygen distances of the endocyclic

Table 2
Kinetic medium effects [a], partial molar isentropic compressibilities [b], and hydration numbers [c] of D-galactose and D-talose in aqueous solution at 298.15 K

Property	D-Galactose	D-Talose
G(C) [a] (J kg mol^{-2})	−142	−280
$K_{2,s}$ [b] (cm^3 mol^{-1} bar^{-1})	−20.4	−11.9
n_h	8.7	7.7

[a] G(C), Refs. 12 and 13. [b] $K_{2,S}$, Ref. 14. [c] n_h, Ref. 14.



β-D-galactose α-D-talose β-D-talose

Scheme 1. Hexoses studied by a molecular dynamics simulation: β-D-galactopyranose, α-D-talopyranose, and β-D-talopyranose.

hydroxy groups. The only significant difference from the crystal data is the position of the hydroxymethyl group. The MD simulations suggest that the hydroxymethyl group (O-6) is sufficiently flexible to adjust its position somewhat in order to generate the best oxygen distance with the oxygens at C-1 and C-3 for a fit into water. It has also been found previously that the hydroxymethyl group is quite flexible and that its relative position is solvent-dependent [28,34,35]. The differences between the O-1–O-6 and O-3–O-6 distances in the crystalline state and in water indeed confirm that the hydroxymethyl group is flexible and that its orientation is solvent-dependent. For β-D-galactopyranose, it is found that within the O-2–O-4–O-5 plane only the O-4–O-5 distance matches oxygen–oxygen distances in water, whereas in the O-1–O-3–O-6 plane two of its O–O distances match the next-nearest neighbour oxygen distance of water. By contrast, α-D-talopyranose has a rather perfect fit with the nearest neighbour oxygen distances in water as far as the O-2–O-4–O-5 plane is concerned. This is also the case for β-D-talopyranose. Both O-1–O-3–O-6 planes of the taloses fit reasonably well with the next-nearest neighbour oxygen distances of water. It is known that in O···H-O hydrogen bonds the O–O distances may vary from 2.5 to 3.5 Å

Table 3
Average number of hydrogen bonds from water to water, from water to oxygen of carbohydrate, and from carbohydrate to water

	H_2O	α-Talose	β-Talose	β-Galactose
$O_w\cdots H\text{-}O_{water}$ [a]	3.14	3.09	3.09	3.10
HO_{carb} is hydrogen-bond acceptor [b]				
$O\text{-}1\cdots H\text{-}O_{water}$		0.87	0.96	1.04
$O\text{-}2\cdots H\text{-}O_{water}$		0.87	0.71	1.12
$O\text{-}3\cdots H\text{-}O_{water}$		1.22	0.90	1.10
$O\text{-}4\cdots H\text{-}O_{water}$		0.83	0.91	0.96
$O\text{-}5\cdots H\text{-}O_{water}$		0.13	0.22	0.09
$O\text{-}6\cdots H\text{-}O_{water}$		1.31	1.19	1.24
HO_{carb} is hydrogen-bond donor [c]				
$O\text{-}1\text{-}H\cdots O_{water}$		0.85	0.79	0.70
$O\text{-}2\text{-}H\cdots O_{water}$		0.34	0.50	0.74
$O\text{-}3\text{-}H\cdots O_{water}$		0.86	0.86	0.81
$O\text{-}4\text{-}H\cdots O_{water}$		0.62	0.25	0.84
$O\text{-}6\text{-}H\cdots O_{water}$		0.90	0.84	0.88

[a] Calculated from the distribution of the number of hydrogen bonds between O-5 during 100 ps.
[b] Calculated from the distribution of the number of hydrogen bonds between O-3 during 100 ps. HO_{carb} is the hydroxyl group of carbohydrate.
[c] The number of hydrogen bonds was 0 or 1.

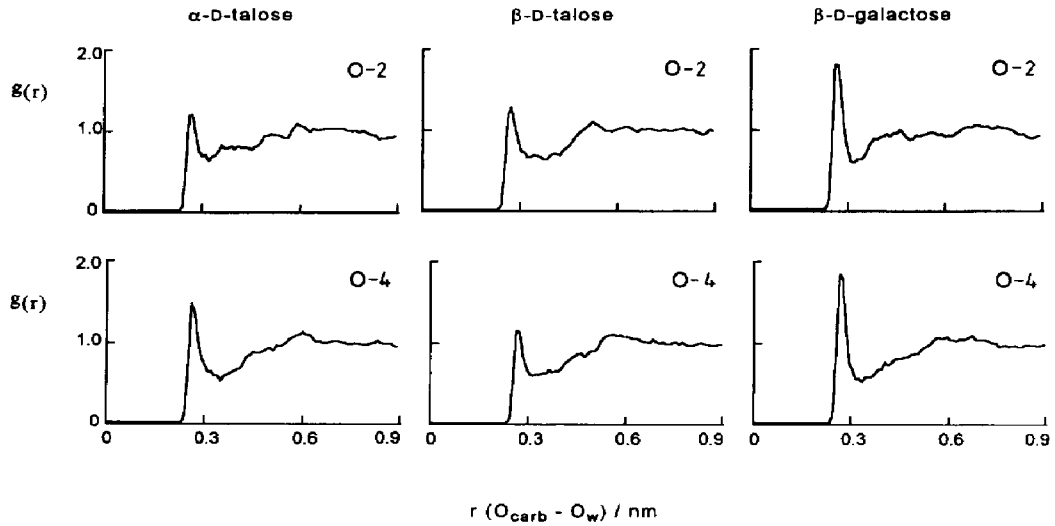


Fig. 1. Radial distribution functions of water around carbohydrate oxygens: distribution of $r(O_{carb}–O_{water})$ for the HO-2 and HO-4 groups of α-D-talopyranose, β-D-talopyranose, and β-D-galactopyranose.

[55]. Hence, the oxygens in the O-2–O-4–O-5 plane of D-talose are at such short distances that even an intramolecular hydrogen bond is possible in this plane.

Partial attention has been paid to the distance from the oxygen of a carbohydrate molecule to the position at which the radial distribution function of an oxygen atom of water has the highest probability. For most oxygen atoms attached to the ring of the carbohydrate, these distances are between 2.7 and 2.9 Å. It is observed that the ring oxygen (O-5) is shielded from interaction with water; the distance in question is 3.2–3.5 Å. There is no sharp maximum in the distribution function (this is not shown in a figure, but can also be derived

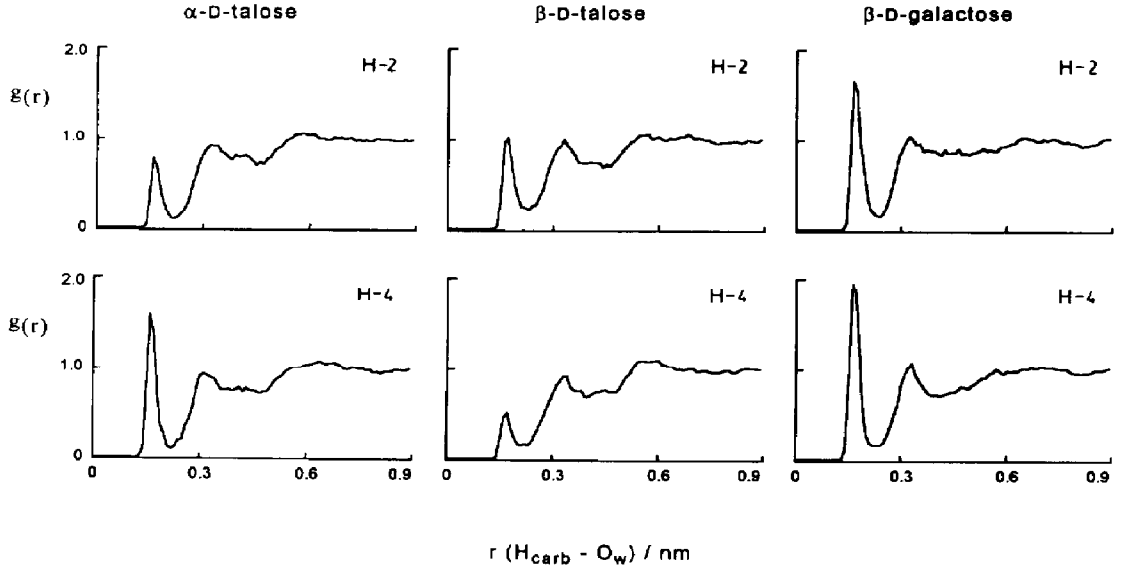


Fig. 2. Radial distribution function of water around carbohydrates: distribution of $r(H_{carb}–O_{water})$ for HO-2 and HO-4 of α-D-talopyranoside, β-D-talopyranoside, and β-D-galactopyranoside. H_{carb} is the proton which is part of OH_{carb}.

from the fact that the average number of hydrogen bonds which O-5 has as a hydrogen-bond acceptor (Table 3) is considerably lower than that for the other functional groups). This observation was previously made for α-D-glucopyranose [28]. The oxygens on the 1-, 3-, and 6-positions all have sharp, well-defined distances at which the radial distribution function of water has the highest probability. This indicates that there is a strong intermolecular hydrogen bond between these hydroxy groups and water. Brady [28] claimed that a carbohydrate is a structure breaker, because there is only one sharp maximum in the probability of finding a water molecule near a hydroxy group of a carbohydrate. Interestingly, the presence of a well-defined O_{carb}–O_{water} distance is very much dependent on the stereochemistry of the hydroxy groups at the 2- and 4-positions.

In Fig. 1, the distribution function is given as a function of the O_{water}–O_{carb} distance. The plots have been made for the HO-2 and HO-4 groups of α-D-talopyranose, β-D-talopyranose, and β-D-galactopyranose. The difference between D-galactose and D-talose is clear.

Intermolecular hydrogen bonds between water molecules in the hydration layer.—In Table 3, the average number of hydrogen bonds between water molecules in water and in the presence of α-D-talose, β-D-talose, and β-D-galactose are given. This number of hydrogen bonds is calculated over the last 90 ps of the simulation and between zero and five hydrogen bonds are taken into account. The largest number of hydrogen bonds (3.14) is found in water.

The presence of α-D-talose, β-D-talose, and β-D-galactose disturbs the average number of hydrogen bonds between water molecules only very slightly, as the water molecules have an average number of mutual H-bonds of 3.09 or 3.10. This illustrates how well these carbohydrates are accommodated in water.

Average number of hydrogen bonds: carbohydrate as an H-bond acceptor.—If the average number of hydrogen bonds is considered (Table 3) for those cases where the oxygen atoms of the carbohydrate serve as hydrogen-bond acceptors (water is the hydrogen-bond donor), it is observed that the exocyclic hydroxy group (O-6) is on average a good H-bond acceptor; for all three aldohexoses, the average number of hydrogen bonds is higher (1.25) for this primary hydroxy group in comparison with that for the secondary hydroxy groups (0.96). The endocyclic oxygen (O-5) is very much shielded as a hydrogen-bond acceptor (average number of hydrogen bonds is 0.15).

Average number of hydrogen bonds: carbohydrate as an H-bond donor.—In Table 3, the average number of hydrogen bonds in which the hydroxy groups of a carbohydrate are H-bond donors (water serves as a hydrogen-bond acceptor) is given. Clearly this number depends on the stereochemistry of the carbohydrate. O-1, O-3, and O-6 have a comparable average number of hydrogen bonds (0.83) with water for both (α,β)-talose as well as β-galactose. The average number of hydrogen bonds of HO-2 and HO-4 is very much lower for both α- and β-talose (0.43) in comparison to β-galactose (0.79). This provides evidence that HO-2 and HO-4 in α- and β-D-talose are shielded from water as a hydrogen-bond donor. Fig. 2 illustrates this observation; it shows that the $r(H_{carb}$–$O_{water})$ is not sharply defined for the HO-2 and HO-4 of D-talose in contrast to these groups in D-galactose.

Intramolecular hydrogen bonds.—For carbohydrates in water, there has been much interest in the possible formation of intramolecular hydrogen bonds. The differences in solubility of maltose and cellobiose were claimed to be caused by an intramolecular hydrogen bond between the two monosaccharide moieties, present in maltose, but absent in

cellobiose [56]. In this context, sucrose was considered to be rather rigid, because of an intramolecular hydrogen bond between the saccharide units [57]. Previously, it was suggested that this intramolecular hydrogen bond is needed to elicit the sweet taste [58]. These intramolecular hydrogen bonds have been observed both in the crystal structure and in aprotic solvents. However, the possibility of the formation of an intramolecular hydrogen bond in water was considered to be small, because intermolecular hydrogen bonds with water will be entropically much more favorable. Recent NMR and MD investigations [33,59,60] have again shown that for disaccharides the intramolecular hydrogen bond is virtually non-existent in water. However, in *N*-acetyl-α-D-galactosamine the presence of a weak intramolecular hydrogen bond in water has been established [36]. The results reported previously [12–14] suggest that the aldohexoses, which are being discussed here, possess a different apparent hydrophobicity, because they exert a different kinetic medium effect on a water-catalyzed hydrolysis reaction. This suggests that some carbohydrates behave as rather hydrophobic species in water. Because carbohydrates are readily soluble in water, due to their hydroxy functionalities, this hydrophobicity in water is an "apparent hydrophobicity". The "apparent hydrophobicity" has been attributed to a camouflage effect [11,61]; the hydroxy groups of a carbohydrate fit into the three-dimensional hydrogen-bond structure of water and therefore are not recognized by a spectator molecule. An additional reason why D-talose has a greater "apparent hydrophobicity" than D-glucose and D-galactose could be that its hydroxyl groups are shielded from water by the formation of an intramolecular hydrogen bond. D-Talose has the possibility of forming an intramolecular hydrogen bond between the O-2–O-4–O-5 groups. Although it appeared logical that this intramolecular hydrogen bond would be destroyed in water because an intermolecular hydrogen bond is entropically more favorable, it is very likely that the alignments of the hydroxyl groups in D-talose and in water are so similar, that entropically there is no significant difference between an intramolecular hydrogen bond between two hydroxyl groups of D-talose and an intermolecular hydrogen bond with water. The O_{carb}–O_{water} distances are not as sharply defined for both HO-2 and HO-4 for D-talose as they are for D-galactose (Fig. 1). No significant differences in the average number of hydrogen bonds for HO-2 and HO-4 as a hydrogen-bond acceptor are observed for D-talose and D-galactose. However, hydroxyl groups possess two lone pairs which can accept a hydrogen bond, and therefore shielding might not be completely borne-out by this number. The average number of hydrogen bonds of HO-2 and HO-4 of D-talose (HO is H-bond donor) shows a much smaller value in comparison to D-galactose. These values, as well as the plots of the radial distribution functions of $r(H_{carb}–O_{water})$ versus distance, show that HO-2 and HO-4 are shielded considerably as hydrogen-bond donors. A probable reason for shielding could be the formation of an intramolecular hydrogen bond in D-talose. After the 100-ps simulation, it was found that in D-galactose there are no intramolecular H-bonds. For β-D-talose an intramolecular H-bond is observed from HO-2 to HO-4 for 16% of the time, whereas from HO-4 to HO-2 there is one for 45% of the time. The roles are reversed for α-D-talose: HO-2 is involved as a hydrogen-bond donor in an intramolecular H-bond to HO-4 31% of the time, and HO-4 is donating a hydrogen bond to HO-2 intramolecularly for 19% of the time.

4. Conclusions

Quantitative studies of kinetic medium effects of carbohydrates [12,13] as well as thermodynamic studies of aqueous carbohydrate solutions [14,15] have supplied relevant

questions concerning the effect of stereochemistry on carbohydrate hydration. It is shown that the hydration characteristics of a carbohydrate are revealed in some detail by molecular dynamics simulations. We find that the hydration of D-galactose and D-talose depends largely on the relative distances of the next-nearest neighbour oxygens as compared with the oxygen–oxygen distances of water. The oxygens of an aldohexose can be divided into two planes, namely the O-2–O-4–O-5 plane and the O-1–O-3–O-6 plane. The latter plays a minor role in determining the compatibility of a carbohydrate with the three-dimensional hydrogen-bonded network of water, because the anomeric position can be either equatorial or axial and the hydroxymethyl moiety is flexible and can therefore adjust itself to a better fit. The O-2–O-4–O-5 plane is clearly the most rigid plane and therefore plays the most important role in determining the fit of a carbohydrate into water. The distances between the next-nearest neighbour oxygen atoms of a carbohydrate can either match the nearest neighbour or next-nearest neighbour oxygen distances of water or have no fit at all. The greater apparent hydrophobicity of D-talose in comparison to D-galactose is caused by the formation of an intramolecular H-bond in D-talose in which HO-2 and HO-4 share the role of H-bond donor and acceptor.

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