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Molecular dynamics simulation of the aqueous solvation shell of cellulose and xanthate ester derivatives[†]

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ABSTRACT: MD simulations of a pentasaccharide having D-glucopyranoside residues connected by $(1 \rightarrow 4)$-β glycosidic linkages, as a model of cellulose solvated in water, were carried out comparing the solvation of the hydroxyl group at C_2 of the central ring of the pentamer and that of a single glucopyranose ring. MD simulations of 10 nsec were carried under NPT and periodic boundary conditions at 298 K and 1 atm. Explicit solvent (TIP3) and the force field CHARMM27 (modified for xanthate ester derivatives) were used in the molecular dynamics simulations. RDF calculations with respect to O_2 of the central ring of the pentamer showed a well structured first solvation shell followed by secondary shells. When comparing the simulations of the pentamer to a single glucopyranose ring, it was observed that the solvation of O_2 was lower for one repetitive unit, indicating that the pentamer had a stronger H-bond structure of water around O_2 due to the cooperative effect of the neighboring residues. When the O_2 of the central ring of the pentamer was substituted by a *p*-nitrobenzylxanthate moiety (pentXNB) there was a strong decrease in the hydration of the substituted O_2 but the carbon and the sulfur of the thiocarbonyl group were clearly hydrated compared to the sulfur bridge. The global minimum energy conformation showed the *p*-nitrobenzyl group folded over the neighboring glucose ring. However, the simulations showed that the XNB group oscillates over the pentamer in periods of *ca.* 3000 psec. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: MD simulation; cellulose aqueous solvation; cellulose model; cellulose xanthate esters

INTRODUCTION

The essential role of water in chemical processes is closely related to dynamics of the aqueous solvation shell of the reacting molecule and many reactions only occur after water molecules have been removed from the solvation shell to form an encounter complex. The structure of the solvation shell can become of paramount importance when water acts as a nucleophile and/or catalyzes the reaction as a general base or acid.

The dynamic behavior of the water molecules in the solvation shells of dissolved ions is recently being revealed. The hydrogen bond dynamics of the water molecules in the solvation shells of ions (Cl^-, Br^-, I^-) was studied using femtosecond midinfrared nonlinear spectroscopy and it was found that the dynamics was slow, indicating that the aqueous solvation shell is rigid. This rigidity can be important in the overall dynamics of chemical reactions in aqueous solution.[1] The water molecules in the solvation shells of these anions move comparatively slowly, with mean lifetimes of 12–20 psec for 1–6 M NaCl solutions, and of 18–25 psec for NaI under similar conditions.

Computer simulations based on *ab initio* molecular dynamics (Car–Parrinello molecular dynamics or CPMD) are providing an increasingly important complement to experimental data in this area.[2] CPMD quantitatively reproduces the properties of bulk water under a variety of conditions. Such simulations are now being used to probe the behavior of ions in solution[3] and the complex mechanism of autoionization of liquid water.[4]

MD simulation of solvation of a disaccharide (Man*p*-$(1 \rightarrow 3)$-β-D-Glc*p*-OMe) in a 1:3 DMSO-water mixture showed that the disaccharide imposes a strong anisotropic structuring on the surrounding associated solvent. The DMSO: water molar ratio in the first solvation shell was estimated to be 1:5 while the composition of the second shell was close to that of the bulk solvent.[5] MD simulations of a series of pentose sugars in solution, modeled as pyranose rings, also showed that these molecules do indeed impose on water molecules a considerable 3-D structure that depends on the substrate's molecular topology. The structuring is stereospecific, and probably the most favorable hydration occurs when the hydration requirements of the functional groups of the solute molecules are mutually compatible. The first and second solvation shells are well defined around

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the sugar molecule, with specific locations determined by the arrangements of the functional groups of the solute.[6] Polymers such as collagen, DNA, and cellulose showed that the interproton distances and symmetry of molecular orientation are consistent with their compatibility to the 3-D hydrogen-bonded structure of water.[7]

Although the hydration of carbohydrates is now better understood, a detailed description of the cybotactic region is not available because of the experimental difficulties involved. However, some insight has been obtained by comparing the reactivities of mono- and polysaccharide derivatives to small molecules with the same functionalities. It has been observed that the water-catalyzed reaction of cellulose[8] and amylose[9] xanthate

charged spherical ions, like iodide, known by their effect of decreasing the H-bonded network of water, decrease the rate of hydrolysis. These results support the theory that the supramolecular catalysis induced by modified polysaccharide esters is due to the 3-D H-bonded network of water of the solvation shell.[9]

In the present work we carried out MD simulations of a pentasaccharide having the D-glucopyranoside residues connected by $(1 \rightarrow 4)$-β glycosidic linkages, as a model of cellulose, in an NPT ensemble using TIP3 water molecules. The solvation of the hydroxyl group at C_2 of the central ring of the pentamer **II** was compared to the corresponding OH of a single independent dynamics of pentXNB. This is a powerful approach to study saccharides because glucopyranoside unit and also

R=H,—C(S)SCH₂—⟨ ⟩—NO₂
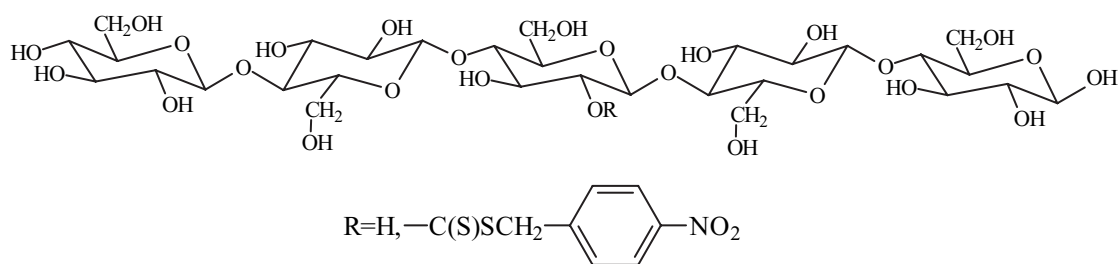
II

esters, substituted at position C2 (or C3) of the glucopyranose unit, is about three orders of magnitude faster than that of the small analog molecule, and it has been proposed that the acceleration is a consequence of the strong 3-D hydrogen-bonded network of water of the solvation shell induced by the polysaccharide. The hydrolysis occurs with a rate-determining nucleophilic attack of a water molecule,[10] catalyzed by a second water molecule that acts as a general base where the transition state would be **I**.[11] The water catalysis is not due to a neighboring OH effect[12] and the effect is mainly entropic, since the entropy of activation is nearly zero.

I
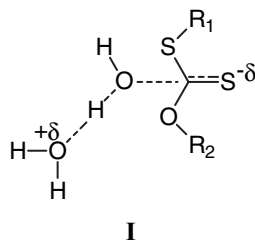
For the water-catalyzed hydrolyses of *p*-nitrobenzyl amylose xanthate, small ions, such as Li^+, that produce an increase of the 3-D hydrogen-bonded network of water, accelerate the hydrolysis further. Large single-

when it was substituted by a S-*p*-nitrobenzylxanthate moiety (pentXNB). We also studied the conformational information obtained from MD simulations is compared to experimental data.

METHODOLOGY

MD simulations of the D-glucopyranosyl penta- and monosaccharide

MD simulations of the pentasaccharide and monosaccharide were carried out under periodic boundary conditions (NPT) at 298 K and 1 atm, using a cube cell of $31.5 \times 31.5 \times 31.5\,\text{Å}^3$ (915 water molecules) and $25 \times 25 \times 25\,\text{Å}^3$ (500 water molecules), respectively. All the MD simulations were performed using the program NAMD,[13] the CHARMM27 force field,[14] periodic boundary conditions, and particle-mesh Ewald (PME) full electrostatics.[15] The latter was computed over $31 \times 31 \times 31$ grid.

The simulations included several cycles of energy minimization and short molecular dynamics of 25 psec, to relax the system. Then 1 nsec molecular dynamics was carried out. The trajectory during this period was quite stable after 200 psec of simulation. The radial distribution functions (RDF) were calculated with a VMD tcl script.

MD simulations of the pentasaccharide *p*-nitrobenzylxanthate (pentXNB)

The parametrization of pentXNB was done adapting the CHARMM27 bond parameter set to the topology of *p*-nitrobenzylxanthate. The partial atomic charges were calculated using the approach implemented in the RESP program,[16] at the HF/6-31G** level using Gaussian 98 package.[17]

Conformational analysis of the pentamer substituted at the position O_2 of the central glucopyranose ring with a S-*p*-nitrobenzylxanthate group (pentXNB) was performed using InsightII and Discover, with the force field CVFF. The lowest energy conformation was used as initial conformation for the molecular dynamics simulations.

The MD simulations of pentXNB were carried out under NPT and periodic boundary conditions at 298 K and 1 atm, in explicit solvent simulation, in a water cubic cell of $45 \times 45 \times 45 \text{ Å}^3$ (3846 water molecules). Force Field CHARMM27 with no additional constraints was used for the calculations. A molecular dynamics of 5 nsec was carried out for this system. RDFs were calculated with a tcl script for VMD.

RESULTS AND DISCUSSION

Dynamics of the pentasaccharide

The structure of the solvent shell around the solute is determined by the interaction of the solute–solvent sites. In the case of the pentamer in water, these sites are primarily oxygens and hydroxyl protons which can serve as acceptors and donors, respectively, readily forming hydrogen bonds with water molecules. The O_{sugar}–O_{water} RDF for the O_2 of the central ring of the pentamer (Fig. 1)
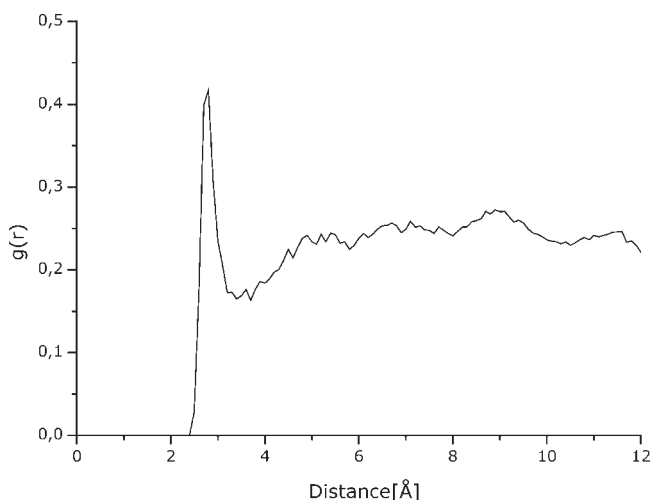
Figure 1. O_{sugar}–O_{water} RDF of O_2 of the central unit of the pentamer. MD simulations of 1 nsec were carried out in an NPT ensemble at 1 atm and 298 K
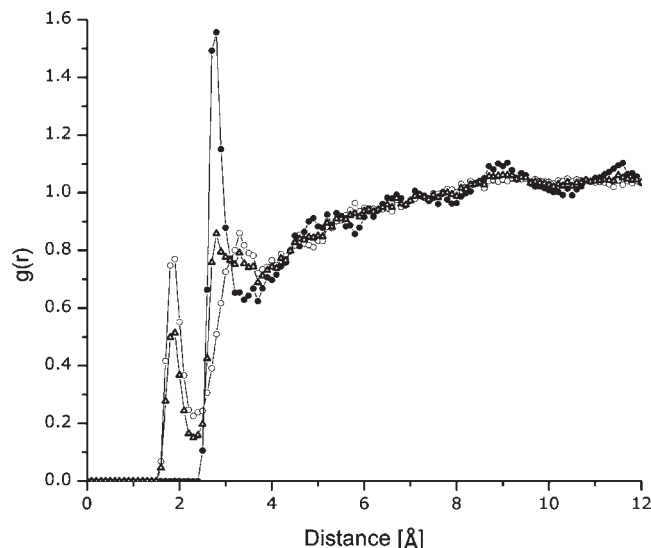
Figure 2. RDF of the hydroxyl group of C_2 of the central unit of the pentamer; (●) O_{sugar}–O_{water}; (▲) O_{sugar}–H_{water}; (○), O_{sugar}–H_2O

shows the first peak fairly pronounced at 2.8 Å of the hydroxyl at C_2 followed by not clearly defined broad peaks, as has been found for a series of pentose sugars in solution, that have been assumed to correspond to secondary solvation shells.[6] In Fig. 2, the orientation of the water molecules in the neighborhood of O_2 is due to two kind of hydrogen bonds: O_2 is not only hydrogen-bonded to a water molecule through the hydroxyl-H, but also directly to another water-H, as expected from the strong 3-D hydrogen-bond network of water of the first solvation shell that controls the ordering of water molecules around the saccharide.

When comparing the RDF profiles of the pentamer to a single independent glucopyranose ring, it is observed that for all cases the solvation of O_2 is lower for one independent repetitive unit than for the central unit of the pentamer (Fig. 3). We therefore concluded that the pentamer has a stronger H-bond structure of water around O_2 due to the cooperative effect of the neighboring residues.

Dynamics of the pentasaccharide *p*-nitrobenzyl xanthate (pentXNB)

Conformational analysis can reveal the lowest-energy state although the barriers of interconversion between the states may be small. Calculation of the rotational barriers around the angle C2—O2—C2′(=S2′)—S3′ of the central ring allowed the determination of the global conformational energy minimum of the substituted pentamer (Fig. 4a). The most stable linear conformation is shown in Fig. 4b.

Substitution at O_2 by the *p*-nitrobenzylxanthate moiety resulted in a dramatic decrease of the probability to find a
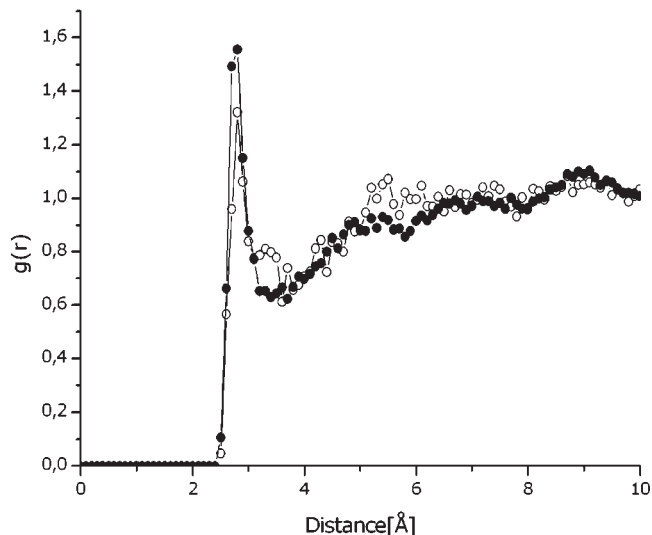
Figure 3. Comparison between the RDFs of the O_2 of the central unit of the pentamer (●) and the O_2 of a single glucopyranose ring (○) with respect to the oxygen of water

water molecule nearby O_2 (Fig. 5). However, both the C2′ and the S2′ of the thiocarbonyl group of the *p*-nitrobenzylxanthate moiety are clearly hydrated compared to the sulfur bridge (S3′) (Fig. 6), suggesting that there could be a nucleophilic attack by water on the carbon with a minimum change of entropy, as has been observed experimentally.[8,9,12]

These results support the proposal that the acceleration of the water-catalyzed reaction of cellulose[8] and amylose[9] xanthate esters, with respect to small analog molecules, is due to the stronger 3-D H-bonded network of the water in the solvation shell induced by the polysaccharide. Also, for the polysaccharide esters, the entropy of activation of the water-catalyzed hydrolysis is zero, while for the small analog molecules it is ca. $-40\,\mathrm{cal\,K^{-1}\,mol^{-1}}$.[12] All known water-catalyzed reactions present these negative values. Our results were interpreted as a consequence of the well-oriented water molecule that acts as a nucleophile in the reaction of the polysaccharide.

The minimum energy conformation in Fig. 4b shows the *p*-nitrobenzyl group folded over the neighboring glucose ring. It has been observed that this kind of
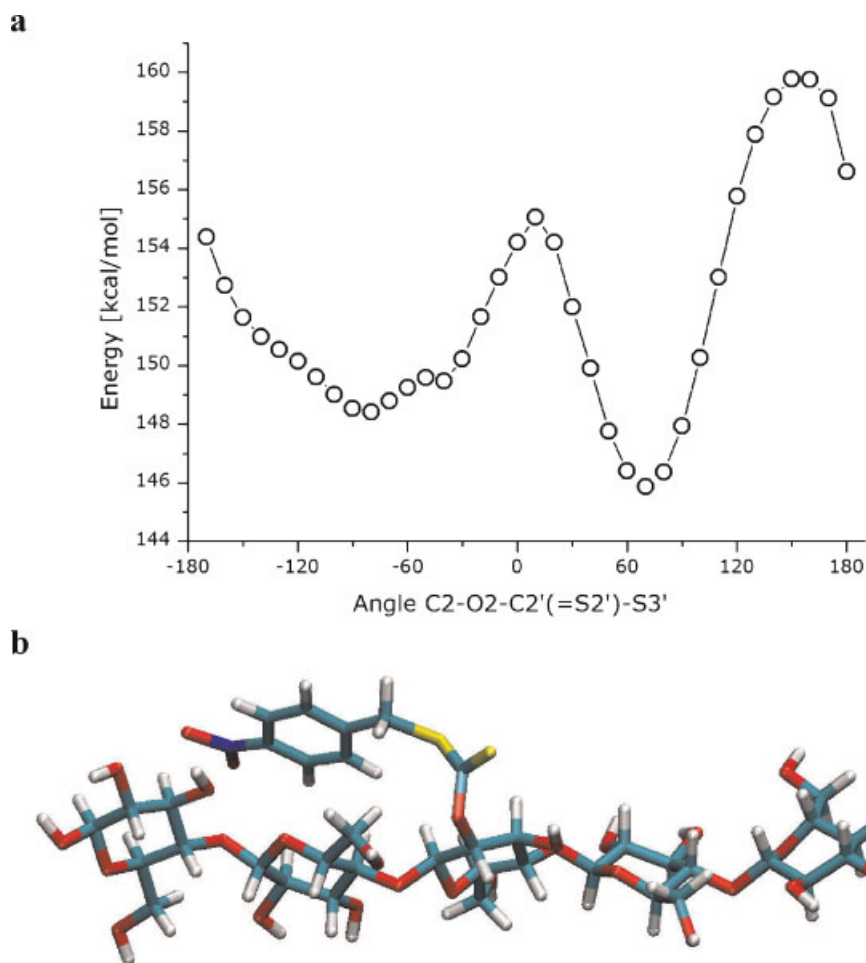

Figure 4. Simulation (NPT) of pentXNB; (a) rotational barriers around the angle C2—O2—C2′(═S2′)—S3′ of the central ring showing the global conformational energy minimum of the substituted pentamer; (b) this conformation is shown
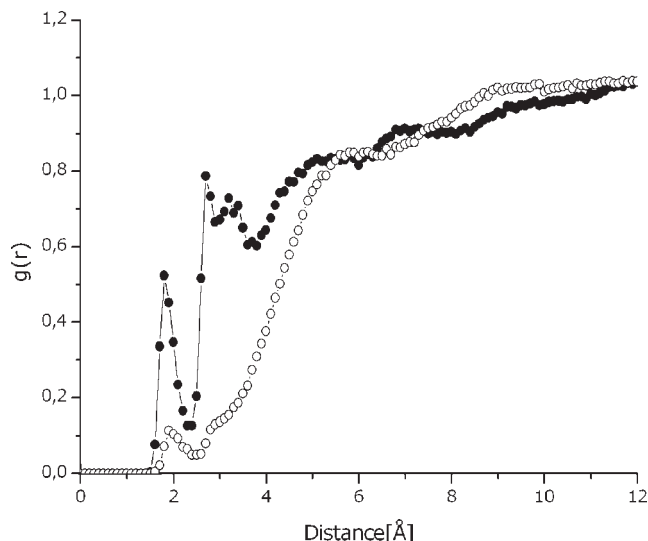
Figure 5. Comparison of the hydration (O_{sugar}–O_{water}) of the O_2 bound to the *p*-nitrobenzylxanthate group of pentXNB ($\bigcirc$) to an equivalent O_2 without substitution ($\bullet$)
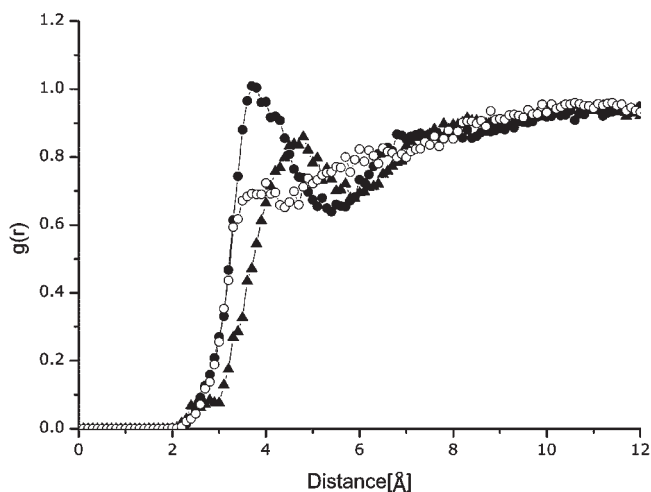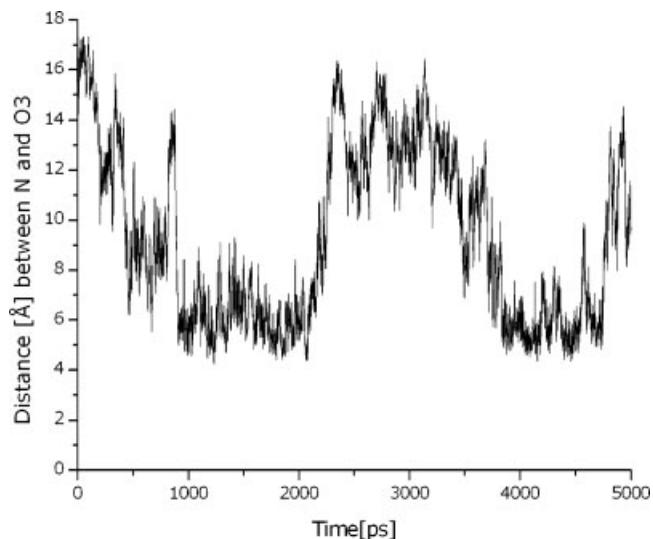

Figure 7. Oscillation of the *p*-nitrobenzylxanthate group along a 5 nsec simulation; one frame corresponds to 1 psec. The distance is between the nitrogen and oxygen O_3 of ring 1

Figure 6. Hydration of the thiocarbonyl group of the *p*-nitrobenzylxanthate moiety. Thiocarbonyl (C2′=S2′): ▲, C2′; ●, S2′; bridge sulfur: ○, S3′

interactions, stacking like, between aromatics and saccharides, might be more important than hydrogen-bonding interactions with respect to the dynamic behavior of carbohydrates.[18] Flexible glycophanes adopt a folded conformation in water as a result of intramolecular interactions between a glucose moiety and a phenyl ring. Water is necessary for this hydrophobic collapse because it is not observed in methanol or DMSO.[19] Glucocalixarenes preferentially bind to guests having an anionic headgroup and an aromatic tail. The observed selectivity order suggests that, in addition to hydrogen bonding, sugar-aromatic interactions might be capable of stabilizing the complexes.[20]

In our case, the simulations show that the XNB group oscillates between a maximum distance of 17.3 Å (Fig. 7,

$t = 103$ psec) between the nitrogen and the O_3 of ring 1 and a minimum of 4.2 Å (Fig. 7, $t = 1232$ psec). The simulations shown in Fig. 7 indicate that the oscillation occurs in periods of ca. 3000 psec with minimum distances between the nitrogen and the O_3 of rings 1 and 5. The oscillation might be a consequence of the influence of water on the population distribution and the dynamics of the conformational states of pentXNB.[21]

The minimum distance of the nitrogen and the oxygen was 4.2 Å. Considering the bond lengths N=O (1.19 Å) and O—H (0.96 Å), the distance of the $O_{N=O}$ and the H_{OH} was 2.05 Å, close to the water hydrogen bond length. Therefore, it is possible that the hydrophobic interaction of the phenyl group is competing with the electrostatic interaction of the nitro group.[22]

The conformations at $t = 28$ and 403 psec are shown in Fig. 8. The time required for an oscillation is sufficiently long to allow the restructuring of water around the thiocarbonyl group that would be about two orders of magnitude faster. Reorientation of water in the solvation shell of ions occurs with mean lifetimes of 12–25[1] and 10–45 psec for disaccharides.[5a] Indeed, considering the central substituted ring, the number of water molecules within a 5 Å shell, in the last nanosecond of the simulation, changes in the range of 31–37 molecules. Therefore, the reorientation motion of the water molecules is fast enough as to maintain the hydration shell of the thiocarbonyl group.

CONCLUSIONS

The pentasaccharide of D-glucopyranoside residues connected by (1→4)-β glycosidic linkages shows a well-defined first solvation shell followed by several secondary
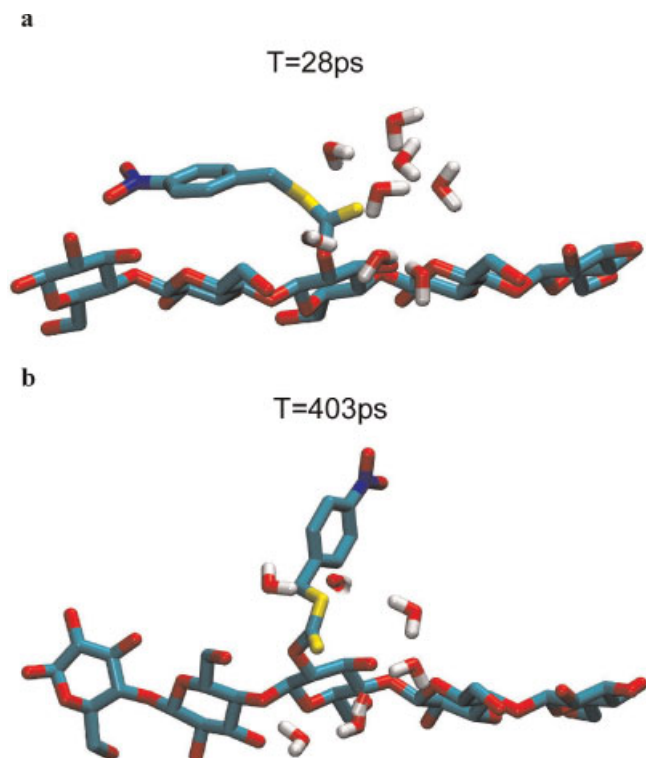
Figure 8. Oscillation of the *p*-nitrobenzylxanthate group; (a) close to ring 5 ($t = 28$ psec); (b) orthogonal to backbone ($t = 403$ psec)

shells. The pentamer shows a stronger H-bonded structure of water than a single glucopyranose ring due to the cooperative effect of the neighboring residues.

Substitution of O_2 of the central ring of the pentamer by a *p*-nitrobenzyl xanthate moiety (pentXNB) produced a strong decrease in the hydration of the O_2, but the carbon and the sulfur of the thiocarbonyl group were clearly more hydrated compared to the sulfur bridge.

The *p*-nitrobenzylxanthate group folds over the saccharide backbone, but the XNB group periodically oscillates over the pentamer at a rate that allowed the restructuring of water around the thiocarbonyl group.

The results are consistent with the interpretation that the acceleration of the water-catalyzed hydrolyses of substituted polysaccharides compared to the monosaccharides is due to the strong structuration imposed by the polysaccharide that increases the 3-D hydrogen-bond network on the surrounding associated solvent.

Acknowledgements

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