Molecular dynamics, molecular mechanics and DFT modeling of the conformational properties of spin-labeled chitosan in water

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Modification of polysaccharide chitosan by stable nitroxide radicals provides biomaterial with many useful biological properties [1]. In this report we consider conformational dynamics of spin-labeled chitosan in water that has been systematically explored using microscopic force-field (FF) molecular dynamics (MD) simulations, FF molecular mechanics, and density functional theory (DFT) calculations with implicit water model [2]. The low-molecular-weight chitosan oligomers of 2–6 D-glucosamine (GA) subunits, and two stable nitroxide radicals – 2,2,6,6-tetramethylpiperidine-1-oxide (TEMPO) and 2,2,5,5-tetramethylpyrroline-1-oxide [1] were considered.

Eight conformers in total for rotation about the β(1→4) glycosidic bond were found for the GA–GA dimer from the MM-FF and DFT calculations. Populations of the conformers were accessed from MD simulations at T=300K in the periodic box with explicit TIP3P water molecules. The bent structures with the shape of left and right helix with a small helix pitch were formed upon elongation of chitosan chain. The gas-phase calculations predict greater stability of the bent conformations whereas calculations with inclusion of solute–solvent interactions give a linear structure of polysaccharide in water. The found activation barriers for rotations around the glycosidic bond show that transitions between the bent structures only occur via the linear conformation of chitosan. This was supported by 50-ns MD simulations of chitosan hexamers. The free energies of transition states ~26–28 kJ mol^{-1} from the DFT results agree with the lifetimes of the chitosan conformers in MD simulations. According to the MD calculations, the nitroxide substituents do not form intra-molecular hydrogen bonds with saccharide rings in water. Nitroxide moieties enhance the variety of visited conformational states of neutral and protonated monosubstituted chitosan chains, but the linear conformation remains most populated. Overall, the polar environment has strong influence on the stability of chitosan rotamers.

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