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RESEARCH

Molecular dynamics investigations of the polysaccharide scleroglucan: first study on the triple helix structure

Antonio Palleschi,[a,*] Gianfranco Bocchinfuso,[a]
Tommasina Coviello[b] and Franco Alhaique[b]

[a]Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma 'Tor Vergata', Via della Ricerca Scientifica, 00133 Roma, Italy
[b]Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università di Roma 'La Sapienza',
P.le Aldo Moro 5, 00185 Roma, Italy

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Abstract—Explicit solvent molecular dynamics (MD) simulations on the triple helix of the polysaccharide Scleroglucan (Sclg) at two temperatures (273 and 300 K) were carried out. Owing to the complexity of the system, a united-atom force field, based on the properly modified GROMACS parameters, was adopted. To test these parameters for our system, MD simulations of the two disaccharidic units, representing the main chain and the side-chain linkages of the Sclg repeating unit, were performed and the results were compared with the literature data. The simulated triple helix of Sclg retained the main experimentally determined features of the polymer. The residence times of the solvent molecules at 273 and 300 K were analyzed. The results show that the more internal water molecules, interacting with the core of the Sclg triplex are not influenced substantially by changing the temperature, on the contrary the water molecules, interacting with the side-chain glucose residues show more significant differences. These data suggest that the more external water molecules, interacting with the side chain, play a major role in the conformational transition experimentally observed at low temperature.

Keywords: Carbohydrate; Scleroglucan; Glucan; Modeling; Gentiobiose; Laminarabiose

1. Introduction

Scleroglucan (Sclg), a polysaccharide secreted by fungi of the genus *Sclerotium*, has a backbone build up by (1→3)-linked β-D-glc*p* units with single glc*p* side chains linked β-(1→6) to every third residue in the main chain (Fig. 1). Sclg exhibits a triple helix conformation (triplex) both in aqueous solution and in the solid state. Solid state (fiber) diffraction reveals a triple helical core sustained by a network of interchain H-bonds among the hydroxyl groups linked to the C-2 atoms of the glucose units of the backbone (O-2(A), O-2(B), and O-2(C) in Fig. 2); the strands are aligned parallel and the side chains are directed away from the helix core.[1,2] Due to its special properties, Sclg has been successfully used for various applications (secondary oil recovery, ceramic glazes, food, paints, cosmetics, etc.).[3] Furthermore, as we have shown in previous papers, the polymer can be used in the formulation of monolithic swellable matrices for modified drug delivery.[4,5] More recently, by addition of borax to a Sclg solution, we have obtained a new hydrogel that, in the form of tablets, is capable of remarkable asymmetric swelling.[6]

Some years ago, we proposed a force field suitable for studying peptides, glycopeptides and carbohydrates making use of energy minimization calculations.[7–9] Using this approach, we have proposed different possible configurations in which three Sclg triplexes arrange to form a channel suitable to contain different drug molecules. We propose that the anomalous swelling of the

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* Corresponding author. Tel.: +39 6 72594466; fax: +39 6 72594328; e-mail: antonio.palleschi@uniroma2.it

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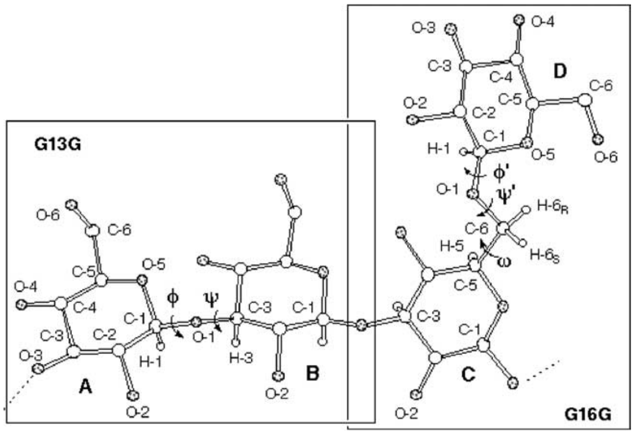

Figure 1. Sclg repeating unit consisting of three β-(13)-D-glucopyranose residues (A–C) with one branched β-(1→6)-D-glucopyranose (D). The torsional angles ϕ and ψ refer to the linear backbone; ϕ', ψ' and ω are the torsional angles relative to the side chain. G13G and G16G correspond to the two disaccharides characterizing the repeating unit, and are known as β-laminarabiose and β-gentiobiose, respectively. For the sake of clarity, only the hydrogen atoms necessary to define the torsional angles are shown. Oxygen atoms are dotted.

array of Sclg chains, observed when a borax group is added, is due to altered stability of the array structure. In addition, we propose that the release properties for different drug molecules are related to different mobilities through these channels.

Since energy minimization techniques do not provide quantitative data to compare with release experiments, we have undertaken studies with molecular dynamics. Our long-term goal is to perform simulations in which different molecules will be pulled through the channels to simulate drug release.

Because of the very large number of atoms in these system of channels, along with a correspondingly large number of water molecules, we have elected to use a so-called united atoms force field (FFGMX in the GROMACS software package).[10,11] This reduces the required computer time by nearly an order of magnitude.[12] Some modifications have been introduced in the original FFGMX parameters in order to better reproduce the structural features of carbohydrates. Validation of our modifications is emphasized by the reproducibility with previously determined O-6 orientations (*gauche* effect[13–16]) and the *exo*-anomeric effect[17] through studies of the disaccharides laminarabiose,[18–21] β-D-Glc*p*-(1→3)-β-D-Glc*p* (G13G), and gentiobiose,[14,22,23] β-D-Glc*p*-(1→6)-β-D-Glc*p* (G16G), that mimic the glycosidic linkages of the backbone and the side chain, respectively, of the Sclg repeating unit (Fig. 1). We analyzed the behavior of water molecules around the disaccharides and the triplex models, as well as the ω torsional angle transitions in G16G and triplex, both involved in a cooperative transition occurring at about 280 K as underlined by Teramoto and co-workers.[24,25] In addition, the same authors underlined that this transition is strongly depending on the molecular weight.

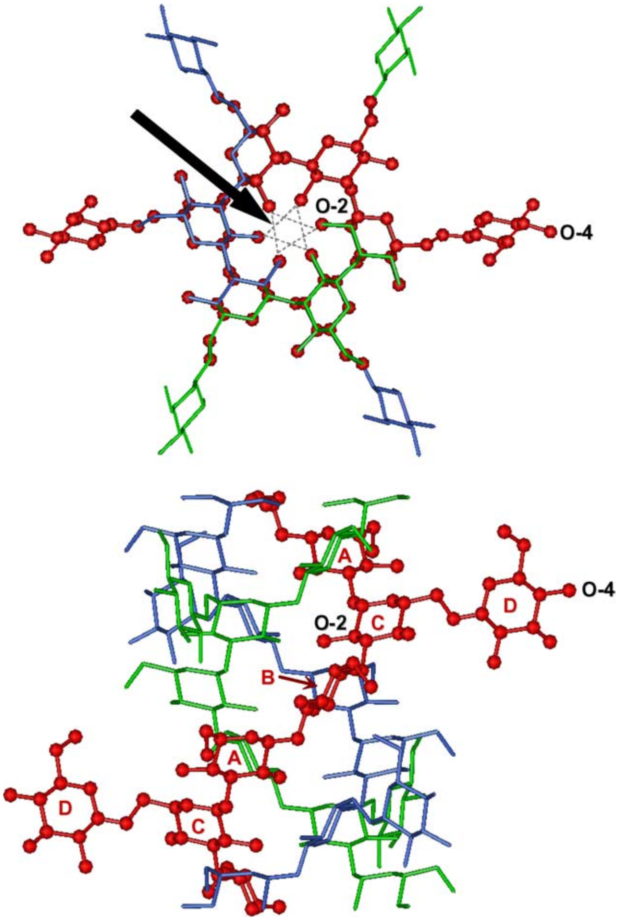

Figure 2. (top) Top view of a fragment of the triple helix of the Sclg. The triple helix is stabilized by inter-chain hydrogen bonds in which each backbone O-2 hydroxyl serves as donor and acceptor to link it to O-2 hydroxyl of a backbone glucose residue in each of the other two chains of the helix. The arrow indicates the network of hydrogen bonds that links the three strands of the triplex. (bottom) Side view of the same triple helix. For the sake of clarity, only one strand is evidenced.

2. Experimental

2.1. Molecular dynamics settings

According to FFGMX, the CH and CH_2 groups were considered as united atoms, and the hydrogen atoms of the hydroxyl groups were explicitly introduced; the tetrahedral geometry of carbon atoms was maintained by means of improper torsional potentials. The dynamic trajectories were performed using GROMACS software package and analyzed by means of the standard routines of GROMACS and a home-made software. The torsional angles were defined according to IUPAC[26] starting from related angles when the H atoms are lacking. In particular, ϕ, defined as [H-1(A)–C-1(A)–O-1(A)–C-3(B)],