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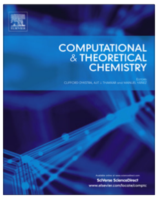

DFT and MP2 conformational study of 3,6-anhydro-α-D-galactose in gas phase and in aqueous solvent

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ABSTRACT

Density functional and MP2 calculations have been carried out on 3,6-anhydro-α-D-galactose, one of the monosaccharides constituting carrageenans. In order to determine the impact of the orientations of the hydroxyl groups on the energy landscape, we generated three isoenergetic maps using B3LYP/6-31G(d) first in the gas phase and then in aqueous medium using two models to simulate the solvent effect; the Onsager and the polarized continuum models. In order to test the effect of the influence of the diffuse function, we decided to produce two others isoenergetic maps using B3LYP/6-31+G(d) level, first in the gas phase and the second in the implicit solvent using the PCM model. The obtained lower energy conformers were then fully optimized using B3LYP, B3PW91 and MP2 with different basis sets. The results are then compared with those reported in previous works using molecular mechanics or dynamics calculations.

1. Introduction

Carrageenans are sulfated galactans extracted from red seaweeds; they are used in food industry as thickeners and gelling agents [1]. Their repeating disaccharide [→4)-α-d-Galp-(l→3)-β-d-Galp(l→] is usually sulfated in different positions and often, the α-d-galactose unit is replaced by an 3,6-anhydro-α-d-galactose [2]. In a global way, substituted or non-substituted monosaccharide units are joined by alternating α(1→3) and β(1→4) linkages to form carrageenans [3–5]. The physical properties of these polysaccharides depend on their conformations and mostly on the intrinsic flexibility of the glycosidic linkages [1]. Galactose saccharide is an important component in many biological systems and has been subject of many investigations [6,7]. In contrast, very little work has focused on the rather rigid sugar 3,6-anhydro-α-d-galactose so far, although the latter is a key constituent of some seaweed polysaccharides and carrageenans particularly [8–10]. Yet, it is also widely used in carbohydrate chemistry to selectively modify sugar residues [11–13], and the importance of its configuration in polysaccharides was recognized in the last decade [14–17]. Early works were mostly performed using molecular mechanics [17,19–24] or normal mode calculations [25–27]. However, more recently, QM methods have become increasingly used in this field and more particularly when it comes to studying structural properties of carbohydrates [18,19,28–39]. A common observation emerged and allowed to state that the role of the choice of basis sets is crucial since relative energies and conformations obtained with a large basis set are not necessarily similar to those obtained with a smaller basis set [7], and this leads in some cases to significant errors [33]. For example, for glucose and its epimers, substantial differences in relative energies obtained from different basis set on the same geometry of have been reported [40,41], the inclusion of the diffuse functions have been found to be very important [42]. This was confirmed by a number of studies using the B3LYP/6-311++G∗∗ level of theory and dealing with carbohydrates [7,40,53–55].

In a previous theoretical work, the orientations of the hydroxymethyl and their impact on the total electronic energy were reported [56]. While the conformational preferences of d-galactose and its derivatives were explored experimentally by ^{1}H NMR spectroscopy [40,43–46] and X-ray diffraction [46–52]. It was concluded that the pyranose ring occurs mainly in a $^4C_1$ chair configuration in crystals except in the case of an unusually constrained analog which confirms a $^0S_2$ skew-boat configuration [46].

In an earlier review [5], it has been pointed out that the molecular mechanics MM3 [4,57,58] force field is also very useful to determine structures of carbohydrates, because it includes a term that accounts for the directionality of hydrogen bonds.

The most important goal of the present paper is to consider the effect of the variations of the hydroxyl groups orientations on the total energy of the 3,6-anhydro-α-d-galactose unit (Fig. 1) in two

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middle; the gas phase and in presence of implicit water solvent and this by using *ab initio* quantum chemistry methods including the second order perturbation Moller-Plesset method (MP2) as well as two density functional methods namely B3LYP and B3PW91. The strategy consisted in varying the orientations of the three hydroxyl groups confined in related dihedral angles $\chi_n = H_{(n)}–C_n–O_n–H_{(On)}$. For this aim, relaxed isoenergetic maps were performed following the same methodology employed in previous papers on κ-carrabiose [59], κ- and ι-neocarrabiose [60] and β-D- neocarrabiose [61]. Calculations were first carried out using B3LYP/6-31G(d) level of theory [19] in the gas phase and in water implicit solvent. In this step, two models were used to simulate the implicit solvent; the Onsager model [62] and the polarized continuum model (PCM) model [63] which differ from each other in the definition of the solute cavity. Then, to measure in which extend the addition of a diffuse function to the basis set could be important, two additional isoenergetic maps were performed using B3LYP/6-31+G(d) level, in the gas phase and taking into account the presence of an implicit solvent using the PCM model.

For all cases, the lower energy conformers determined from the isoenergetic maps, were further fully optimized at either at B3LYP/6-31G(d), B3LYP/6-31+G(d), B3LYP/6-311++G(d,p), B3PW91/6-31G(d), B3PW91/6-31+G(d), B3PW91/6-311++G(d,p) or MP2/6-31G(d) levels.

2. Computational details, starting structures and nomenclatures

All calculations were performed with Gaussian 03 program (version 6.0, revision B.03) [64], results were explored using Gaussview software and all maps were plotted using Surfer software [65]. Optimizations were considered satisfactory using the tight condition (RMS force criterion of $1 * 10^{-5}$). Frequency calculations were performed for the fully relaxed conformations to confirm the absence of imaginary frequencies.

The orientations of the hydroxyl groups were varied by performing relaxed isoenergetic maps, each involving two dihedral angles as coordinates, defined as: $\chi_n = H(n)–Cn–On–H_{(O)n)}$ (Fig. 1). Three cases were considered: a – variations of χ_2 and χ_1, b – variations of χ_4 and χ_1 and c – variations of χ_4 and χ_2. The initial structure of 3,6-anhydro-α-d-galactose unit was extracted from that of β-neocarrabiose monohydrate determined by a combined use of X-ray diffraction, NMR spectroscopy and molecular mechanics calculations [66], the β-galactopyranosyl as well as the water molecule were removed; the former was replaced by an hydrogen atom. The monosaccharide obtained in that way have been then fully optimized at B3LYP/6-31G(d) level. The resulting structure is characterized by the following values: (χ_2, χ_1) = (50°, −65°), (χ_4, χ_1) = (159°, −65°) and (χ_4, χ_2) = (159°, 50°) exhibiting a GgT configuration of the exocyclic groups. These structures were respectively used as starting geometries to perform the three isoenergetic maps [60,67]. Each map was obtained by incrementing the two dihedral angles χ_n by 20°, their values being fixed while optimizing all other degrees of freedom [59,60]. This procedure generated a total of 324 conformations for each map. Once the maps drawn, the minima were identified and the lower energy conformers were further optimized using different levels of theory. It is to note that the 3,6-anhydro-α-d-galactose monosaccharide has a chair $^1C_4$ configuration, as reported in previous papers [1,61].

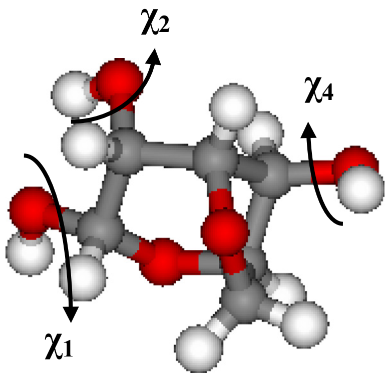

Fig. 1. Structure of 3,6-anhydro-α-D-galactose, dihedral angles χ_1, χ_2 and χ_4 around the exocyclic angles of the hydroxyls groups.

The same methodology was used when dealing with the saccharide in presence of implicit water [59,60]. Two solvent models were tested: the Onsager model [19] and the polarized continuum model (PCM) [63,68,69]. After full optimization of the starting geometry in presence of implicit solvent, using the Onsager model, the obtained values of (χ_2, χ_1), (χ_4, χ_1) and (χ_4, χ_2) were (48°, −61°), (159°, −61°) and (159°, 48°) respectively, while the PCM model yielded after optimizations (61°, −45°), (158°, −45°) and (158°, 61°) for the quoted couples of dihedrals respectively. These latter differ from the formers which are very close to those obtained for the gas phase.

The orientations of hydroxyl hydrogen [70] designated in this work by the dihedral angle χ_n, defined as: H(n)–Cn–On–H(O)n, (Fig. 1). Their corresponding values are described by an one-letter code [71] S for angles between −30° and +30°, g between 30 and 80°, p between 80 and 100°, e between 100 and 150°, T for angles with absolute values larger than 150°, G for angles between −30° and −80°, and E for angles between −80° and −150°.

The aim is mainly to explore and identify conformational space conformations corresponding to the lower energies, taking into account geometrical parameters, characterized in that the dihedral angles and the different orientations of the hydroxyl groups present in the structures of our compound.

3. Results and discussion

3.1. (χ_2, χ_1), (χ_4, χ_1) and (χ_4, χ_2) adiabatic maps in gas phase

The three relaxed energetic maps using B3LYP/6-31G(d) and a 18 × 18 grid corresponding to the couples (χ_2, χ_1), (χ_4, χ_1) and (χ_4, χ_2) are shown in Figs. 2a, 3a and 4a, with the contour line values drawn in kcal/mol with respect to the lowest energy point. In the first map in Fig. 2a, there are three minima, designated as A_1-g, A_2-g and A_3-g according to their (χ_2, χ_1) values: A_1-g at (−90°, −105°), A_2-g at (30°, 154°) and A_3-g at (170°, 154°). Their relative energies are 0.0, 0.76 and 0.79 kcal·mol^{-1}. In the second map in Fig. 3a, two minima are found and designated B_1-g and B_2-g according to their (χ_4, χ_1) values: B_1-g at (59°, −85°) and B_2-g at (159°, −165°). Their relative energies are 0.00 and 0.30 kcal·mol^{-1}. In the third map in Fig. 4a, three minima C_1-g, C_2-g and C_3-g are found at the following (χ_4, χ_2) values: C_1-g at (159°, −90°), C_2-g at (59°, −90°) and C_3-g at (−41°, −90°) and their relative energies are 0.00, 0.31 and 0.85 kcal·mol^{-1} (Table 1). Since hydrogen bonding constitutes a significant factor to the energy [37], we checked for the occurrence of hydrogen bonds and found that all the minima, in each case are free of any H-bond (supplementary data, Fig. S1).

The distances used to determine that there was no hydrogen bond are given on Table 1S (in Supplementary data).

The dihedral angles of the secondary exocyclic hydroxyl groups (χ_1, χ_2 and χ_4) adopt different configurations. They have EET, TST and TTT configurations in the minima A_1-g, A_2-g and A_3-g; EEg and EGT configurations in B_1-g and B_2-g, and GET, GEg and GEG configuration in the minima C_1-g, C_2-g and C_3-g. All the hydroxyl groups have clockwise orientations in the minimum A_1-g, while the