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Conformational search and spectroscopic analysis of *bis*-β-D-glucopyranosyl azacrown derivative

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ABSTRACT

1,10-N,*N*′-bis-(β-D-ureidoglucopyranosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane is a new, recently synthesized compound, which exhibits complexation ability towards drugs. In the present study various theoretical methods, including molecular mechanics, computer simulations, semiempirical and DFT calculations, are applied to find the lowest energy conformers of this molecule in vacuo and in aqueous solution. For the most stable structures the vibrational frequencies as well as the C and H chemical shifts were computed. Along with the theoretical investigation the IR in the KBr discs and the NMR spectra in water and in pyridine were experimentally recorded. It is shown that in the lowest energy structures the two glucosyl units are placed on the same side of the diazacrown ring with their mutual orientations favoring formation of hydrogen bonds. The "open" structure, in which no such hydrogen bonds can be formed, is found to have much higher energy. The computed and measured IR spectra and NMR chemical shifts are compared and discussed in detail. The most stable structures are analyzed with respect to the possible mechanism of complexation of drugs.

1. Introduction

The history of crown ethers dates back to the interwar period of the 20th century, when Lüttringhaus and Ziegler attempted to create large ring molecules possessing donor groups able to bind a cation. Although the new compounds did not exhibit any affinity to cations, the publication[1] from 1937 is appreciated as the first report on synthesis of such macrocyclic molecules. Some progress has been achieved about 30 years later by Pedersen, Cram and Lehn,[2–5] who detected experimentally some complexation ability of crown ethers and in 1987 were awarded jointly the Nobel Prize for this discovery. Their work constitutes the basis for all further developments and achievements in the supramolecular chemistry, and the number of publications reporting various properties of crown ethers is constantly increasing. These molecules are used as chelating agents, surfactants, selective transporters, as well as in chromatography, phase transfer catalysis, and ion recognition; they are also molecular receptors used in biological systems.[6–12] and references therein

The scope of applications of crown ethers can be greatly expanded by their various structural modifications, such as varying the size of the crown or replacing partially oxygens by heteroatoms (N, S, P).[7–12] It was shown that the azacrown ethers exhibit complexation ability towards much wider range of ions than "pure" crown ethers, and that the position of nitrogen has some influence on the selectivity toward a metal ion.[7–10] Another way of modifying/enhancing some properties of crown ethers is to create their derivatives by introducing to these molecules various substituents.

In recent years there has been extensive research on the crown ethers derivatives containing sugar units, either as a part of the crown or as its substituents.[11,13–15] and references therein. A very specific type of saccharides derivatives of crown ethers was synthesized by Marsura, Porwanski and Kryczka,[16–19] in which the saccharide units are linked to the diazacrown ethers via the urea bridges. It was also determined experimentally that such compounds can form the host-guest complexes with busulfan, aspirin and paracetamol,[16,17] thus may find potential applications as drugs carriers. In our very recent work we made an attempt to get deeper insight into properties of one of these macrocycles, namely 1,10-N,*N*′-bis-(β-D-ureidocellobiosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane, and its complex with aspirin.[20] Along with experimental measurement we applied computational methods, which are a powerful tool for reproducing molecular properties

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and, what more important, can provide data inaccessible experimentally. In that preliminary work some disagreement between the computed and measured data was observed, which clearly indicates that more extended theoretical study of the structural properties of such compounds are needed.

In the present article we continue investigation of these interesting molecules. One of the major problems faced by experimentalists is the difficulty to obtain good quality crystals for X-ray measurements. In such a situation theoretical methods are the unique way to gain insight into the energetically preferred structures. However, their configurational space is very vast, therefore we start with a smaller macrocycle synthesized in ref. 17, namely 1,10-N,*N*′-bis-(β-D-ureidoglucopyranosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane (Fig. 1). This molecule contains two glucose substituents instead of cellobiose units, thus has much smaller number of possible conformers resulting from rotations of its various fragments around single bonds.

The aim of this study is to increase knowledge about this new molecule and, by investigating a large number of low energy structures, to indicate the possible ground state conformer. This is a first and very important step that must be accomplished before conducting further theoretical studies on the complexes of this macromolecule with drugs, which are the main, final goal of this project. The ground state structure not only constitutes a very good starting point for creation of models of such complexes, but also allows to estimate the lowest limit of the complexation energy that is an essential information about stability of the system.

In the present work the conformational space of the macrocycle was explored in vacuo and in water (described by an implicit solvent model) using various theoretical methods, such as molecular mechanics, semiempirical calculations and the density functional theory (DFT). For the lowest energy structures the NMR and IR spectra are analyzed and compared to experimental data available. We show that each of the methods points toward a different conformer as the most stable geometry. The energy differences between the lowest energy structures are also compared. Additionally, the most stable conformers found from the DFT calculations are analyzed with respect to the possible mechanism of formation of their complexes with drugs.

2. Results and discussion

As described in detail in Section 4.2, the conformational space of the macrocycle was explored by using sequentially several different theoretical methods, including structure optimization at the semiempirical (PM6 and PM7) and DFT (B3LYP-GD2) theory levels, followed by the single point B3LYP-GD3, B3LYP-DCP and M06-GD3 calculations. First we briefly comment on the relative energy differences ΔE with respect to the most stable conformer obtained with different methods.

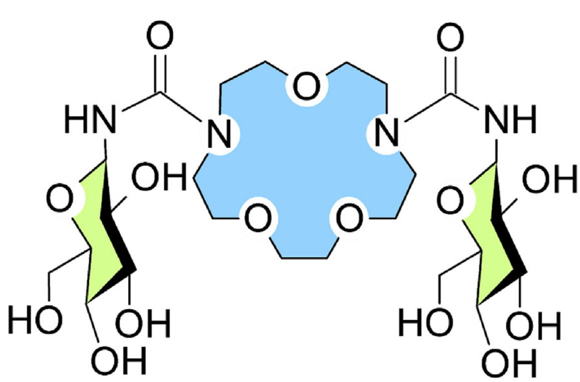

Fig. 1. Molecule studied 1,10- *N*,*N*′-bis-(β-D-ureidoglucopyranosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane. The glucose units and azacrown ring are highlighted blue and green and blue, respectively.

The range of the PM6 and PM7 ΔE values in each set of 50 conformers selected from semiempirical calculations is relatively narrow, within several kilocalories per mol (Fig. S2 in the Electronic Supplementary Information (ESI) to the present article). The corresponding values obtained from the B3LYP-GD2 optimizations are much more differentiated and cover a wider range, reaching up to 50 kcal/mol. There is also no correspondence between the trends observed in the PM6, PM7 and DFT results, although generally the PM7 ΔE values appear to deviate from B3LYP-GD2 less than PM6. However, the most stable structure found with the B3LYP-GD2 method in water is among those selected with the PM6 method (conformer 38 in Fig. S2c). Our further cross-check (reoptimization of 5 lowest B3LYP-GD2 energy conformers in different environment) proved that this structure is also the most stable in vacuo.

In Fig. 2 the ΔE energies for 15 lowest energy conformers obtained from the B3LYP-GD2 optimizations in vacuo and in water are compared to the corresponding values from the single point calculations B3LYP-GD3, B3LYP-DCP and M06-GD3, while in Fig. 3 structures of the six lowest energy conformers in vacuo and in water are presented. These can be compared to the conformers indicated by less advanced theoretical methods, which are shown

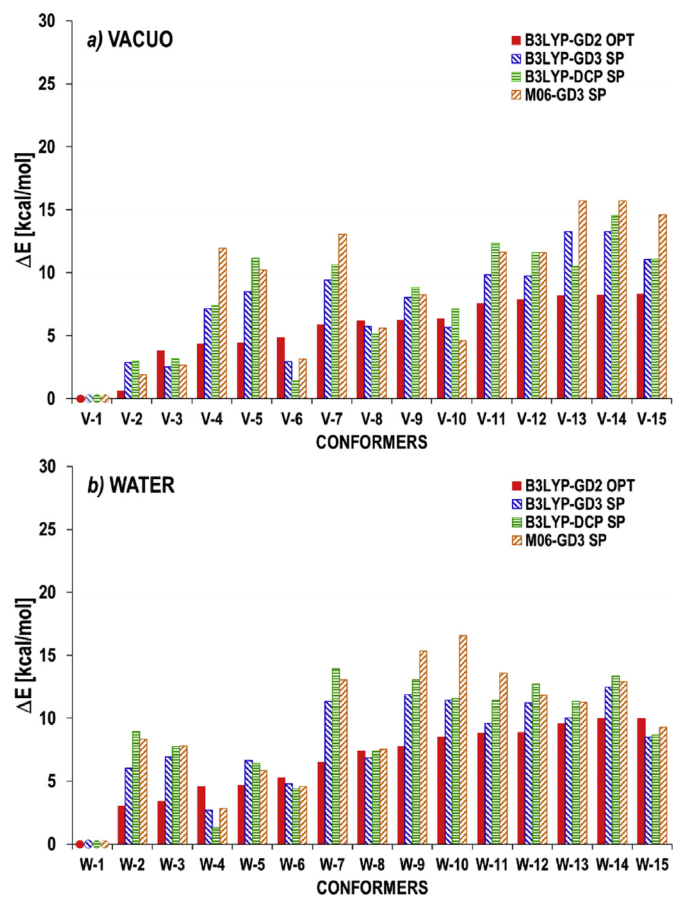

Fig. 2. The relative energy differences $\Delta E = E_{conf} - E_0$ for 15 lowest energy conformers obtained from the B3LYP-GD2 optimizations (OPT) in vacuo and in water (including the cross-check points) and from the corresponding single point (SP) calculations with the B3LYP-GD3, B3LYP-DCP and M06-GD3 functionals. The circles on the horizontal axis indicate the conformers having the lowest energy E_0.