



DFT application in conformational determination of cellobiose



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ABSTRACT

The potential energy of β -cellobiose in water, as a function of the H1'-C1'-O'-C4 (ϕ) and C1'-O'-C4-H4 (ψ) dihedral angles, is investigated using DFT methods and three energy minima (*syn- ϕ /syn- ψ* , *anti- ϕ /syn- ψ* , and *syn- ϕ /anti- ψ*) are identified. It is found that the hydrogen bonding and the H...H repulsion are vital for the energy variation of cellobiose. The geometry structure varies significantly when cellobiose is surrounded by 52 water molecules. NMR chemical shift calculations suggest that the C4 (C1') chemical shifts (δ) are sensitive to the conformational changes, with the values of 80.4 ppm (103.3 ppm) at *syn- ϕ /syn- ψ* , 70.0 ppm (98.9 ppm) at *anti- ϕ /syn- ψ* , and 75.6 ppm (95.3 ppm) at *syn- ϕ /anti- ψ* . The chemical shifts detection of characteristic positions is helpful for the determination of conformations, especially for those with equivalent energies. The chemical shielding tensor analysis shows that for C1', the directions and amplitudes of two shielding components (σ_{22} and σ_{33}) vary distinctly with ϕ and ψ whereas for C4, σ_{33} of C4 remains unchanged, but σ_{22} varies by 13 (26) ppm from *syn- ϕ /syn- ψ* to *anti- ϕ /syn- ψ* (*syn- ϕ /anti- ψ*). The distinctive C4 and C1' chemical shifts at different conformations suggest that they can be useful in (ϕ , ψ) dihedral angle determinations.

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1. Introduction

The conformational flexibility of saccharides is pivotal for the molecular recognition by biological targets, such as lectins, enzymes, and antibodies.^{1–4} Structural determination is crucial for understanding these recognition processes. Conformational analyses of saccharides, especially lactose and cellobiose, have been carried out by using X-ray crystallography,⁵ NMR⁶ (such as NOE,⁷ J -coupling constant,^{8,9} residual dipolar couplings (RDCs),^{10–12} and paramagnetic pseudocontact shifts (PCSs)¹³), and theoretical calculations.^{14–24} The cellobiose or lactose flexibility mainly arises from two dihedral angles ϕ (H1'-C1'-O'-C4) and ψ (C1'-O'-C4-H4), which in principle vary from -180° to 180° (Fig. 1). Theoretical studies have identified three stable conformers for cellobiose or lactose, namely *syn- ϕ /syn- ψ* ($\phi \sim 30^\circ$, $\psi \sim 0^\circ$), *anti- ϕ /syn- ψ* ($\phi \sim 180^\circ$, $\psi \sim 0^\circ$), and *syn- ϕ /anti- ψ* ($\phi \sim 30^\circ$, $\psi \sim 180^\circ$). But it is not clear which conformer is the most stable one, depending on the computational method used.^{18,21–23} NMR studies have suggested that the *syn- ϕ /syn- ψ* conformer is the most stable one in solution.^{7,17,25–27} But the population of the other two states cannot be agreed on and is actively debated. An early work using RDCs combined with molecular dynamics (MD) simulations shows that *syn- ϕ /syn- ψ* is the sole conformation of lactose.¹⁰ But a more recent work using RDCs and

PCSs demonstrates that *syn- ϕ /syn- ψ* only accounts for 75% of total population and the remaining 25% is from *anti- ϕ /syn- ψ* and *syn- ϕ /anti- ψ* .¹³ Similarly for cellobiose, Wildmalm and co-workers concluded that the population of *syn- ϕ /syn- ψ* is about 93%,^{17,25} while Bell and his colleagues suggested that *syn- ϕ /syn- ψ* is the dominant conformation and the flexibility of cellobiose is very limited.¹² All NMR measurables such as RDCs or J -couplings reflect the population average of the quantities with respect to different conformations. Extraction of the population of different states relies on the measurement accuracy and the property of these quantities, specifically their sensitivity to the conformational differences. Apparently, identifying more NMR measurables that are sensitive to carbohydrate conformations will help to determine the population with better accuracy.

The relationship between chemical shifts and structures is well studied in proteins. Theoretical calculations have been successfully performed in both NMR shielding tensors^{28–30} and chemical shifts^{31–35} to explore the structural and environmental effects. The chemical shifts are extremely sensitive to structural changes.³⁶ The accurately predicted ¹³C chemical shifts^{37–39} provide a powerful measure for the protein structure validation. It is likely that a similar correlation between chemical shifts and carbohydrate structures exists as well though such a study has not been carried out systematically.

In this work, we explored the relationship between ¹H, ¹³C chemical shifts, and (ϕ , ψ) dihedral angles of β -cellobiose by using

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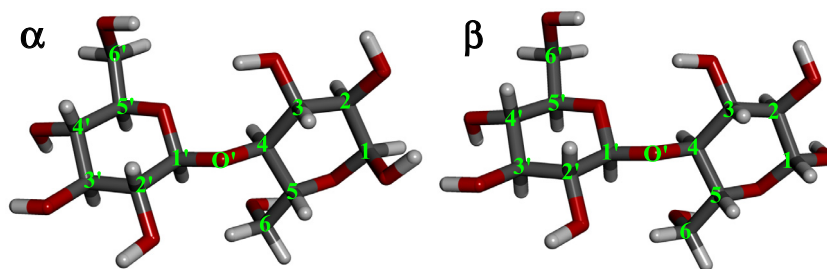


Figure 1. Molecular structure of α - and β -cellobiose with atomic numbering (ϕ : H1'C1'O'C4, ψ : C1'O'C4H4).

quantum mechanics DFT calculations.^{18,40} Our results show that the ^{13}C chemical shifts change considerably with the (ϕ , ψ) dihedral angles, while the variation of ^1H chemical shifts is smaller. The three stable conformers, *syn- ϕ /syn- ψ* , *anti- ϕ /syn- ψ* , and *syn- ϕ /anti- ψ* , have distinctive ^{13}C chemical shifts especially for C1' and C4 which thus can be used to distinguish the glycoside (ϕ , ψ) conformations.

2. Computational methodology

The calculations were performed with the Gaussian 09 program package.⁴¹ The solvation effect was included using the self-consistent reaction field (SCRf) method employing the polarizable continuum model (PCM)⁴² with a dielectric constant of 78.5. The NMR calculations were performed employing the gauge independent atomic orbital (GIAO)^{43,44} approach. Tetramethylsilane (TMS) was used as the reference molecule.

The multi-standard approach (MSTD) has a low dependence on the level of theory employed during the GIAO NMR calculation.⁴⁵ It is employed for the ^{13}C NMR chemical shift (δ_{calc}^x) calculation according to the following equation:

$$\delta_{\text{calc}}^x = \delta_{\text{ref}} - \delta_x + \delta_{\text{ref}} \quad (1)$$

where σ_{ref} and σ_x are the NMR isotropic magnetic shielding values for the reference compound and the corresponding nucleus respectively, computed at the same level of theory, and δ_{ref} is the experimental chemical shift of the reference compound in deuterated chloroform ($\delta_{\text{ref}}(\text{TMS}) = 0$; $\delta_{\text{ref}}(\text{Methanol}) = 50.41$).

To search for the optimum DFT and basis set combination, the ^1H and ^{13}C chemical shifts (δ) of α - and β -cellobiose in the *syn- ϕ /syn- ψ* conformation were calculated using B3LYP,⁴⁶ M062X, and WB97XD functionals at the 6-311+G(d) basis set level, as well as the PW1PW91⁴⁷ method at the 6-311+G(d), 6-311++G(d,p), 6-311++G(3df,3pd), Aug-cc-pVDZ, and Aug-cc-pVTZ basis set levels, after the energy minimization using the same method. The IR spectra are analyzed and the primary hydrogen bond stretching modes are assigned. The potential energy surface and the chemical shifts of cellobiose as the function of ϕ , ψ were determined with an angle interval of 10° at the PW1PW91/Aug-cc-pVDZ level.

The solvent is also explicitly modeled with the cellobiose surrounded by 52 water molecules. The water molecules are added with the O...O distance of 3.0 Å between the terminal hydroxyl (O1 and O4') and water molecule. Other water molecules are filled all around the cellobiose with the length of O...O between water molecules ~ 3.0 Å.

3. Results and discussion

3.1. Optimum DFT method for chemical shift calculations

To find out which DFT functional gives the best predicted chemical shifts for cellobiose at the *syn- ϕ /syn- ψ* conformation, B3LYP, M062X, PW1PW91, and WB97XD methods were tested with the

basis set of 6-311+G(d), and the results are listed in Table 1. The best functional is PW1PW91, with the root mean square deviation of carbon (δ_{CRMSD}) and hydrogen (δ_{HRMSD}) chemical shifts from the experimental values of 2.70 ppm and 0.19 ppm, respectively. The experimental and computational data were also fitted using the linear equation (Fig. S1). The PW1PW91 functional is the best with a correlation coefficient $R^2 = 0.994$ and a slope of 1.026 for ^{13}C chemical shifts and a correlation coefficient $R^2 = 0.898$ and a slope of 1.008 for ^1H chemical shifts.

To identify the optimum basis set, the chemical shift calculations were then performed with the PW1PW91 functional at the 6-311++G(d,p), 6-311++G(3df,3pd), Aug-cc-pVDZ, and Aug-cc-pVTZ levels, respectively. The δ values are collected in Table 2. It can be seen that the smaller basis set yields slightly better accuracy for both Slater and Dunning type basis sets. A similar phenomenon has been observed by Case³⁵ and coworkers when they compared the calculated NMR shielding parameters in peptides. Furthermore, the basis sets of Dunning-type producing chemical shifts agreed better with the experimental values than the Slater-type, which is not surprising because the former describes the core region electron density better. Better results were obtained at the PW1PW91/Aug-cc-pVDZ level, with the δ_{CRMSD} and δ_{HRMSD} values of 1.38 and 0.13 ppm, respectively, in accordance with the linear fitted equations (Fig. S2) between theoretical and experimental δ values.

The ^{13}C NMR signals were also calculated using the multi-standard approach (MSTD)⁴⁵ with the reference molecule of methanol. This method is likely to improve the agreement between the calculated and the experimental data as has been shown by Watts et al.⁴⁸ The δ_{CRMSD} obtained with the MSTD method is 1.25 ppm (Table 2), even better than that obtained at the same level with TMS as the reference molecule (1.38 ppm) while the δ value of hydrogen atom cannot be obtained with the MSTD method. Therefore, all the following calculations of β -cellobiose were carried out at the PW1PW91/Aug-cc-pVDZ level with the reference of TMS molecule.

3.2. Potential energy surface

The 2D potential energy surface (PES) contour of β -cellobiose is shown in Figure 2. Three energy minima are found, centered at the following ϕ/ψ torsion angles: $30^\circ/0^\circ$ (*syn- ϕ /syn- ψ*), $10^\circ/180^\circ$ (*syn- ϕ /anti- ψ*), and $180^\circ/5^\circ$ (*anti- ϕ /syn- ψ*) with *anti- ϕ /syn- ψ* being the lowest energy state. The minimum energy path demonstrates that the conversion from *syn- ϕ /syn- ψ* to the other two is facile owing to their low energy barriers ~ 8.0 kcal/mol (Fig. 2). This characteristic may attribute to the high flexibility of cellobiose. The direct transformation between *syn- ϕ /anti- ψ* and *anti- ϕ /syn- ψ* is obviously more difficult due to its higher barrier (over 20 kcal/mol) located at the ϕ/ψ angle of $120^\circ/-60^\circ$, where atoms O5', C1', O', and C4 are approximately in a plane and the distance between O3 and O5' is too short (1.9 Å). So the transformation between *anti- ϕ /syn- ψ* and *syn- ϕ /anti- ψ* more likely goes through *syn- ϕ /syn- ψ* .

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