Kinetic characteristics of conformational changes in the hexopyranose rings

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ABSTRACT

The shape of the hexopyranose ring is an important factor which can influence the properties of carbohydrate molecules and affect their biological activity. Due to a limited availability of the experimental data, the conformational rearrangements (puckering) which occur within the pyranose rings are studied extensively by using various computational approaches. Contrary to the basic structural and energetic features characterizing the process of ring flexing, the kinetic and dynamics properties of puckering remain less recognized. We performed the first, molecular dynamics-based, systematic calculations aimed at description of the kinetic characteristics of the conformational changes in the rings of α-D- and β-D-glucopyranose molecules. The rate constants representing particular molecular events which comprise the chair–chair inversion are determined and analyzed in the context of the available experimental data. Furthermore, several various variables (e.g. transmission coefficients) and issues (e.g. memorylessness of the puckering process) are investigated and discussed. As several different parameter sets were used during the study (GROMOS 56A6$_{CARBO}$, GLYCAM, GROMOS 53A6$_{GLYC}$), the results provide the conclusion on the capability of the carbohydrate-dedicated force fields to describe the kinetic properties of pyranose ring flexing.

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1. Introduction

The conformational changes which occur in the rings of hexopyranoses are problematic to describe for both experimental and theoretical methods. The experimental estimation of populations of the particular puckers in the aqueous solution is not straightforward and the direct, NMR-derived data, related to the unfunctionalized hexopyranoses, are available only in the two cases of altrose[1] and idose.[2] Therefore, the semi-empirical schemes proposed by Rao[3] and Angyal[4] are often used to distinguish between the free energies of ring inversion characteristic of hexopyranoses of D-series.[5] The limited availability of the experimental data is partially compensated by a relatively large number of theoretical studies aiming at detailed description of the conformational rearrangements in the pyranose ring. There is a growing number of evidence that the ring flexing affect the measurable properties of the carbohydrate polymers (e.g. the radius of gyration[6,7]) and may modulate the carbohydrate biological activity.[7,8] Therefore, development of the

new, more accurate, carbohydrate-dedicated force fields,[5,9–11] proposing the computational approaches designed for studies on the carbohydrate-inherent molecular properties[12,13] and testing the accuracy of the available approaches[14] or force fields[1,11,15,16] became the subject of primary importance.

Equilibrium populations of the particular puckers can be effectively studied by applying numerous methods of enhanced sampling such as metadynamics[14,17] or local-elevation umbrella sampling.[5,12,13] On the contrary, the kinetic and dynamic features of pyranose ring puckering are more enigmatic. Unfortunately, very scarce literature data based on ultrasonic-relaxation spectroscopy are available only for several systems and provide only rough estimation of the timescale at which rearrangements of the ring occur.[18–22] From the perspective of molecular modeling, the main hindrance are high free energy barriers (of order of tens of kJ/mol) which have to be overcome during the conformational rearrangements within the pyranose ring. Only very recently, the dynamics of the rearrangements of the $^4C_1 \leftrightarrow {}^1C_4$ type has been described by using the transition path sampling approach.[23] (See Fig. 1 for definition of the ring conformers.) Furthermore, in the recent years Almond and coworkers have employed the GPU-based hardware to perform exceptionally long, unbiased molecular dynamics (MD) simulations which eventually allow for reaching the state of dynamic equilibrium between puckers.[7,8,24,25] The estimation of the average residence times can be interpreted in terms of the forward and backward rate
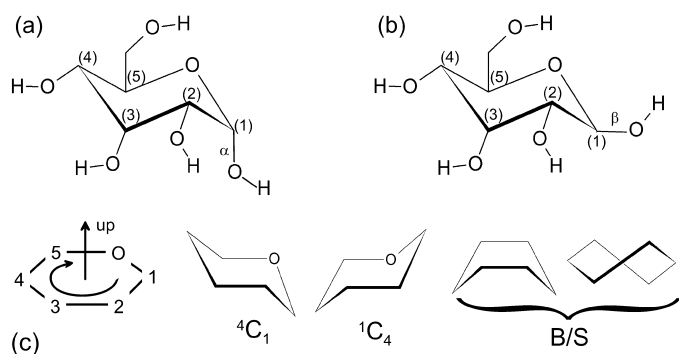

Fig. 1. (a,b) The chemical structure of the D-glucopyranose molecule; (A) α-anomer (GlcA); (B) β-anomer (GlcB). The atom numbering is indicated whereas the aliphatic hydrogens are not shown for clarity. (c) Schematic representation and nomenclature of idealized pyranose ring conformations according to Ref. 5. Conformations are labeled with the type of conformation (chair C, boat B, or skew-boat S) and indices 4 and 1 represent the atom numbers of two atoms pointing upward (superscript) or downward (subscript).

constants related to the $^4C_1 \leftrightarrow {}^1C_4$ transition.[8,24] Such approach has been applied in the case of N-acetyl-D-glucosamine,[8] amylose chain[24] and other pyranose-containing systems.[7,25] The estimated rate constants remain in agreement with the available, approximate experimental data, indicating that the $^4C_1 \rightarrow {}^1C_4$ exchange undergoes at a rate of 0.05–1 μs. In spite of these successes there exist a number of uncertainties which can be recalled in the context of the kinetics of pyranose ring puckering.

(1) The available experimental kinetic data are at best, estimates, which concern only a limited number of systems.[18–22] Therefore, during the procedure of force field parameterization the ring conformational properties are modeled on the basis of only equilibrium data or semi-empirical schemes[3,4]

which do not concern any kinetic variables. As a result, the free energy differences corresponding to given conformers are (roughly) independent of the force field choice and, at the same time, the free energy barriers can vary significantly differing even by 30 kJ/mol (data based on the present study; see details in the further sections; compare Fig. 2b and d). As a result, the unbiased MD simulations can lead to the convergent puckering characteristics only for some cases. To date, it has been proven only for the selected systems studied by using the GLYCAM force field.[7,8,24,25]

(2) The use of transition state theory (TST)[27] can be proposed as an alternative approach which can serve for the approximate determination of the rate constants representing the puckering processes. However, in the absence of kinetic information on the transition MD trajectories, TST can be treated only as a crude approximation in which all transmission coefficients are equal to unity (see the further section for mathematical details). Furthermore, TST is highly dependent on the height of the free energy barriers, i.e. on the value which is dependent on the set of coordinates used to quantify the puckering process.

(3) The results of the previously conducted MD simulations[23] (confirmed in the present study) indicate that the $^4C_1 \rightarrow {}^1C_4$ puckering process is composed of a series of very rapid molecular events. Therefore, the mean lifetime of the given ring conformer can be of order of 1–2 ps. This especially concerns the lifetimes of the boat and skew-boat conformers (denoted further collectively as B/S). The MD trajectories are usually saved every 1–10 ps (see e.g. Refs. 8 and 24) so there exists a possibility that some of the ring conformational rearrangements will be omitted. This obviously would not affect the equilibrium features (providing that the simulation is sufficiently long) but can significantly affect the kinetic characteristics.

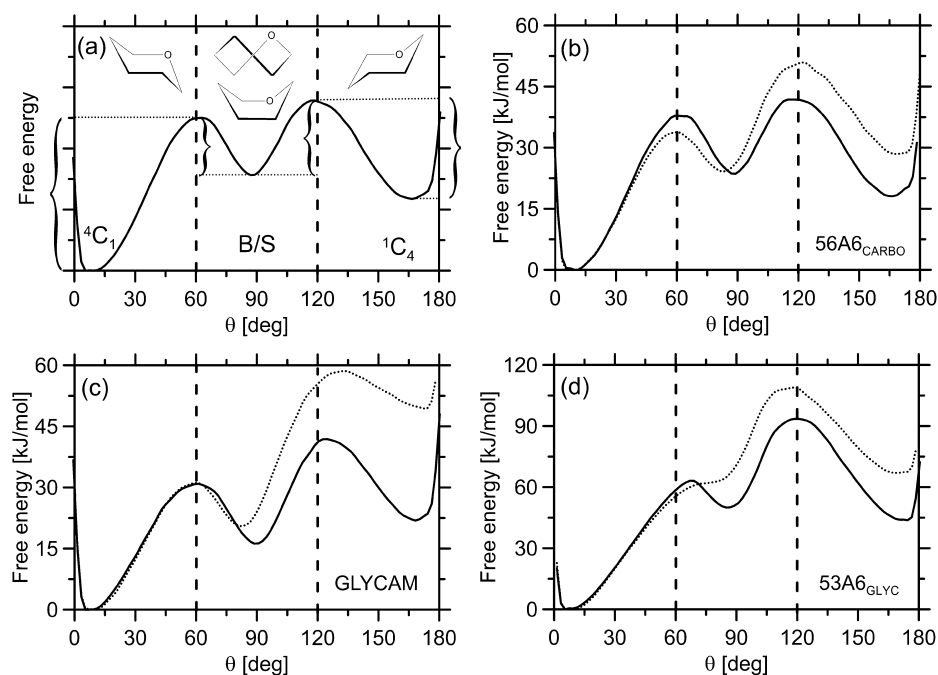(4) One can easily design a computational procedure aiming at estimation of both forward and backward rate constants

Fig. 2. (a) The schematic depiction of free energy profile for the hexopyranose molecule, associated with the θ parameter of the Cremer–Pople coordinates.[26] The conformer label and barrier types are given. (b,c,d) The free energy profiles calculated for GlcA (solid line) and GlcB (dotted line) by using the three different, carbohydrate-dedicated force fields: GROMOS 56A6$_{CARBO}$, GLYCAM06, GROMOS 56A$_{GLYC}$.