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Research paper

Puckering transitions in cyclohexane: Revisited

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ABSTRACT

The interconversion pathways along the puckering transitions in cyclohexane were explored on the two-dimensional projection of the Cremer-Pople sphere using DFT methods and the CCSD(T), MP2, and dispersion-corrected DFT methods with various basis sets were assessed for the relative energies of local minima and transition states for the representative puckering transition pathways. The ωB97X-D/cc-pVTZ and ωB97X-D/def2-QZVP levels of theory well reproduced the relative energies with RMSD = 0.13 kcal/mol against the CCSD(T)/CBS-limit energies. The calculated activation parameters for chair to twist-boat interconversion of cyclohexane at the ωB97X-D/cc-pVTZ//(PCM) M06-2X/6-31+G(d) level of theory were consistent with the observed values.

1. Introduction

Cyclohexane and its derivatives are the simplest models with a six-membered ring in organic and biological molecules and has been the subject of extensive experimental and theoretical investigations to understand the puckered structures and interconversion of the six-membered ring in cyclohexane [1–3]. In particular, the conformational transition of the pyranose ring was responsible for the elasticity of polysaccharides [4] and was an essential factor in the synthesis and hydrolysis of glycosidic bonds in saccharides [5,6].

Schwarz suggested the conformational nomenclature for six-membered rings by assigning a capital letter, designation the type of ring shape, and numericals, distinguishing between the variants of each shape (e.g., $^{1}C_{4}$; see Fig. 1a) [7]. Cremer and Pople (CP) derived a general definition of spherical polar coordinates of the puckering amplitude and two phase angles to describe the geometry of the puckering of six-membered ring relative to the mean plane [8]. The 38 canonical basic conformations of pyranoses were represented by Bércea and co-workers in terms of endocyclic torsion angles following the IUPAC conformational nomenclature (Fig. 1b and Table 1) [9]. Each six-membered ring conformations could be obtained by linear combinations of the basic reference conformations, each of which takes only three independent spherical polar coordinates as suggested by the CP model. The 38 canonical puckered conformations contain two chairs, six boats, six twist-boats (also called skew), 12 half-chairs (also called half-boat), and 12 envelops (the types of ring shape are represented by the capital letters C, B, S, H, and E, respectively). Recently, Beckham and co-workers proposed a two-dimensional projection of the CP sphere to designate the 38 canonical puckerings of pyranoses [10]. The two-dimensional projection of the CP sphere to represent the 38 canonical puckered structures of cyclohexane was shown in Fig. 2a, in which only the oxygen atom of pyranose ring was replaced by the carbon atom (see Fig. 1).

Considerable theoretical [1–3,8,11–14] and experimental studies [15–24] were performed to investigate the most stable structure and/or the puckering transitions of cyclohexane. The chair form of cyclohexane was confirmed to be the most stable structure from electron diffraction [18], microwave spectra [21], and rotational Raman spectroscopy [16,22–24]. The accurate structural data of cyclohexane were suggested by the femtosecond rotational Raman coherence spectroscopy with the degenerate four-wave mixing (fs-DFWM) technique in a pulse supersonic jet [23,24]. The activation free energy and free energy difference for the interconversion of chair and twist-boat conformations of cyclohexane were obtained from NMR [15,19,20] and IR [17] experiments in solution and/or in the gas phase. Although several quantum chemical calculations were performed to elucidate the most stable chair conformation of cyclohexane [14,22–30], only a limited works focused on the puckering transitions in cyclohexane at moderate levels of theory [14,25,29]. Dixon and Komornicki obtained six structures of cyclohexane with D_{3d} (chair), D_2 (twist-boat), C_{2v} (boat), C_2, C_s, and C_1 symmetry at the MP2 level of theory with DZ+P and TZ+P basis sets, from which the activation free energies ($\Delta G^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) were calculated for chair → chair and twist-boat → chair isomerizations [25]. Inonescu et al. reported

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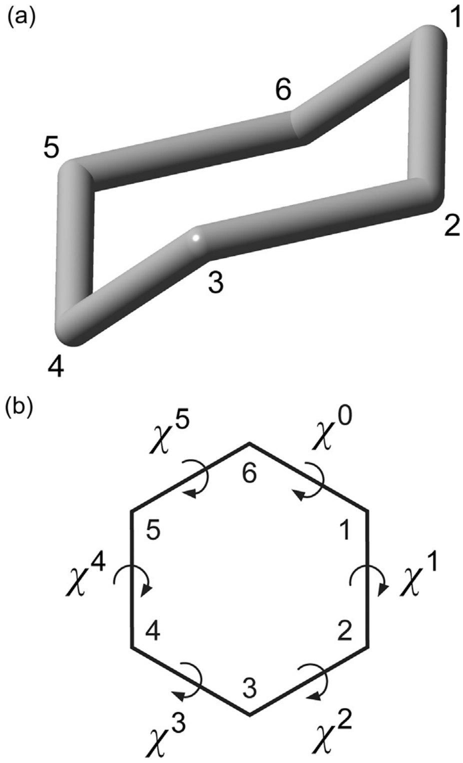

Fig. 1. (a) Conformation $^1C_4$ and (b) endocyclic torsion angles of cyclohexane. Torsion angles χ^0, χ^1, χ^2, χ^3, χ^4, and χ^5 are defined for the sequences 5–6–1–2, 6–1–2–3, 1–2–3–4, 2–3–4–5, 3–4–5–6, and 4–5–6–1, respectively. Hydrogen atoms are omitted for clarity.

the activation enthalpies ($\Delta H^{\ddagger}$) and free energies for chair → twist-boat and twist-boat → chair conversions of cyclohexane using dynamic and static DFT calculations [14]. Kakhiani et al. performed the direct dynamic simulations of cyclohexane at the HF/6-31G level of theory to investigate the unimolecular dynamic of the twist-boat intermediate and calculated the energetics of stationary points and their conversions at MP2/aug-cc-pVDZ level of theory [29].

Beckham and co-workers explored the pathways for puckering interconversion of oxane and five pyranose sugars on a two-dimensional projection of the CP sphere at the CCSD(T)/6-311+G(d,p)//B3LYP/6-311+G(2df,p) level of theory [10]. They obtained the aggregate properties of puckered conformations from individual conformations with exocyclic groups in different orientations using Boltzmann-weighted averaging method. The feasible pathways for puckering interconversions of pyranose sugars were more complicated than those of oxane due to the exocyclic substituents. Recently, we reported that the β-peptide pentamer of *cis*-2-aminocyclohexanecarboxylic acid (*cis*-ACHC) residues with alternating chiralities of (1*S*,2*R*) and (1*R*,2*S*) adopts both left- and right-handed 12/10-helices in the crystal state and in solution [31]. In the crystal state, cyclohexane of the β-peptide pentamer adopted the different puckered structures depending on the helix handedness; $^4C_1$ and $^1C_4$ puckered structures in the left- and right-handed helices, respectively. The variable-temperature ^1H NMR spectra of the β-peptide pentamer and its derivatives supported the coexistence of both handed helices in solution. Hence, we proposed that the helix inversion of this pentamer may be achieved via cooperative ring flipping of the cyclohexane ring moiety of each residue along the peptide chain.

Here, we explored the interconversion pathways along the puckering transitions in cyclohexane on the two-dimensional projection of the CP sphere using density functional theory (DFT) methods and assessed the CCSD(T), MP2, and dispersion-corrected DFT methods with various basis sets for the relative energies of local minima and transition states for the representative puckering transitions. In addition, we calculated the activation free energies and relative free energies for puckering transitions of cyclohexane in the gas phase and in organic solvents, and compared with the corresponding experimental values.

2. Computational methods

Chemical structure and endocyclic torsion angles of cyclohexane are defined in Fig. 1. All calculations were carried out using the Gaussian 09 program [32]. GaussView [33] was used to generate and edit the structures of cyclohexane. First, the chair conformation of cyclohexane (Fig. 1a) was optimized at the M06-2X [34] and ωB97X-D [35] levels of theory with 6-31+G(d), 6-311++G(d,p), and def2-QZVP basis sets, respectively, in order to know which can be a good level of theory to provide the rotational constants of the most stable chair conformation of cyclohexane consistent with those of the fs-DFWM experiments in a pulse supersonic jet [23,24]. In the recent studies, both the ωB97X-D/6-311++G(d,p) and M06-2X/6-31+G(d) levels of theory well provided the rotational constants of the most stable structures of the alanine dipeptide [36], *N*-methylacetamide (NMA) [37], and water hexamers [37] consistent with the values from microwave experiments. In addition, the chair conformation of cyclohexane was optimized at the B3LYP/6-311+G(2df,p) level of theory, which was used for exploring the pathways for puckering interconversion of oxane and pyranose sugars [10]. The vibrationally averaged rotational constants were calculated at the M06-2X/6-31+G(d) level of theory using vibrational perturbation theory (VPT2), in which the cubic and semidiagonal quartic force constants were computed by finite differentiation of the Hessian along the normal mode coordinates [38].

The initial structures of 38 canonical puckered structures of cyclohexane on the two-dimensional projection of the CP sphere (Fig. 2a) were generated using the endocyclic torsion angles suggested by Bércea and co-workers [9] and optimized at the M06-2X/6-31+G(d) level of theory. Each local minimum and each transitions state (TS) were confirmed by verifying the absence of imaginary frequencies and by checking whether it had one imaginary frequency, respectively, after frequency calculations. In addition, each TS was confirmed using the intrinsic reaction coordinate (IRC) method [39,40] at the M06-2X/6-31+G(d) level of the theory to determine whether it connects the reactants and products. However, as in most cases, the IRC calculation did not step all the way to the minimum on either side of the path. Further optimizations were conducted starting from the reactants and products obtained by the IRC method to reach the two minima connected by the TS at the same level of theory.

As described later, the structures with the same type of puckering had the same conformational energies despite different atomic numberings; e.g., six twist-boats ($^3S_1$, $^5S_1$, $^2S_6$, $^1S_3$, $^1S_5$, and $^6S_2$ in Fig. 2a) had the same relative energy of 6.17 kcal/mol to the chair conformation ($^4C_1$ or $^1C_4$) at the M06-2X/6-31+G(d) level of theory. Hence, the two pathways of (a) $^4C_1 \rightarrow {}^4H_3 \rightarrow {}^1S_3 \rightarrow {}^1H_6 \rightarrow {}^1C_4$ and (b) $^1S_3 \rightarrow {}^{1,4}B \rightarrow {}^1S_5$ can be representative for the chair → chair and twist-boat → twist-boat conversions in cyclohexane, respectively (see blue lines in Figs. 2b and 3). The conformational energies of $^4C_1$, $^4H_3$, $^1S_3$, and $^{1,4}B$ structures are enough to describe the energetics for puckering transitions in cyclohexane.

Single-point energies of the four representative puckered structures ($^4C_1$, $^4H_3$, $^1S_3$, and $^{1,4}B$) optimized at the M06-2X/6-31+G(d)