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A study on the conformational space of the all-trans retinal deprotonated Schiff base

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ABSTRACT

The conformational space of the all-trans retinal deprotonated Schiff base (DSBT) molecule around its four internal backbone torsional angles was studied. A total of eight different conformers were detected from potential energy surface exploration corresponding to the four internal backbone torsional angles. The standard split-valence 6-311++G(d,p) basis set in combination with MP2 and B3LYP levels were carried out to analyze the structural characteristics (relative energies, dipole moments and bond length alternation) and spectral properties (electronic absorption spectrum and Raman spectrum) of the conformers. Results presented in this paper showed that the relative stability order of the conformers might be independent of the level of theory used. It was also reconfirmed that the TD-DFT method would systematically underestimate the excitation energy by 38.60–67.54 kJ mol^{-1}; a trend had been reported in several previous studies. The characteristic peak nearby 1600 cm^{-1} corresponding to the ECC mode could be notably observed from the predicted Raman spectrum calculated at both the MP2 and the B3LYP level of theories. Moreover, the spectral profile acquired based on the B3LYP level was more apparent and distinguishable than that from the MP2 method. It is suggested that B3LYP level may be a proper choice for theoretically study of Raman spectrum, especially concerning the polyene conjugated systems.

1. Introduction

Rhodopsin is a membrane bound photoreceptor protein responsible for dim light vision in the rod cells of the vertebrate eyes [1–3]. The protein consists of opsin protein moieties and *11-cis* retinal covalently bound via a protonated Schiff base (PSB) linkage to Lys-296. The protonated Schiff-base linkage between Lys-296 and *11-cis* retinal bears a net positive charge NH^+, compensated by the Glu-113 counteranion, forming a salt bridge [4,5]. Upon absorption of a photon, the *11-cis* retinal (PSB11) can be converted to the *all-trans* isomer (PSBT), depicted in Fig. 1. The photoisomerization of the retinal is believed to be the first step of the visual process [6,7]. It is one of the fastest processes in nature, occurring within 200 fs [8]. Photorhodopsin (Photo) is the primary photoproduct of the rhodopsin, it can generate a series of intermediates to activate the heterotrimeric G protein transducin, initiating the signal transduction process in the visual cascade as illustrated in Fig. 2 [9–14].

As a structural prototype for the study of G-protein coupled receptor, the role of rhodopsin has been evaluated in an historical perspective. Working started on rhodopsin over 100 years ago substantial progresses have been made every year. The first three-dimensional X-ray structure of bovine rhodopsin was solved by Palczewski in 2000 [15]. The structures of squid rhodopsin [16,17] and bovine opsin [18] were solved and deposited in the Protein Data Bank later on. In order to understand the mechanisms of action, many attentions have been paid to reveal their structures [19–23]. Optical spectroscopy is a very valuable tool to study the structures of biomolecules due to the high sensitivity in monitoring the conformational changes of biomolecules. Some research groups have investigated the relevant characteristics of rhodopsin by using the optical spectroscopy method. For example, Polli [24] utilized high time resolution pump and femtosecond stimulated Raman scattering to explore the photoisomerization process. Results provided detailed evolutions of the electronic structure of retinal. Heberle [25] presented the first resonance Raman spectra to study the channelrhodopsin-2 and suggested that the Schiff base proton is strongly hydrogen-bonded to a nearby water molecule. Besides, the methods of computational chemistry also provided a profound way to understand the activation mechanism of

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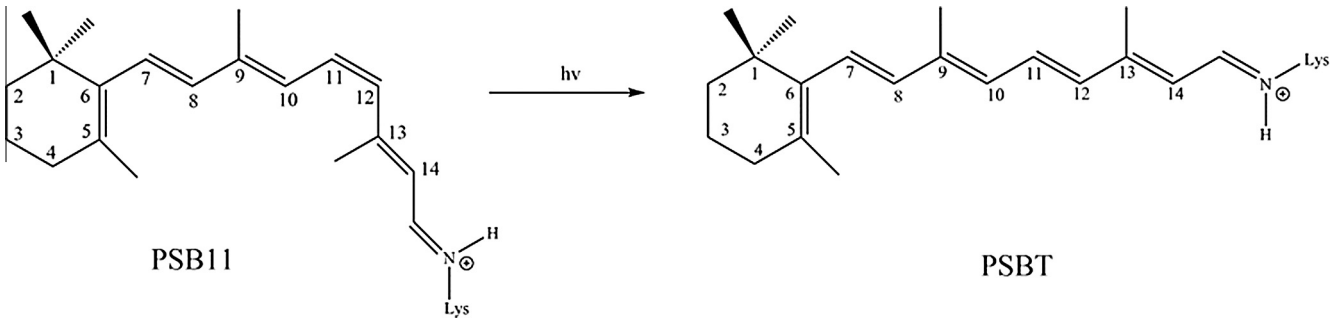

Fig. 1. PSB11-PSBT photoisomerization process passes along the C_{10}-C_{11} = C_{12}-C_{13}.

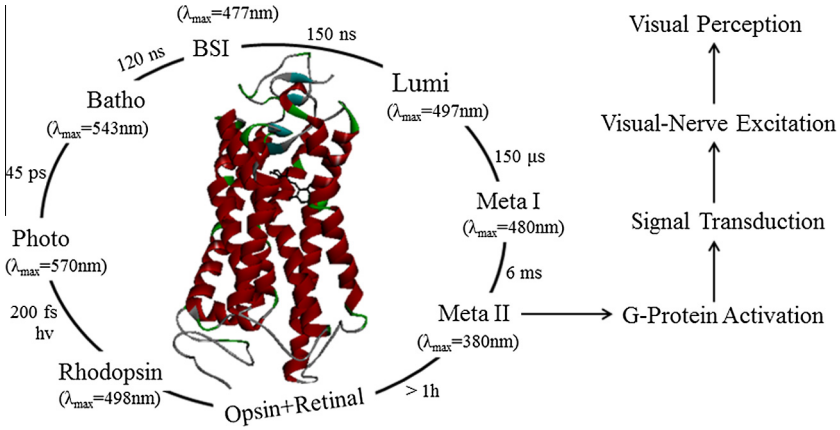

Fig. 2. The photoactivation mechanism of rhodopsin. The experimental absorption maxima of the early intermediates are reported within parentheses.

rhodopsin. Martinez [26] used the hybrid quantum mechanics/-molecular mechanics (QM/MM) method to simulate the time-resolved fluorescence spectra of retinal. The calculated results were in good agreement with those from the experimental values. By using frozen density embedding theory, Kaila [27] reported that the calculations exactly reproduce the experimental absorption maxima of rhodopsin and the red[1], green, and blue color pigments.

However, there remained many critical details of the intermediate processes to be elucidated, such as the crucial deprotonation of the Schiff base required for MII formation [28], which could only be observed in low temperature FTIR experiments at acidic conditions [29] and such conditions in the experiment is not easy to achieve. The current work was a study on the conformational space of DSBT molecule about its four structurally significant internal backbone torsional angles. Attempts were made to investigate the relative stabilities of eight different conformers of DSBT molecule on the energy surface, and to provide theoretical results on the dipole moments, HOMO-LUMO energy gaps, bond length alternation, vertical excitation energy as well as Raman spectrum that may serve as future preliminary guidelines to characterize the conformers of the DSBT molecule. Results presented are expected to provide valuable insights regarding the intrinsic conformational properties of DSBT molecule which in turn may assist in understanding the structure-activity relationship and the intermediate processes of rhodopsin in activation mechanism.

[1] For interpretation of color in Fig. 2, the reader is referred to the web version of this article.

2. Computational methods

In this retinal analogue, a methyl amino group had replaced the Lysine side chain that provides the linkage to the protein in rhodopsin (Fig. 3). The potential energy surfaces corresponding to the four internal backbone torsional angles of the DSBT molecule, namely ψ_1, ψ_2, ψ_3 and ψ_4 were depicted in Fig. 4. The photoisomerization process passes along the C_{10}-C_{11}-C_{12}-C_{13} torsional angle, making it the major component of the reaction coordinate. The neighboring torsional angles, such as C_9-C_{10}-C_{11}-C_{12} and C_{11}-C_{12}-C_{13}-C_{14} were taken into consideration as well because it can facilitate the photoisomerization process. The fourth coordinate was the C_5-C_6-C_7-C_8 torsional angle, which determines the orientation of the β-ionone ring with respect to the retinal chain.

In order to carry out the conformational search about the four internal backbone torsional angles, the molecular geometry of the DSBT molecule was subjected to full geometry optimization and vibrational frequency calculations using the B3LYP/6-311++G (d,p) level of theory [30,31]. Absence of imaginary frequency value in the vibrational frequency calculations proved the optimized geometry to be precise minimum. To confirm the other possible minima on the conformational potential energy surfaces corresponding to the four rotatable internal torsional angles of the DSBT molecule, relaxed potential energy surface scans were performed at B3LYP/6-31++G(d,p) level by rotating the four dihedral angles from 0° to 360° at 10° increments. For each conformation, the changed torsional angle was held fixed while the remaining variables were fully optimized. The eight stable molecular geometries were detected on the basis of potential energy surfaces. The conformers were then subjected to full geometry optimization and