



# Theoretical analysis of the geometrical isotope effect on the hydrogen bonds in photoactive yellow protein with multi-component density functional theory



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## ABSTRACT

To theoretically analyze the nuclear quantum effects of protons on two hydrogen bonds around the chromophore (CRO) in the photoactive yellow protein (PYP), we have calculated simple cluster model consisting of CRO, Glu46, and Tyr42 residues in PYP with the multi-component molecular orbital method and multi-component density functional theory, which can take account of quantum fluctuations of light mass particles. The average OO distances between CRO and Glu46 and between CRO and Tyr42 with our methods are shorter than the corresponding equilibrium ones, while the OH distances become longer due to the anharmonicity of the potential. The H/D geometrical isotope effect is also found, that is, the distances between oxygen atoms are elongated by the deuterium substitution, known as Ubbelohde effect.

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## 1. Introduction

Nuclear quantum effects, such as zero-point vibration, nuclear tunneling, and vibrational excitation, play important roles in the modern chemistry, physics, and other related fields [1]. Especially in the case of molecular systems containing protons and deuterons, the effect has a major influence on their properties, such as stable geometrical structure, NMR signal, etc., due to a large quantum nature of light-mass particles. Recently, we have developed *ab initio* methods which allow us to analyze both electrons and nuclei quantum-mechanically [2–5]. We have also developed a theoretical method to analyze the nuclear quantum effects on the nuclear magnetic shielding constant [5,6], and have demonstrated that the low-barrier hydrogen bonded (LBHB) systems such as  $\text{N}_2\text{H}_3^+$  and  $\text{H}_3\text{O}_2^-$  have characteristic  $^1\text{H}$  NMR signals [7].

Photoactive yellow protein (PYP) is a putative photoreceptor protein for negative phototaxis of the purple phototropic bacterium (*Halorhodospira halophila*) [8]. The chromophore (CRO), *p*-coumaric acid, of PYP is buried inside the protein, and is bound to Cys 69 by a thioester bond [9–11]. After absorbing a photon, the CRO undergoes isomerization from *trans* to *cis* form, which triggers subsequent thermal photo-reaction cycle [12]. The CRO has two hydrogen bonds (HBs) between the CRO and Glu46 and between the CRO and Tyr42. During the reaction, proton transfers occur within these hydrogen bonds, which triggers a tertiary

structural change responsible for the signal transduction [13,14]. Recently, Yamaguchi et al. report the crystallographic structural analysis of PYP with the joint method of neutron and X-ray diffraction measurements [15]. Analyzing the hydrogen bonded distances around the CRO, they showed that the HB between the CRO and Glu46 is the LBHB, while the HB between CRO and Tyr42 is not.

In order to analyze the hydrogen-bonded feature around the CRO from the viewpoint of electronic structure, theoretical approaches such as *ab initio* molecular orbital method and density functional theory are quite useful. In addition, nuclear quantum effect should be indispensable for the analysis of hydrogen-bonded system, since such effect highly affects the geometrical structure, charge density, etc. as demonstrated in our previous work [7]. However, to our knowledge, no theoretical analysis of PYP including nuclear quantum effect has been reported so far.

In this study, thus, we have theoretically analyzed the nuclear quantum effect of protons on the HBs around the CRO in PYP with multi-component molecular orbital (MC\_MO) method [16] and multi-component density functional theory (MC\_DFT) [17], which can take account of the quantum effect of both electrons and nuclei. We have also calculated deuterium substitution, to elucidate the geometrical isotope effect.

## 2. Theory

The details of MC\_MO and MC\_DFT methods are described in the literatures [16,17]. In this section, thus, we briefly explain theoretical frameworks of both methods.

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### 2.1. MC\_MO method

The non-relativistic Hamiltonian of a molecular system that contains  $N$  quantum particles ( $N_e$  electrons and  $N_p$  quantum protons/deuterons) and  $M$  classical nuclei, is given by

$$H = -\sum_i^N \frac{1}{2m_i} \nabla_i^2 + \sum_i^N \sum_{j>i}^N \frac{q_i q_j}{r_{ij}} + \sum_i^N \sum_l^M \frac{q_i Z_l}{r_{il}}, \quad (1)$$

where the first term is the kinetic energy operator of quantum particles, the second and third terms the Coulombic interaction operators between charged particles,  $m_i$  the mass of  $i$ -th quantum particle,  $Z_l$  the nuclear charge of  $l$ -th classical nucleus, and  $r_{ij}$  the distance between charged particles, respectively. In the Hartree–Fock (HF) level of MC\_MO method, a trial wave function of the system is expressed as

$$\Psi_{\text{MC-HF}}(\mathbf{R}) = \Psi_{\text{HF}}^e(\mathbf{R}_e) \times \prod_p^{N_p} \varphi^p(\mathbf{r}_p), \quad (2)$$

where  $\Psi_{\text{HF}}^e$  and  $\varphi^p$  is a single Slater determinant of electrons and a proton (or deuteron) orbital, respectively. Since each proton are considered as distinguishable particles in the MC\_MO and MC\_DFT methods, we neglect the exchange contribution between quantum nuclei in the following discussion. For electronic closed-shell systems, Fock operators of electrons and protons are written as

$$f^e(\mathbf{r}_e) = h^e(\mathbf{r}_e) + \sum_i^{N_e/2} [2J_i(\mathbf{r}_e) - K_i(\mathbf{r}_e)] - \sum_q^{N_p} J_q(\mathbf{r}_e), \quad (3)$$

$$f^p(\mathbf{r}_p) = h^p(\mathbf{r}_p) - 2 \sum_i^{N_e/2} J_i(\mathbf{r}_p) + \sum_{q(\neq p)}^{N_p} J_q(\mathbf{r}_p), \quad (4)$$

where the terms  $h^{e,p}$  are one-particle operators, which contain the kinetic energy and Coulomb interaction potential with nuclei,  $J_i$  and  $K_i$  Coulomb and exchange operators, respectively. Expanding the molecular orbitals of the electrons and protons by the linear combination of basis functions, one can obtain the multi-component wave function consisting of electrons and protons by solving the Roothaan equations simultaneously.

The HF energy of the system is given by

$$E_{\text{MC-HF}} = 2 \sum_i^{N_e/2} h_{ii}^e + \sum_{ij}^{N_e/2} [2(ii|jj) - (ij|ij)] + \sum_q^{N_p} h_{qq}^p - 2 \sum_q^{N_p} \sum_i^{N_e/2} (ii|qq) + \sum_q^{N_p} \sum_{r>q}^{N_p} (rr|qq), \quad (5)$$

where  $h_{ii}^{e,p}$  is the one-particle integrals,  $(ii|jj)$  the Coulomb integrals,  $(ij|ij)$  the exchange two-electronic integrals,  $(ii|qq)$  the Coulomb integral between an electron and proton, and  $(rr|qq)$  the Coulomb integral between protons. The first-derivative of the HF energy of Eq. (5) with respect to the parameters ( $\Omega$ ) such as nuclear coordinate is given as

$$\begin{aligned} \frac{\partial}{\partial \Omega} E_{\text{MC-HF}} = & 2 \sum_i^{N_e/2} h_{ii}^{e(\Omega)} + \sum_{ij}^{N_e/2} \{2(ii|jj)^{(\Omega)} - (ij|ij)^{(\Omega)}\} + \sum_q^{N_p} h_{qq}^{p(\Omega)} \\ & - 2 \sum_q^{N_p} \sum_i^{N_e/2} (ii|qq)^{(\Omega)} + \sum_q^{N_p} \sum_{r>q}^{N_p} (rr|qq)^{(\Omega)} \\ & - 2 \sum_{ij}^{N_e/2} S_{ij}^{e(\Omega)} e_{ij}^e - \sum_q^{N_p} S_{qq}^{p(\Omega)} e_{qq}^p, \end{aligned} \quad (6)$$

where  $S_{ij}^{(\Omega)}$ ,  $h_{ij}^{(\Omega)}$ , and  $(ij|kl)^{(\Omega)}$  are the so-called *skeleton* derivatives of overlap, one-, and two-particle integrals.

### 2.2. MC\_DFT method

In the MC\_DFT method, Kohn–Sham (KS) operators of electron and protons are given by

$$f_{\text{KS}}^e(\mathbf{r}_e) = h^e(\mathbf{r}_e) + \sum_i^{N_e/2} [2J_i(\mathbf{r}_e) - V_i^{\text{XC}}(\mathbf{r}_e)] - \sum_q^{N_p} J_q(\mathbf{r}_e), \quad (7)$$

$$f_{\text{KS}}^p(\mathbf{r}_p) (= f^p(\mathbf{r}_p)) = h^p(\mathbf{r}_p) - 2 \sum_i^{N_e/2} J_i(\mathbf{r}_p) + \sum_{q(\neq p)}^{N_p} J_q(\mathbf{r}_p), \quad (8)$$

where  $V_i^{\text{XC}}$  is the exchange–correlation functional for electrons. In this study, we employed the hybrid exchange–correlation functional of B3LYP. Note that the KS operator of protons,  $f_{\text{KS}}^p(\mathbf{r}_p)$ , is equal to Fock operator of protons,  $f^p(\mathbf{r}_p)$  in Eq. (4), because we neglect electron–proton correlation and exchange term between protons. Kohn–Sham orbitals of electrons and protons are obtained in the same fashion as the MC\_MO procedure.

The total energy of a system is given by

$$\begin{aligned} E_{\text{MC-DFT}} = & 2 \sum_i^{N_e/2} h_{ii}^e + \sum_{ij}^{N_e/2} 2(ii|jj) + E_{\text{XC}} + \sum_q^{N_p} h_{qq}^p - 2 \sum_q^{N_p} \sum_i^{N_e/2} (ii|qq) \\ & + \sum_q^{N_p} \sum_{r>q}^{N_p} (rr|qq), \end{aligned} \quad (9)$$

where  $E_{\text{XC}}^e$  is the exchange–correlation energy, whose functional derivative with respect to a electronic density gives the exchange–correlation functional for electrons. The first-derivative of the energy of Eq. (9) is written as

$$\begin{aligned} \frac{\partial}{\partial \Omega} E_{\text{MC-DFT}} = & 2 \sum_i^{N_e/2} h_{ii}^{e(\Omega)} + \sum_{ij}^{N_e/2} 2(ii|jj)^{(\Omega)} + \frac{\partial E_{\text{XC}}^e}{\partial \Omega} + \sum_q^{N_p} h_{qq}^{p(\Omega)} \\ & - 2 \sum_q^{N_p} \sum_i^{N_e/2} (ii|qq)^{(\Omega)} + \sum_q^{N_p} \sum_{r>q}^{N_p} (rr|qq)^{(\Omega)} \\ & - 2 \sum_{ij}^{N_e/2} S_{ij}^{e(\Omega)} e_{ij}^e - \sum_q^{N_p} S_{qq}^{p(\Omega)} e_{qq}^p. \end{aligned} \quad (10)$$

We used Eq. (10) to calculate nuclear forces of molecular systems in geometry optimization calculations.

### 3. Computational details

First, geometry optimization calculations for a system, which contains whole PYP and surrounding water molecules, were performed with the molecular mechanical (MM) method under the periodic boundary condition. We added 12 Å of water molecules around the PYP, where the system contains 7549 water molecules. The AMBER 9 program package [18] was used for all MM calculations with the Generalized Amber Force Field (GAFF) for the CRO, Amber ff99 parameters for the rest of residues, and the TIP3P for water molecules. The experimental structure of PYP obtained with the joint method of the X-ray and neutron refinements [15] as an initial structure in the geometry optimization calculation, where the root mean square deviation (RMSD) for backbone atoms of PYP between the experimental and theoretical structure is 0.59 Å.

Since *ab initio* calculations of whole proteins are quite time-consuming for our computer resources, we performed quantum mechanical calculations only for a molecular system consisting of CRO, Glu46, and Tyr42 residues in PYP as shown in Fig. 1(a), where the residues of CRO, Glu46, and Tyr42 are terminated by carboxyl (–COOH) and amino (–NH<sub>2</sub>) groups. In order to obtain appropriate molecular orientations of CRO, Glu46, and Tyr42 residues, the carboxyl and amino groups in these residues are fixed in the

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