Full QM description of phytochromes

A fully quantum mechanical treatment of chromophore-protein interactions in phytochromes

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In Short

- Quantum chemical calculations
- The fragment molecular orbital (FMO) method
- Chromophore-protein interactions
- Phytochromes

***Figure 1:** Phytochrome structure with all crystal water molecules (~6159 atoms), this kind of structures can be minimized using a combination of the FMO method with semiempirical QM approaches. For the geometry optimization the chromophore can be treated as a fragment.*

This proposal has two goals: firstly to identify and quantify the chromophore-protein interactions underlying the photochemical process of phytochromes by means of quantum chemical calculations, and secondly to calculate infrared (IR) and Raman spectra of phytochromes structures. To this end, we propose to use the fragment molecular orbital (FMO) method in a set of phytochromes (Figure 1).

The FMO method is a general quantum chemical method and is one of the most efficient approaches for studying biomolecules[1]. In the FMO method, a protein can be divided into small fragments, for example, each residue can be represented as a fragment. In phytochromes, the fragmentation can provide accurate information about the most significant interactions between the chromophore and the rest of the protein. Furthermore, the chromophore can be also represented as an individual fragment or can be fragmented. Thus, a deeper understanding of the activation of the photocycle in phytochromes can be achieved[2]. FMO has also been used for studying the effect induced by amino acid substitutions. Thus, we propose to use this quantum chemical method for evaluating the variation types and energy changes caused by mutations surrounding the chromophore in phytochromes.

Simulations of IR and Raman spectra of chromophore geometries can be compared with the experimental Resonance Raman spectra in order to identify the chromophore structures in the differen states of phytochrome. However, the inclusion of the effect of the protein environment on the chromophore spectra is crucial for getting a good agreement with the experimental spectra. Thus, we propose to performe geometry optimizations, IR and Raman spectra calculations[3] by using the FMO method within the frozen domain with dimers (FDD) approach (Figure 2), which has been applied on proteins with up to 9000 atoms[4].

Because of the computational cost, the most common quantum mechanical (QM) methods cannot be routinely used for the optimization of large molecular systems such as phytochrome structures. An excellent alternative is the combination of the FMO method with semiempirical QM approaches, allowing the minimization of biomolecules with thousands of atoms[5].

Identifying the interactions between chromophore and protein can provide accurate information on the individual contribution of each residue to the different states of the photocycle of phytochromes (Figure 3). However, it is important to note that chromophore-protein interactions can be affected by small errors in the positions of atoms, therefore, it is necessary to minimize crystal structures in order to avoid large deviations in energy values. To this end, a fully quantum mechanical (QM) treatment of phytochromes will be carried out by using the fragment molecular orbital (FMO) method[6].

The fragmentation of the bv-chromophore can provide valuable information on the identification of key interactions with protein. Nevertheless, the bilin chromophore consists of two propionic side chains and four pyrrole rings with a high electron delocalization. Thus, it is crucial to preserve the chemical identity of the bilin chromophore for obtaining a correct description of chromophore-protein interactions. For example, the bilin chromophore can be divided into four fragments; both propionic side chain B (propB) and propionic side chain C (propC) can be treated each as a fragment. For maintaining the electron delocalization of bilin chromophore, rings B,C and D form only one fragment (rings-BCD) and, finally, ring A along with Cys24 form the fourth fragment (ring-A-Cys).

This quantum chemical method can evaluate with high precision and detail biomolecular systems by means of a partition scheme. Additionally, pair interaction energy

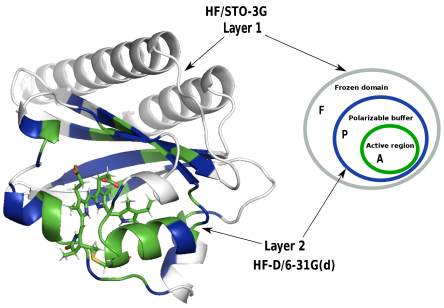

Figure 2: *Phytochrome structure divided into two layers (L1, and L2). The first step in FMO/FDD is the computation of the whole system at the FMO1 level (monomers) for the initial geometry; then, the electronic state of fragments in domain F is frozen for the other geometries during a geometry optimization. Fragments that belong to the polarizable and active region share the same basis set, nevertheless, only fragments that belong to the active region are allowed to move during the optimization.*

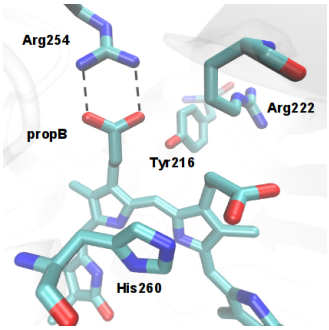

Figure 3: *Chromophore binding pocket of DrBphP phytochrome structure. Visual inspection and molecular mechanics are the most common approaches for the interpretation of the chromophore-protein interactions in phytochromes, as a consequence a significant number of molecular interactions cannot be explained because of their high complexity.*

(PIE)[7] between a pair of fragments can be decomposed into four energy terms: electrostatics, exchange-repulsion, charge transfer, and dispersion (see Figure 4). These energy terms provide a valuable insight into the chemical nature of non-covalent interactions between proteins and ligands or chromophores (Figure 5). Non-covalent interactions like salt bridges, hydrogen bonds, or polar interactions are dominated by the electrostatic and charge transfer terms while hydrophobic interactions are driven by the dispersion term[8]. For the first time a fully quantum chemical (QM) treatment, including infrared and Raman spectra simulations of phytochromes will be carried out by using the computational power of the HLRN.

As shown in Figure 4 the propionic side chain B (propB see Figure 3) is stabilized mainly by three residues; Arg254 (-128.01 kcal/mol), His260 (-50.57 kcal/mol) and Arg222 (-49.77 kcal/mol), these residues form different types of interactions, such as salt bridges, hydrogen bonds and electrostatics. However, for understanding the nature of these interactions, the total interaction energy can be decomposed into different energy terms (see Figure 5), for example, the salt bridge between propB and Arg254 is dominated mainly by the electrostatic energy term, while the nature of the interaction with the Arg222 and His260 is purely electrostatic. Interestingly, PIEs with the Tyr216 and Ser257 are driven not only by the electrostatic component but also by the exchange-repulsion, charge transfer, and dispersion energy terms. In summary, this is just a small example of the capabilities of the FMO method for studying chromophore-protein interactions in phytochromes.

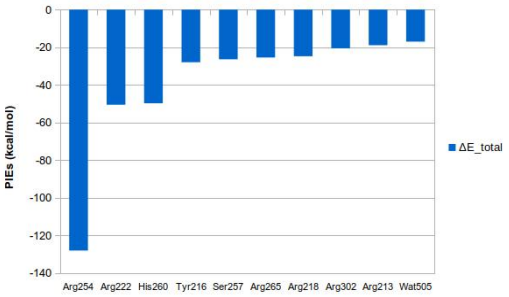

Figure 4: *The FMO calculations identified 10 significant interactions between propionic side chain B and DrBphP phytochrome structure. The salt bridge between propionic side chain B and Arg254 is the most significant interaction with protein (-128.08 kcal/mol), this interaction contributes to the stability of the chromophore pocket.*

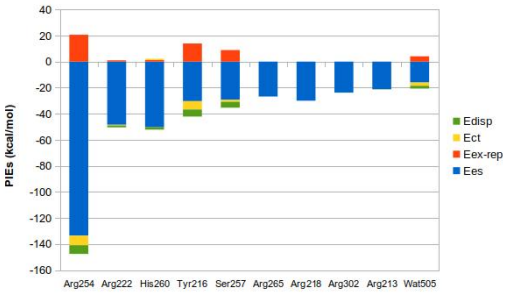

Figure 5: *The plot describes the different types of interactions between propionic side chain B and DrBphP phytochrome structure. The electrostatic, dispersion, charge-transfer, and exchange-repulsion PIE terms are colour-coded in blue, green, yellow and red, respectively.*

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More Information

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Project Partners

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