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REGULAR ARTICLE

The mechanisms of excited states in enzymes

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Abstract Enzyme catalysis is studied on the basis of excited state processes, which are of electronic, vibrational and thermal nature. The ways of achieving the excited state, such as photo-absorption and ligand binding, are discussed and exemplified by various cases of enzymes.

Keywords Barrier heights · Excited states · Enzyme kinetics

1 Introduction

The increase of reaction rate observed in enzyme catalysis is usually explained by the destabilization of the initial reactant, the stabilization of the transition state and the alteration of the reaction mechanism [1]. The catalyzed reaction proceeds continuously on a reaction energy surface where thermal fluctuations provide the energy necessary to overcome the reaction energy barrier. This type of reaction can be described by the transition state theory (TST) in which the reaction rate is a function of an apparent activation energy [2]. Knowledge of the ground state potential energy surface (PES) is invaluable since the transition state can be used to estimate the energy barrier height and thereby determine the catalytic reaction rate as well as other quantities such as the enthalpy, the entropy and the heat capacity for the reaction [3, 4]. However, reactions could take place through different mechanisms in enzymes due to their versatile nature. Enzymes could have evolved to take advantage of alternative reaction mechanisms such as tunneling through the energy barrier [5]. Such an effect cannot be described in classical terms and a specific method is required for the evaluation of the reaction rate constant [6]. A reaction could also be triggered by a transition of the enzymatic complex to a significantly different state from what is reached through thermal fluctuations such as electronic excited states in photoactivated enzymatic reactions. Reaction kinetics involving state transitions is not covered by TST and particular methods have to be considered for the calculation of such reaction properties.

The basic argument for the importance of excited state dynamics in enzyme processes is the lowering of the activation barrier, a mechanism that is clearly seen in the case of the photolyase protein described later in the text. In the case of gene repair, the electrons participating in the repair process are excited to a level where the process proceeds more easily [7], because of a diminished activation barrier. One can give more general solid-state physics arguments for diminished activation barriers on excited state PESs due to larger electronic overlap, see Ref. [8].

Let us pause in this review with a few general remarks on the various different types of excited states considered here. Electronic, vibrational and rotational excitations are possible and are all frequently found in molecular spectroscopy. The electronic excitations have considerably larger energy differences, i.e., transition energies, than the vibrational ones. The latter involve changes in the position of the nuclei and occur at much lower frequencies than the electronic ones. This is also the case in the rotational

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excitations that occur at even lower frequencies, and all these excitations are important for reaction kinetics in chemistry.

The mechanisms involved at the different stages of enzyme activity have to be identified and understood before a method can be developed to calculate the enzyme excited state reaction properties. This work is a collection of observations and ideas on the subject, supported by examples taken from known enzymes with a particular emphasis on the cases of photolyase and ATP-ase within the lipid membrane. In the first section, the excited states of enzymes are identified. Their characteristics are described along with experimental and computational methods used to study them. An attempt is made to identify the role of excited states in enzyme functionality. The following sections describe the mechanisms used at the three different stages of the excited states activity in enzymes. The second section treats the excitation of the enzyme complex by absorption of a photon, chemical reaction or from high energy groups. The third section describes the mechanisms by which the excitation is transferred to the active site. The fourth section describes two catalyzed reactions proceeding by excited state: DNA repair by photolyase and enzymes in membrane systems. The conclusion summarizes the ideas developed and sets a framework for future work.

2 The nature of excited states in enzymes

The name excited states enzymes is used to describe a wide range of enzymes whose reaction mechanisms proceed through states above the ground state. Electronic excited states and radical intermediates are two examples of such states. The reaction mechanism in excited states enzymes is likely to be different from the one in the uncatalyzed reaction. Even though excited states enzymes have very different functions and different reaction mechanisms, they share some characteristics. The transition takes place from the ground state of the enzymatic complex to a state of substantially higher energy. In photoactivated reactions; the electronic excitation is due to absorption in the ultraviolet (UV) and optical region corresponding to energies of approximately 2 eV or more. Specialized moieties in the enzyme complex are responsible for the reversible absorption of energy such as chlorophyll A in photosystem I and II [9]. Excited state intermediates are relatively short lived with, for example, a lifetime of tens of picoseconds for the electronic excited state of photolyase [10]. Each one of the intermediates of the reaction has its own PES, which can differ significantly from the one of the ground state. The transfer of the excitation to the active site involves reactive intermediates such as deprotonated species in the radical transfer mechanism of photolyase. The protection of the excited states seems to be a common feature of the enzymes making use of excited states, probably to avoid loss of the excitation and damages to the surroundings [11], see Fig. 1.

Even though most catalyzed reactions are thought to proceed through the ground state, alternate reaction paths must be considered as they can contribute to the reaction and sometimes even dominate it [12]. The reason for an enzymatic reaction to proceed by transition to an excited state is not immediately clear and deserves some thinking. The first reason comes from the observation of photosynthesis from which it is known that some enzymatic processes function through excited states. In that particular process, excitation by absorption of photons is a way of harvesting energy. The same reason could be invoked for photochemical processes resulting in bond modifications such as dissociation, addition or insertion, abstraction or fragmentation and isomerization. However, it should be noted that modifying a bond requires a large amount of energy, which leads us to a second reason. When collisional kinetic energy is insufficient to overcome the energy barrier, the reaction has to occur by excitation to states of higher energy, for example, reached by absorption of UV radiations. The third reason for excited states enzyme reaction that can be identified has to do with the control of reaction. Some reactions are initiated when the enzyme is activated to a higher energy state, e.g., by absorption of a photon as in photodetection by rhodopsin in the retina [13] or the transfer of a phosphate group from ATP [14]. The triggering of a reaction, independently of random thermal fluctuations can also be achieved by binding of ligands controlling the reaction rate as known from allosteric regulation. The final and maybe most interesting reason is that excited states catalysis could provide an alternative reaction path to circumvent the energy barrier between substrate and product by making use of the excited state's very own PES [8]. For example, the antibonding character of electronic excited state could destabilize the substrate.

Because of their reactivity, excited states are short lived and therefore difficult to observe spectroscopically. Electron spin resonance (ESR) spectroscopy is the experimental method that has provided evidence of free radical intermediates in many enzyme reactions because it is designed to detect species with unpaired electrons. ESR allows the investigation of free radicals and transition elements in biological research. ESR spectroscopy does not allow group identification unlike infrared, nuclear magnetic resonance (NMR) or Raman spectroscopy. However, some ESR signals are typical such as the one for high-spin ferric iron in a rhombic environment. The features of the ESR spectrum depend strongly on the environment of the ion, especially the primary coordination sphere of the ligands. Several other experimental methods have been used in relation to excited states. The photochemical properties of

the excited states are often studied by measurement of the fluorescence and phosphorescence spectra and the luminescence lifetime. They provide information on energy transfer, electron transfer and photoreaction in the excited states. Time-resolved spectroscopy using laser flash photolysis is used to investigate the kinetics and mechanism of photo-reactions (Fig. 1).

The three usual approaches for computing excited states for a many-body problem in biomolecules are the configuration interaction (CI) [15], coupled cluster (CC) [16] and the time-dependent version of density functional theory (TDDFT) [17]. The CC with single, double and triple perturbation [CCSD(T)] approach provides the best trade-off between accuracy and efficiency, but the calculations are limited to small molecules because of the poor scaling to the number of electrons [18, 19]. The CI calculation is used for computing excited states' energies with near degeneracy, which occur in transition metals, breaking of bonds and resonance phenomena [20]. Actually, calculations of excited states with the CC methods can be problematic due to the construction of bra- and ket-states that often end up being not Hermitian conjugate to each other. This problem can, however, be solved by employing proper couple cluster techniques with respect to Hermitian conjugate states (see reference [21]). The advantage of TDDFT is the speed relative to other excited state methods, while it still provides reasonable results for excited states [22]. Some of the most popular program packages for calculating excited states are GAUSSIAN [23], Turbomole [24], COLOMBUS [25] and Molcas [26].

2.1 Excitation to a state of higher energy

Electronic excitation of a molecule can be achieved, especially in two manners. In photosynthesis, a photon can be absorbed by specific cofactors called chromophores functioning as antenna in enzymatic complexes. For an example, folate or deazaflavin extend the absorption range to longer wavelengths when used as co-factors in photolyase [27]. The stable hydrocarbon ring structure results in an extended conjugated π-system, which allows for absorption of photon without bond modifications. The polyene structure is responsible for the strong absorption in the UV and visible region. The absorption of light by an isolated chromophore is followed by thermal degradation and fluorescent emission, while quenching of the chromophores is responsible for the transfer of the excitation. A longer lifetime of the excited state increases the chance of quenching. In general, excited state processes are investigated in pump and probe experiments since these experiments can uniquely relate the photo-absorption to photo-emission and thus provide a clue on excited state occurrence [28].

Electronic excited states can also be induced chemically by exothermic reactions such as dissociative excitation where the excess energy is used to drive the electron transition from the ground state to an excited state. In the process of chemiluminescence, the electron then returns to the ground state by emitting a photon. The luciferase enzymes catalyze light emission of their luciferin substrate. Some luciferins require the presence of a co-factor to undergo oxidation [29]. The chemiluminescence reaction in fireflies between the photoprotein and ATP has been widely investigated. A high-energy cyclic peroxide intermediate is involved in the reaction [30]. The reaction mechanism is dependent on easily oxidized aromatic hydrocarbons to yield an excited non-reactive oxyluciferin. The role of the aromatic residue in the active site has been investigated by simulations and spectroscopy studies. These studies indicate that the tryptophan fluorescence is quenched by a Förster energy transfer mechanism to a luciferin molecule [31, 32] (Fig. 2).

The activation of enzymes can be obtained by transfer of high energy groups like high energy electrons from NADH/FADH or phosphorylation. Phophorylation-dephosphorylation of enzymes are commonly used to control enzymatic cascade processes. Phosphorylation allows the regulation of enzyme activity by transfer of a phosphate group from ATP to the enzyme by reversible and covalent binding to the hydroxy-group of the residues serine, threonine and tyrosine. A phosphorylation of residues in the diacylglycerol kinase upregulates its enzymatic activity [33]. It is assumed that protein phosphorylation stabilizes

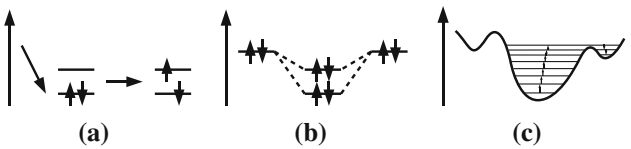

Fig. 1 Energy diagrams of various transitions from the ground state to an excited state of electrons in a molecule. The electrons are depicted as *arrows* symbolizing the spins. **a** Photoexcitation of an electron. **b** Ionization of electrons in a molecule. **c** Heat-induced conformational changes of a molecule that make transitions from higher states (e.g., vibrational) to lower ones within a well on the potential surface. *Horizontal lines* are energy states, while *vertical lines* symbolize transitions

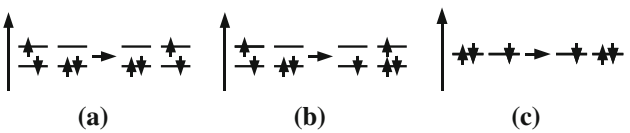

Fig. 2 A schematic energy diagram of excited electrons exchange. **a** Förster mechanism. **b** Electron transfer mechanism. **c** Hole mechanism. These figures are simplified sketches of the spin states of energy levels and are all allowed in Coulomb interactions, provided no spin-flips occur

different conformational states. The free energy of phosphorylation is large, −50 kJ/mol and can change the conformational equilibrium between different functional states of the enzyme as seen by phosphorylation of the H^+/K^+-ATPase [34]. Phosphorylation by the glycogen phosphorylase enzyme of a serine residue in the N-terminal changes a disordered polypeptide fragment into a distorted helix, strengthening the interaction between the subunits in the enzyme resulting in a functional enzyme [35].

2.2 Transfer of excitation

Once the enzyme complex is excited, some energy has to be transferred to the active site for a reaction to take place. Several excitation transfer mechanisms have been observed in enzymes.

The exchange of an excited electron can proceed by a Dexter mechanism [36] or a Förster mechanism [37]. The Dexter mechanism is the exchange of the excited electron from the donor for a non-excited electron from the acceptor. In the Förster mechanism, the excited electron on the donor molecule is de-excited while an electron on the acceptor molecule is excited. Quantum mechanical calculations based on CI expansions show that the Förster mechanism is efficient. The original paper of Förster [37] was intended for different processes involving interactions between electronic clouds under influence of changes in the inter-nuclear distance. The enzymatic process under consideration has been studied using different spectroscopic techniques, which reveal excitation energy transfer on a time scale of femtoseconds as in the photosynthetic complex II [38].

Excited electrons can be also transiently accepted by groups such as transition metals, which play a preponderant role in the process of reducing other groups. The reaction, by which a high potential iron sulfur protein supplies an electron to *S*-adenosylmethionine (SAM), making it a radical, is an example of such a reaction [39]. The subsequent transport of the electron results in the formation of charge-separated species. A redox potential is an indication of the thermodynamic driving force, and optimal electron transfer happens if the redox potentials are well adjusted. Charge-separated species are used as reducing and oxidizing reagents in reactions such as the dark reaction of photosynthesis due to the photoexcited singlet state of chlorophyll. The charge transfer can also proceed with hole transfer characterized by high quantum yield with longer lifetime [40]. The proton-coupled electron transfer (PCET) is important in many biological systems such as photosynthesis, respiration and detoxification reactions [41, 42]. The mechanisms of the PCET reactions have been studied theoretically to understand the process in detail. One of the theoretical approaches for simulating the PCET uses the molecular dynamics quantum transition (MDQT) surface hopping method [43, 44]. The principle of MDQT is an ensemble of trajectories propagated on a single adiabatic surface except for instantaneous transitions among the adiabatic states. To include the vibrationally excited states, a range of states are included using the state-averaged FGH-MCSCF method and these energy surfaces are included into the simulation [45–48]. At each step, the Tully's "fewest switches" algorithm [49] is invoked to determine if a quantum transition to another adiabatic or excited state should occur. This theoretical approach has been used on two different enzymes with proton-coupled electron transfer: "alcohol dehydrogenase (ADH) and dihydrofolate reductase (DHFR). The ADH enzyme catalyzes the reversible oxidation of alcohols to their corresponding aldehydes [50]". Nonadiabatic transitions occur in some of the real-time dynamical trajectories like the oxidation of benzyl alkoxide to benzaldehyde. The number of nonadiabatic transitions is found to increase the number of recrossing [51]. For the DHFR enzyme the vibrational excitations play a lesser role [52].

The radical mechanism is another way to transfer the excitation. The radical reaction is initiated by the formation of a radical, which then propagates the radical formation by hydrogen abstraction. A cascade reaction can be achieved through a sidechain network of cysteine such as in pyruvate formate-lyase [39].

Most of the excitations described here are of vibrational character, which involves the motion of the nuclei at much lower frequency than the electronic excitations. These vibrations of the nuclei also arise as nuclear relaxation every time the corresponding electrons are excited [53].

2.3 Reaction from excited states

The reactions from the excited states and the radical intermediates, which follow the transfer of an excitation to the enzyme active site have the particular property of proceeding through alternate reaction paths. Such an alternate path making use of electronic excited states has been suggested for the isomerization of photoactive yellow protein chromophore [54]. The catalysis of DNA repair by photolyase and membrane proteins with cation–pi effects are prototypical examples of proteins with a visible electronic functionality, which have been studied extensively in our research center. We describe in two examples how electronic, excited state processes can serve particular enzyme functions (Fig. 2).

2.3.1 Photolyase

The DNA-repair enzyme photolyase uses blue light to catalyze the splitting of thymine dimers formed by

exposure to UV radiation. The repair process involves the absorption of light by a chromophore, the reduction of the flavin cofactor and the subsequent injection of an electron into the thymine dimer, which result in spontaneous splitting. UV radiations in the region of 200–300 nm corresponding to energies of roughly 4–6 eV are sufficient to damage thymine even though the ionization energy of thymine is about 12 eV. The incident UV radiation provides the 4–5 eV required to break one of the many covalent bonds causing a major disruption of the thymine structure. The incident UV radiation could initiate a non-diagonal Frank–Condon transition in thymine, exciting an electron from the ground state structure to one of the unoccupied electronic states, followed by intra-bond or inter-bond energy transfer transitions (Fig. 3). A cascade along the vibrational levels gives the inter-nuclear distance sufficient time to adjust, allowing for intersystem crossing (ISC). The process may repeat itself a couple of times. Quite often, a spin-flip transition takes place during the ISC. Once this transition to a triplet state occurs, the excited state cannot decay quickly to ground state and forms an isomeric state of thymine (Fig. 4). There are many examples for the formation of such long-lived excited states in the photolysis of relatively simple polyatomic molecules such as formaldehyde and glyoxal [28]. The calculations of electronic structure of thymine and the dimer in the extended Hückel approximation have already indicated the presence of a number of excited states in this energy range and the energy of the dimer is about one-half to 1 eV lower than that of two thymine monomers. The occurrence of electronically excited states in the 4–5 eV range is further supported by preliminary DFT calculations using hybrid DFT B3LYP method [55, 56]. This involves a simple calculation of the HOMO/LUMO gap, which automatically comes out of the DFT calculation of the electronic structure of thymine dimer.

It is worth noting that the photo-induced repair process uses radiations of wavelength 400–580 nm corresponding to energies of 2–3 eV which is insufficient to split the

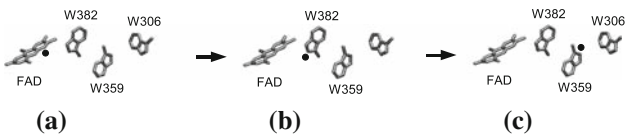

Fig. 3 Schematic representation of an excitation transfer in an enzyme complex: the radical transfer cascade for the photo-reduction of the FAD cofactor in the type I photolyase. The figure illustrates **a**, **b** the electron transfer from the three-ring co-factor, FADH, to the first of the three tryptophan amino acids, believed to be crucial, for the electron path in photolyase, and then **c** to the next tryptophan, etc. The excited electrons at one of the rings of FADH are transferred to the adjacent tryptophans consecutively as the *black dot*, representing an excited state electron, is transferred from one molecule at the left side to the molecules at the right

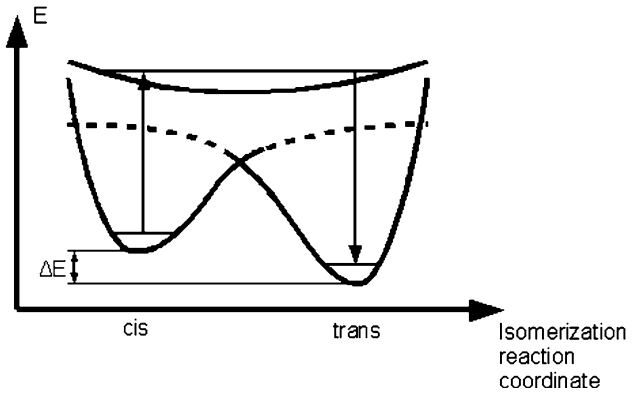

Fig. 4 Schematic energy diagram of an electronic, excited state isomerization where the barrier from cis to trans is overcome via an immediate transition to the electronic, excited state potential surface in full line above the two ground state wells. The excited potential surface contains a state (e.g., vibrational state) depicted by a *thin straight line*

damaged structure. The DFT calculation indicates that the deactivation process could release about 3–4 eV of energy per dimer splitting. This energy could cause impairment if it was radiated and absorbed resonantly by the environment, whereas radiative damages of the surroundings would be avoided if the splitting involved a radiationless transition. In atomic physics, such radiationless relaxation or deactivation is the characteristic of the Auger process. The hole-excited thymine dimer upon coming in the proximity of $FADH^{\bullet}$ interacts electrostatically with the loosely bound electron causing radiationless transition of one electron to the hole, which splits the thymine into two monomers. Another electron takes up the excess energy and is ejected into the medium or to the ground state of FADH, Fig. 3. In general, this process is allowed. It is usually a fast transition, although it's quantitative value depends on the nature of the orbitals used. Such fast transition in the final stage of the repair process supports the observations of Mees et al. [57] and Heelis [58]. In case $FADH^{*}$ is not a pure anion but representing a solvated electronic state, the Auger transition would return the solvated state to its ground state instead of ejecting the electron. As with the Auger effect, an electron falls to an orbital of lower energy and the excess energy is taken up by another electron. However, the hole is located in a molecular orbital rather than in an atomic inner shell and the energy involved is therefore much lower [7] (Fig. 5).

2.3.2 *Cation–pi interactions and excited states*

Cation–pi interactions are increasingly being recognized as an important factor in protein structure and function. The stabilization energy originates in part from electrostatic interaction between the cation and high-electron density

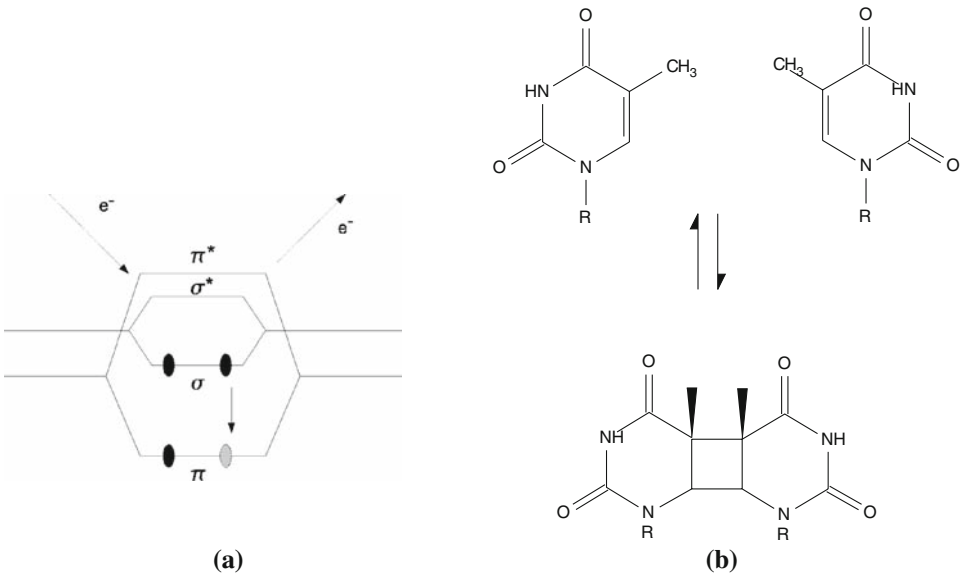

Fig. 5 The Bio-Auger effect. **a** A schematic illustration of the molecular orbitals and a possible mechanism for repair process. An electron is added from the enzyme and destabilizes the σ-bonds in the thyminedimer. The electrons are transfered into the hole of the π orbital, which regenerated the two thymines. **b** The dimerisation of the thymine and the reverse process

pi-orbitals from the aromatic moiety of Tyr and Trp residues (e.g., [59]).

Cation–pi interactions are directly related to excited states. For example, in the model peptide *N*-acetyl-Pro1-Pro2-Lys3-Tyr4-Asp5-Lys6-NH2 in solution, a perturbing field from the cationic (Lys3) ground state charge intermingles the excited state of the Tyr4 aromatic group [60]. Also, fluorescence studies of a diethylenetriamine, bearing two end pyrene fragments, reveal dual-mode fluorescence consisting of monomer and excimer emissions. The monomer emission intensity decreases with an increase in pH because of an electron transfer from the unprotonated nitrogen atoms to the excited pyrene fragment. The excimer emission is due to the static excimer formed via a direct photoexcitation of the intramolecular ground-state dimer of the end pyrene fragments. Addition of metal ions leads to pyrene-metal cation pi-complexes which suppresses the monomer photoexcitation. Eximer emission also decreases upon addition of metal cations, because the pyrene-metal cation pi-complex weakens pi-stacking interaction of the end pyrene fragments, leading to decreased stability of the dimer ground state [61].

3 Conclusion

The described excited state enzymes function by transition to excited states followed by transfer of energy to the active site for reaction known in photoactivated enzymes. The classification of enzymes with very different function and functioning was encouraged by the observation of shared general properties. The three excitation methods described, namely the absorption of a photon, chemical induction and binding of high energy groups correspond to relatively high energies for biological systems, thereby requiring specific structures for the absorption and the transfer of the excitation. The transfer process is achieved by efficient mechanisms involving interactions and transfers relying heavily on a precise structure. The photolyase and the Cation–pi interactions were described to illustrate excited state reactions. The specialized functions requiring the excited states evoked can thus be linked to the specialized structures observed.

The difficulty of experimental characterization of the excited state intermediates could be alleviated by time-resolved spectroscopy. Excited states enzyme reactions cannot be properly described by TST, and the development of a method to calculate the reaction properties will require a detailed description of all the mechanisms involved in the reactions. Computer calculations of excited states properties are limited to small molecules, so future studies should deal with model compounds such as flavin, tryptophan and active site metal ions with coordinated side chains.

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