

# Proton tunneling in hydrogen bonds and its implications in an induced-fit model of enzyme catalysis

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The role of proton tunneling in biological catalysis is investigated here within the frameworks of quantum information theory and thermodynamics. We consider the quantum correlations generated through two hydrogen bonds between a substrate and a prototypical enzyme that first catalyzes the tautomerization of the substrate to move on to a subsequent catalysis, and discuss how the enzyme can derive its catalytic potency from these correlations. In particular, we show that classical changes induced in the binding site of the enzyme spreads the quantum correlations among all of the four hydrogen-bonded atoms thanks to the directionality of hydrogen bonds. If the enzyme rapidly returns to its initial state after the binding stage, the substrate ends in a new transition state corresponding to a quantum superposition. Open quantum system dynamics can then naturally drive the reaction in the forward direction from the major tautomeric form to the minor tautomeric form without needing any additional catalytic activity. We find that in this scenario the enzyme lowers the activation energy so much that there is no energy barrier left in the tautomerization, even if the quantum correlations quickly decay.

## I. Introduction

An enzyme is a macromolecule that catalyzes one or more specific biological reactions without being consumed. Each reactant molecule that an enzyme acts upon is known as a substrate of this enzyme. The conversion of the substrate to one or more products involves the formation of unstable intermediate structures called transition states, while uncatalysed reactions can not occur at fast-enough rates because of the high energies of these molecules. Enzymes accelerate such slow-rate reactions by lowering the energy required to form the transition state in several ways [1, 2], e.g. by destabilizing the substrate, by stabilizing the transition state, or by leading the reaction into an alternative chemical pathway.

Enzymes must first recognize their specific substrates before moving on to catalyze the associated reactions. The favoured model for the enzyme and the substrate interaction is the induced-fit mechanism [3, 4], which enhances the recognition specificity in a noisy environment [5]. This model states that although initial intermolecular interactions are weak, they trigger a continuous conformational change in the binding site of the enzyme. This provides the structural complementarity between the enzyme and the substrate, in the manner of a lock and key. The catalytic site of the enzyme then accelerates the intermolecular conversion.

Another mainstream model for the enzyme - substrate interaction is the conformational selection [6, 7]. This model states that the enzyme exists in an equilibrium between the active and inactive conformations until the incoming substrate binding. Then, the intermolecular interaction stabilizes the active conformation of the enzyme. Unlike the induced-fit model, the conformational change upon the substrate binding is not so significant in the conformational selection model. However, it is still of importance in the catalytic activity of the enzyme.

Enzymes are divided into six major classes depending on the type of chemical reaction they catalyze: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. The role of proton tunneling in enzyme catalysis has been investigated so far particularly focusing on the class of oxidoreductases that oxidize a substrate by transferring its hydrogen (H) to an acceptor molecule through intermolecular H-bonds.

According to the kinetic isotope effects studies, observed rates of several enzyme-catalyzed oxidoreduction reactions cannot be explained solely in terms of a semi-classical transition-state theory without a quantum-mechanical correction for the tunneling of H species [8–15]. Moreover, a number of different studies, including the kinetic isotope experiments [11, 12], molecular dynamic simulations [16–18], quantum mechanical molecular mechanics calculations [19–23], and qualitative quantum rate models [24] give prominence to the role of the conformational change in promoting tunneling.

Conversely, some experimental tests using artificial catalysts [25] and realistic simulations based on path integral formulation [26–31] suggest that quantum tunneling in some oxidoreductase (and also lyase) enzymes does not enhance reaction rates sufficiently enough to be regarded as catalytic. Hence, the role of tunneling of H species in catalytic reactions is still open to debate [32–34].

The debate summarized above generally focuses on the enzymatic reactions that involve a proton transport between carbon atoms, rather than the nitrogen or oxygen atoms that are expected to form H-bonds strong enough to show a quantum character. Also, the conformational changes of the enzymes are usually considered in the context of conformational selection model rather than the induced-fit model that requires a significant change in the conformation. We extend the present debate to include strong H-bonds and large conformational changes by taking into account the tautomerization reactions in which protons are relocated inside the substrate molecules.

A special subclass of structural isomerases known as the tautomerase superfamily is normally responsible for the tautomerization reactions. The reactions catalyzed by the known members of this superfamily usually involve proton transport from and/or to a carbon atom [35] too. However, neither the nature of tautomerization nor its role in biocatalysis is limited to tautomerase activity. In particular, tautomerization of nucleotides occurs generally via proton transfer between nitrogen and oxygen atoms, and is also in charge of the initial stages of various bio-catalyzed reactions.

Exchange of protons is likely between the carbonyl and/or amino groups of nucleotides and solvent molecules. Thus, a single nucleotide can exist in many tautomeric forms due to the solvent-mediated tautomerization. One of these forms predominates under physiological conditions and is called the major tautomer. However, tautomeric preferences of different enzymes may be also different, i.e., whereas the major tautomeric form of a nucleotide is the substrate of an enzyme, another enzyme may require one of the possible minor tautomeric forms of the same nucleotide. As an example, to prevent point mutations, members of the transferase class of enzymes that drive DNA replication should ensure that each thymine nucleotide exists in its major tautomeric form during catalytic activity. On the other hand, the DNA repair enzyme Nei-like 1, a member of hydrolase class of enzymes, converts thymine glycol nucleotides to minor tautomeric forms during the substrate binding stage, and this tautomerization gives rise to a more efficient catalytic activity [36]. Moreover, nucleotide tautomerization also plays a direct role in a number of different functions of RNA enzymes [37].

In addition to the likelihood of quantum H-bonds in nucleotide tautomerization and its importance in biological functions, the induced-fit mechanism also appears to be common in nucleotide recognition [38–42].

## II. Model and Methods

We examine a generic molecular recognition event in which two quantum H-bonds are formed between the substrate and a multifunctional enzyme that requires the tautomerization of the substrate to execute a different biological function which is outside the scope of the paper. Consistent with the induced-fit model, we allow a significant conformational change in the binding site of the enzyme. Then, we approach the problem of proton motion in these H-bonded system using the tools of quantum information theory where correlations are routinely regarded as a resource for specific tasks. Although the binding site is reshaped in a fully classical way, we find that this classical motion increases the quantum correlations in the intermolecular H-bonds and spreads them among all of the four H-bonded atoms. Finally, we discuss the possibility of using these quantum correlations as a resource for the tautomerization of the substrate in the first catalytic stage of multi-step enzyme catalysis.

### A. Biological scenario

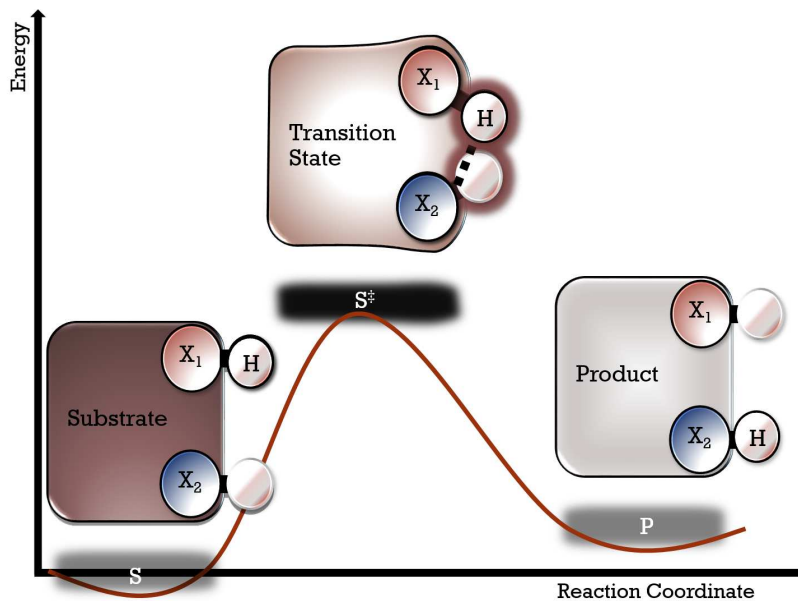


FIG. 1. A substrate (S), transition state structure ( $S^\ddagger$ ), and product (P) in a generic tautomerization reaction. S and P are constitutional isomers. Although the intermolecular conversion from S to P is nothing more than the movement of a proton from  $X_1$  to  $X_2$ , a more reactive intermediate ( $S^\ddagger$ ) is involved in the reaction. Since  $S^\ddagger$  corresponds to a saddle point on the potential energy surface, the spontaneous tautomerization occurs very slowly.

We consider a generic nucleotide existing in its major tautomeric form as the substrate (S) in a putative tautomerization event as shown in Fig. 1. Here, S is converted to a product (P) that corresponds to a minor tautomeric form of the molecule originating from the relocation of a proton from one electronegative atom/group ( $X_1$ ) to another ( $X_2$ ) like oxygen or nitrogen. A direct relocation due to the tunneling is not possible because of the large bond angle  $\phi_{12} \equiv \angle HX_1X_2$ . Thus, the molecule undergoes a conformational change resulting in an unstable intermediate structure denoted by  $S^\ddagger$ . This new conformation of the molecule allows a bond angle smaller than  $\pi/2$  that facilitates orbital interactions and proton tunneling between  $X_1$  and  $X_2$ . However, as  $S^\ddagger$  corresponds to the highest potential energy along the reaction coordinate, this tautomerization reaction is not likely to occur on its own.

In aqueous solution, water molecules can mediate the interconversion from S to P in a two-step reaction consisting of subsequent protonation and deprotonation processes. If a proton-donating water molecule interacts with  $X_2$  first, a cation intermediate  $S^\ddagger_+$  precedes the P. Otherwise, the water-mediated reaction involves the formation of an anion intermediate  $S^\ddagger_-$ . However, P is expected to be rapidly converted back to S in both cases. Hence, the probability of P in the equilibrium should not be high enough for an enzyme that requires P to initialize its catalytic function.

Conversely, consider now the enzyme-catalyzed tautomerization during a generic induced-fit recognition event where two H-bonds are formed between the enzyme (E) and S (Fig. 2). The atoms/molecules  $X_3$  and  $X_4$  that participate in this intermolecular interaction are continuously tilted by the interaction until the bond angles  $\phi_{13}$  and  $\phi_{42}$  reach

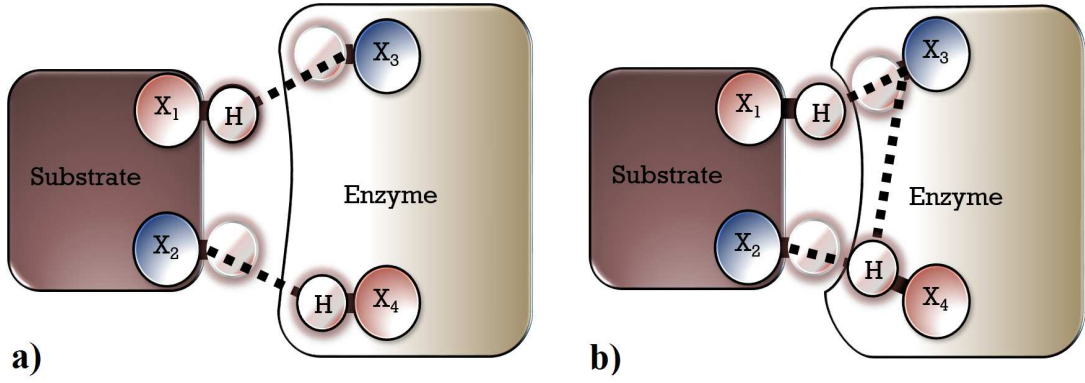


FIG. 2. The generic induced-fit model under consideration. (a) Hypothetical interaction where two intermolecular H-bonds are formed between an enzyme and the substrate. (b) Changes occur in the binding site of the enzyme in accordance with the induced-fit model. Note that not only  $\phi_{13}$  and  $\phi_{42}$ , but also  $\phi_{43}$  becomes smaller.

to the values that maximize the strength of intermolecular H-bonds. We assume here that (i) the binding site of E returns back to its initial configuration at end of the first catalytic stage and (ii) the following second catalytic stage cannot be initialized unless S is converted to P before that moment.

We can comprehend time-scales associated with the conformational transitions of the enzyme's binding site by using the following analogy. We visualize an imaginary spring that connects the unoccupied and the occupied proton locations near  $X_3$  and  $X_4$  in the binding site (see Fig. 2-a). The first conformational change that occurs according to the induced-fit mechanism (Fig. 2-b) corresponds to the compression of the spring, whereas the second conformational change that returns the enzyme back to its native conformation corresponds to the extension of the spring. Note that there is a close relationship between the first conformational change and the binding energy of intermolecular H-bonds: the initial binding energy of weak intermolecular H-bonds triggers the first conformational change that in turn increases the strength and the binding energy of H-bonds. Thus, the binding energy should be visualized as an external force exerted on the spring that is responsible for the compression of the spring from its equilibrium length, as it increases with compression. However, the deformation of the enzyme's conformation stops at the end of the binding stage, which means that the compression of the spring should come to an end at this point. This can be provided only by a restoring force that applies to the spring and quantifies the enzyme's tendency to return back to its initial state. This restoring force should be initially smaller but increases faster than the external force during compression. That is to say, the spring under consideration is a nonlinear spring that hardens as it is compressed. In this case, the compression of the spring constantly decelerates and finally stops when the restoring force becomes equal to the external force.

The enzyme - substrate complex does not become frozen after the binding stage. Instead, the molecules decouple from each other and the enzyme undergoes the second conformational change. This corresponds to the point when the external force exerted on the spring disappears and the spring immediately starts to extend to reach its equilibrium length. The extension motion is rapid compared to the preceding compression as the net force that drives the process is not the difference between the external and restoring forces but the restoring force itself. Thus, it is plausible to describe the conformational change that decouples the binding site of the enzyme from the substrate and converts it back to the initial state on a time-scale  $\tau_2$  that is much smaller than time-scale  $\tau_1$  over which the enzyme - substrate complex reaches the optimum intermolecular binding energy.

## B. Physical model

### 1. Motion of the proton between two atoms/molecules

The locations between which the proton tunnels back and forth can be regarded as the sites of an interaction network in such a way that each site  $j = \{1, 2\}$  is associated with the bonding orbital  $\sigma_{X_j-H}$  (Fig. 3-a). Then the proton is expected to move from one site to another in accordance with the Hamiltonian

$$H_{HB} = \sum_{j=1}^2 W_j \hat{n}_j - J_{12}(a_1^\dagger a_2 + a_1 a_2^\dagger) + V_{12} \hat{n}_1 \hat{n}_2 + \lambda_{12} \mathbb{I}_{12}, \quad (1)$$

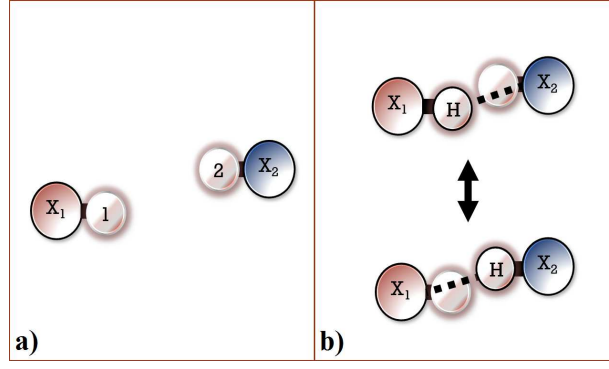


FIG. 3. Definition of H-bonding. (a) A simple depiction of the H-bonded atoms/groups  $X_j$ . When the proton of the H atom resides at location  $j = \{1, 2\}$ ,  $X_j$  is called the proton-donor. (b) Elongation of the covalent bond between the H atom and the proton-donor (solid black stick) is an indicator of a H-bond (dashed black line). Due to intermolecular orbital interactions, the proton tunnels back and forth through the H-bond as shown by the two-sided arrow.

where  $\hat{n}_j = a_j^\dagger a_j$  is the proton number operator at site  $j$ ,  $a_j^\dagger$  and  $a_j$  are respectively proton creation and annihilation operators that obey the fermion anticommutation relations. On-site energy  $W_j$  can be taken to be the total potential felt by a proton at  $j$ th site.  $J_{12}$  stands for the orbital interactions that drive proton tunneling.  $V_{12}$  is introduced to penalize the case in which there is one proton at each site.  $\lambda_{12}$  is a constant responsible for the total intermolecular interactions between  $X_1$  and  $X_2$ .

Each of the coefficients in Eq. (1) exhibits a different functional dependence on geometric parameters such as the length of the single  $X_j$ -H covalent bond ( $r_j$ ), the separation between  $X_1$  and  $X_2$  ( $R_{12}$ ) and the angle ( $\phi_{12} \equiv \angle HX_1X_2$ ). The key coefficient here is the hopping constant  $J_{12}$ . Its functional dependence on the geometric parameters can be written in a similar way to the coupling constant of diabatic state models [43, 44] as:

$$J_{12} = J_0 \cos(\phi_{12}) \frac{R_{12} - r_1 \cos(\phi_{12})}{\sqrt{R_{12}^2 + r_1^2 - 2R_{12}r_1 \cos(\phi_{12})}} e^{-b_0(R_{12}-R_0)}, \quad (2)$$

where  $J_0$ ,  $b_0$ , and  $R_0$  depend on the chemical identities of  $X_1$ ,  $X_2$  and their environment. This functional dependence guarantees the directionality that is a critical property of H-bonds.  $J_{12}$  becomes  $J_0 e^{-b_0(R_{12}-R_0)}$  for linear H-bonds and decreases slightly by the increase of  $\phi_{12}$ . When  $\phi_{12}$  reaches to the value of  $\pi/2$ , it vanishes and the proton can not tunnel between  $X_1$  and  $X_2$  anymore even if the separation  $R_{12}$  is sufficient for the formation of a quantum H-bond. However, it is important to note that our results in this study do not require the exact form given in (2). The only requirement is that  $J_{12}$  should be non-zero at small bond angles, and should vanish when the bond angle becomes larger.

To obtain a pseudo-spin Hamiltonian by preserving the anti-commutation relations, we apply the Jordan-Wigner transformation to  $a_j$ ,  $a_j^\dagger$ , and  $\hat{n}_j$  in (1) with the convention for Pauli  $z$  operator that  $\sigma_z^{(j)} = |0_j\rangle\langle 0_j| - |1_j\rangle\langle 1_j|$ . Then, we arrive at a two-spin Heisenberg XXZ model under one homogeneous and one inhomogeneous magnetic field,

$$H_{HB} = J_x(\sigma_x^{(1)} \otimes \sigma_x^{(2)} + \sigma_y^{(1)} \otimes \sigma_y^{(2)}) + J_z \sigma_z^{(1)} \otimes \sigma_z^{(2)} + (B + b) \sigma_z^{(1)} + (B - b) \sigma_z^{(2)} + \tilde{\lambda}, \quad (3)$$

with parameters  $J_x = -J_{12}/2$ ,  $J_z = V_{12}/4$ ,  $\tilde{\lambda} = \lambda_{12} + (2W_1 + 2W_2 + V_{12})/4$ ,  $B = -(W_1 + W_2 + V_{12})/4$ ,  $b = -(W_1 - W_2)/4$ . The eigensystem of this pseudo-spin Hamiltonian can be written in an increasing order of eigenvalues as:

$$\begin{cases} e_1 = -J_z - 2\sqrt{b^2 + J_x^2} + \tilde{\lambda}, & |e_1\rangle = (\eta_-|01\rangle + |10\rangle)/(1 + \eta_-^2)^{\frac{1}{2}}, \\ e_2 = -J_z + 2\sqrt{b^2 + J_x^2} + \tilde{\lambda}, & |e_2\rangle = (\eta_+|01\rangle + |10\rangle)/(1 + \eta_+^2)^{\frac{1}{2}}, \\ e_3 = -2B + J_z + \tilde{\lambda}, & |e_3\rangle = |11\rangle, \\ e_4 = +2B + J_z + \tilde{\lambda}, & |e_4\rangle = |00\rangle, \end{cases} \quad (4)$$

where  $\eta_{\pm} = (b \pm \sqrt{b^2 + J_x^2})/J_x$ . The ground state  $|e_1\rangle$  is just a two-qubit representation of the state  $\alpha|X_1-H \cdots X_2\rangle + \beta|X_1 \cdots H-X_2\rangle$  that describes a generic H-bond. Unlike the one-qubit representation of the same state that is used in the spin-boson and the diabatic states models found in the literature, this two-qubit representation can investigate quantum correlations such as entanglement and discord generated in H-bonds. This is an advantage of our quantum informational perspective that stands to yield new insights since there is a high amount of correlations in biomolecular interactions and quantum physics is better suited to describe all correlations contained in a complex

system in a rigorous way [45]. Also, the ground state energy  $e_1$  goes to the expected energy of a classical bond, i.e.  $W_1 + \lambda$ , when  $J_x$  vanishes. Moreover, this energy seems to be suitable for energy decomposition analysis as it equals  $W_1 + \lambda + J_{12}$  for symmetric H-bonds.

Besides these properties of the ground state, the last two excited states respectively represent the state of  $X_1$  and  $X_2$  atoms of the ionic intermediate structures  $S_+^\ddagger$  and  $S_-^\ddagger$  formed in water-mediated tautomerization.

In the following, each of the locations allowed for the protons is regarded as a pseudo-spin, explained above. The formation of a H-bond between two atoms/molecules  $X_j$  and  $X_{j'}$  in the biological scenario under consideration is then described as the coupling of the corresponding pseudo-spins by the Hamiltonian  $H_{HB}^{(jj')}$  given in (3).

## 2. Tautomeric transitions due to the motion of protons

Here, we will represent S, P, and all the possible transition states between them by different eigenstates of a single Hamiltonian. This may seem like an oversimplification, since each of these different molecules is actually corresponding to the ground state of a separate Hamiltonian with many electronic levels. However, it is just a projection of all the extrema of the potential energy surfaces of the nucleotide onto a single energy spectrum, representing a unification of all the tautomeric forms along possible reaction coordinates from S to P into a hypothetical generic molecule. This type of modeling, which assigns a global time-independent Hamiltonian for a transition from an initial to a final state is quite common in quantum thermodynamics.

In this respect, we collect all the other degrees of freedom apart from the two pseudo-spins in the molecular structure into a single macromolecular configuration  $C$  and label its state as  $|\zeta\rangle_C$ . That is to say, the whole state  $|N\rangle$  representing the nucleotide's tautomeric form  $N = \{S, P, S_+^\ddagger, S_-^\ddagger, S_+^\ddagger, \dots\}$  is taken to be the product of its configuration state  $|\zeta_N\rangle_C$  and its pseudo-spin state  $|\psi_N\rangle_{12}$ .

Let's first consider the states of S and P. To prevent a direct transition between these forms, both  $\phi_{12}$  in S and  $\phi_{21}$  in P are taken to be  $\pi/2$ . Then the hopping constant  $J_{12}$  substituted in  $H_{HB}^{(12)}$  that describes the pseudo-spin interaction in either form vanishes, i.e.  $|\psi_S\rangle_{12} = |10\rangle_{12}$  and  $|\psi_P\rangle_{12} = |01\rangle_{12}$ . In other words, the H-bonding interaction between  $X_1$  and  $X_2$  does not have a quantum character. When one of the forms is converted to the other, the energy of this classical interaction also changes. However, no significant difference in the molecular structure is expected due to this change. Thus, we can assign the same configuration state  $|G\rangle_C$  to both forms:  $|S\rangle = |G\rangle_C \otimes |10\rangle_{12}$  and  $|P\rangle = |G\rangle_C \otimes |01\rangle_{12}$ .

Similarly, neither the protonation of  $X_2$  nor the deprotonation of  $X_1$  is likely to alter the rest of the molecular structure. Hence, the ionic transition states  $S_-^\ddagger$  and  $S_+^\ddagger$  can respectively be described by  $|G\rangle_C \otimes |00\rangle_{12}$  and  $|G\rangle_C \otimes |11\rangle_{12}$ . Conversely, a more energetic configuration,  $|E\rangle_C$ , should be assigned to the neutral transition state  $S^\ddagger$  as the proton tunneling between  $X_1$  and  $X_2$  requires a bond angle less than  $\pi/2$  as is given Fig. 1. Then we end up with  $|S^\ddagger\rangle = |E\rangle_C \otimes |e_1\rangle_{12}$ .

Note that the ground and excited states of the molecular configuration,  $|G\rangle_C$  and  $|E\rangle_C$ , which we can visualize them like macromolecular logic qubits  $|0\rangle_L$  and  $|1\rangle_L$ , need not to include any quantum degree of freedom.

At this point, it is possible to describe tautomerization processes as transitions between energy levels of a single Hamiltonian constructed as:

$$\begin{aligned} H_N = & E_g |G\rangle_C \langle G| + E_e |E\rangle_C \langle E| \\ & + |G\rangle_C \langle G| \otimes H_{HB}^{(12)}(r, R, \phi = \pi/2) \\ & + |E\rangle_C \langle E| \otimes H_{HB}^{(12)}(r', R', \phi' < \pi/2), \end{aligned} \quad (5)$$

with an eigensystem:

$$\begin{cases} \epsilon_1 = E_g + W_1 + \lambda_{12}, & |\epsilon_1\rangle = |G\rangle_C \otimes |10\rangle_{12} \equiv |S\rangle, \\ \epsilon_2 = E_g + W_2 + \lambda_{12}, & |\epsilon_2\rangle = |G\rangle_C \otimes |01\rangle_{12} \equiv |P\rangle, \\ \epsilon_3 = E_e + \epsilon_-, & |\epsilon_3\rangle = |E\rangle_C \otimes |\epsilon_-\rangle_{12} \equiv |S^\ddagger\rangle, \\ \epsilon_4 = E_e + \epsilon_+, & |\epsilon_4\rangle = |E\rangle_C \otimes |\epsilon_+\rangle_{12} \equiv |\tilde{S}^\ddagger\rangle, \\ \epsilon_5 = E_g + \lambda_{12}, & |\epsilon_5\rangle = |G\rangle_C \otimes |00\rangle_{12} \equiv |S_-^\ddagger\rangle, \\ \epsilon_6 = E_g + V_{12} + \lambda_{12}, & |\epsilon_6\rangle = |G\rangle_C \otimes |11\rangle_{12} \equiv |S_+^\ddagger\rangle, \\ \epsilon_7 = E_e + \lambda'_{12}, & |\epsilon_7\rangle = |E\rangle_C \otimes |00\rangle_{12} \equiv |\tilde{S}_-^\ddagger\rangle, \\ \epsilon_8 = E_e + V'_{12} + \lambda'_{12}, & |\epsilon_8\rangle = |E\rangle_C \otimes |11\rangle_{12} \equiv |\tilde{S}_+^\ddagger\rangle, \end{cases} \quad (6)$$

where  $\epsilon_- = e_1(r', R', \phi' < \pi/2)$  and  $\epsilon_+ = e_2(r', R', \phi' < \pi/2)$ . Also,  $\tilde{S}^\ddagger$ ,  $\tilde{S}_-^\ddagger$ , and  $\tilde{S}_+^\ddagger$  are the first possible excitations from  $S^\ddagger$ ,  $S_-^\ddagger$  and  $S_+^\ddagger$  respectively.

### 3. Open quantum system dynamics

The configuration of atoms/groups and the pseudo-spins are expected to be coupled to different phonon environments in different ways. For example, the configuration states are likely to exchange energy with a heat bath  $B$  in a reversible manner

$$H_{BC} = \sum_k g_k |G\rangle_C \langle E| \otimes b_k^\dagger + g_k^* |E\rangle_C \langle G| \otimes b_k, \quad (7)$$

where  $b_k^\dagger$  and  $b_k$  are phonon creation and annihilation operators associated with the  $k$ th oscillator mode of the bath. These bath operators can be related to the rotational vibration modes such as bending or libration modes that change the orientation of  $X_1$  and  $X_2$ . Such rotational vibrations may occur due to the collisions with solvent molecules or as a result of the intramolecular nucleotide dynamics. As  $X_1$  and  $X_2$  are covalently bonded to the rest of the molecule, these vibrations should be dependent on the orientation of the whole other atoms/groups close to them.

However, dominant environmental effect on the proton should be originated from the  $X_j$ -H stretch vibrations that aren't expected to affect rest of the molecule in a significant way. Charge fluctuations in the surrounding molecules may drive these oscillations and we can incorporate them into our model by coupling the position of the proton linearly to the equilibrium positions of phonons through

$$H_{\tilde{B}S} = \sum_{j=\{1,2\}} \sigma_z^{(j)} \otimes \sum_k \tilde{g}_{k,j} (\tilde{b}_{k,j}^\dagger + \tilde{b}_{k,j}). \quad (8)$$

where  $\tilde{b}_{k,j}^\dagger$  and  $\tilde{b}_{k,j}$  are phonon creation and annihilation operators of a second heat bath  $\tilde{B}$  and they are associated with the  $k$ th oscillator mode at the  $j$ th proton location.  $H_{\tilde{B}S}$  guarantees that the interaction of the pseudo-spins with this second heat bath  $\tilde{B}$  destroys the quantum correlations between them and has no further effect on the configuration.

As the magnitudes of  $E_g$  and  $E_e$  are significantly higher than the other components in the eigenenergies given in Eq. (6), the evolution of configuration and pseudo-spins in the nucleotide can be assumed to be separated in such a way that the former is not affected by the latter, but not vice versa. In this respect, we can solve a master equation for the configuration and use this solution in the evolution of the pseudo-spins. Here, the evolution of either the pseudo-spin or the configuration state is described using the Markovian master equation in the Lindblad form [46], which is one of the key elements of the theory of quantum thermodynamics [47],

$$\frac{d\rho}{dt} = -\frac{i}{\hbar} [H + \hbar H_{LS}, \rho] + \mathcal{D}(\rho), \quad (9)$$

where  $H_{LS}$  is the Lamb shift Hamiltonian providing an environment-induced unitary contribution to the dynamics:

$$H_{LS} = \sum_{\omega} \sum_{j,j'} S_{jj'}(\omega) A_j^\dagger(\omega) A_{j'}(\omega), \quad (10)$$

whereas  $\mathcal{D}$  is the dissipator responsible for the irreversible dynamics:

$$\mathcal{D}(\rho) = \sum_{\omega} \sum_{j,j'} \gamma_{jj'}(\omega) (A_{j'}(\omega) \rho A_j^\dagger(\omega) - \frac{1}{2} \{A_j^\dagger(\omega) A_{j'}(\omega), \rho\}). \quad (11)$$

While solving this master equation for the pseudo-spin state,  $\omega$  and  $A_j(\omega)$  are respectively taken to be the Bohr frequencies and the Schrödinger picture eigenoperators of the pseudo-spin Hamiltonian  $H_{HB}$  in (3), i.e.,  $\omega = (e_j - e_{j'})/\hbar$  and  $A_j(\omega) = \sum_{j'',j'''} |e_{j''}\rangle \langle e_{j'''}| A_j |e_{j'''}\rangle \langle e_{j''}|$  where  $A_j$  are the Pauli  $z$  operators in accordance with the Eq. (8). Also, the coefficients  $S_{jj'}(\omega)$  and  $\gamma_{jj'}(\omega)$  are defined as the imaginary part and one half of the real part of the one-sided Fourier transformation of the thermal correlation function of heat bath  $\tilde{B}$ .

Parameters of the pseudo-spin Hamiltonian  $H_{HB}$  used in this solution should change depending on the configuration state in line with the Eq. (5). To do so, if the configuration is in the state  $|G\rangle_C$ ,  $\omega$  and  $A_j(\omega)$  are evaluated using the eigensystem of  $H_{HB}$  that is calculated with a vanishing hopping constant  $J_x$ . This makes the dynamics of the pseudo-spins fully separable from each other and corresponds to a pure two-qubit dephasing process. Conversely, a non-vanishing  $J_x$  is taken into account when the configuration is in the state  $|E\rangle_C$ . This couples the dynamics of the pseudo-spins to each other and leads to an evolution that brings the pseudo-spin states to a detailed balance only between  $|e_1\rangle_{12}$  and  $|e_2\rangle_{12}$  in the stationary state.

On the other hand, the evolution of configuration state should be independent from the pseudo-spin state. Hence, the master equation (9) is solved for the configuration state using the Bohr frequencies and eigenoperators of an effective

Hamiltonian  $H_C \approx E_g|G\rangle_C\langle G| + E_e|E\rangle_C\langle E|$ . However, the eigenoperators  $A_j(\omega)$  cannot be directly constructed from  $H_C$  and  $H_{BC}$ . The interaction Hamiltonian (7) is first decomposed into the form  $\sum_j A_j^{(C)} \otimes B_j^{(B)}$  with  $A_j^{(C)}$  and  $B_j^{(B)}$  are Hermitian operators on the Hilbert spaces of the configuration  $C$  and the bath  $B$ . Moreover, the coefficients  $S_{jj'}(\omega)$  and  $\gamma_{jj'}(\omega)$  are defined for the heat bath  $B$  this time. This solution describes a thermalization process.

#### 4. Enzyme's conformational changes during the induced-fit mechanism

Two allowed proton locations in the binding site of E are also regarded as pseudo-spins, e.g.,  $|\psi_E(t_0)\rangle_{34} = |01\rangle_{34}$ . Furthermore, we take into account the conformation of this site in a similar way and denote it by  $C'$ :  $|\zeta_E(t_0)\rangle_{C'} = |G'\rangle_{C'}$ . However, unlike the nucleotide's conformation  $C$ ,  $C'$  is assumed to change in a classical and gradual way because of the intermolecular interaction so that its pseudo-spins are continuously tilted. Thus, the bond angles  $\phi_{13}$  and  $\phi_{42}$  become smaller and the resultant decrease in the energy of intermolecular H-bonds strengthens the binding interaction.

In accordance with the biological scenario under consideration (see Sec. II A), the time-scale  $\tau_1$  of the binding interaction due to the induced-fit mechanism is supposed to be much larger than  $\tau_2$ , the time-scale over which E undergoes a conformational change that converts  $C'$  back to the initial state  $|G'\rangle_{C'}$ .

As the interaction Hamiltonian changes slowly in time relative to the conformational change that follows, the instantaneous eigenstates of the binding interaction are assumed to evolve independently. Hence, the enzyme - substrate complex (ES) is considered to be in the corresponding ground state at every instant of time until it reaches the maximum complementarity between E and S. On the other hand, as E rapidly returns back to its initial state after this point due to the relation  $\tau_2 \ll \tau_1$ , the reverse conformational change is supposed to be driven by a sudden post-selection measurement on the pseudo-spins of E which accompanies the loss of energy from its configuration  $C'$  to the heat bath  $B$ .

### C. Model Parameters

Bath descriptions in our model can be made to include realistic correlation functions that allow us to probe the actual dynamics in real-time. It is also possible to work in the equilibrium without specifying the bath correlation functions. In fact, as will be shown in the following section, the steady state of the chosen master equation requires the extraction of only two parameters,  $E_e - E_g$  and  $\epsilon_+ - \epsilon_-$  from the biochemical data.

$E_e - E_g$  can be estimated using the activation energy values of the nucleotide tautomerization processes found in the literature. As an example, the energy barrier for the intramolecular single proton transfer on the Watson-Crick edge is calculated in the gas phase as 41.90 and 47.42 kcal/mol for thymine [48], 34.3 kcal/mol for guanine [49], and 45.6 kcal/mol for adenine[50]. To be consistent with these values, we set  $E_e - E_g$  to 42 kcal/mol when required in what follows.

Since  $\epsilon_+ - \epsilon_-$  equals to  $((W_1 - W_2)^2 + 4J_{12}^2)^{1/2}$ , we write  $\epsilon_+ - \epsilon_- \geq W_2 - W_1 = \epsilon_2 - \epsilon_1$ . That is to say, the value of  $\epsilon_+ - \epsilon_-$  is bounded below by the energy difference between the S and P tautomers of the nucleotide. This difference is calculated as 13.08 and 18.75 kcal/mol for thymine [48], 1.3 kcal/mol for guanine [49], and 12.6 kcal/mol for adenine[50] in the tautomerization processes given in the previous paragraph. Hence, the ratio of  $(E_e - E_g)/(\epsilon_2 - \epsilon_1)$  is equal to 3.20336 and 2.52907 for thymine, 26.3846 for guanine, and 3.61905 for adenine. Excluding the guanine because of the apparent incompatibility with the others, the mean of this ratio is found to be 3.11716. Then we can substitute  $1/3 \times (E_e - E_g) = 14$  kcal/mol for  $\epsilon_+ - \epsilon_-$  since it should be just above the value of  $\epsilon_2 - \epsilon_1$  for relatively small values of  $J_{12}$ .

Unless stated otherwise, we generate numerical predictions from the model using the values given above. To explore the sensitivity of the predictions to these values, we squeeze the energy levels of the Hamiltonian given in (5) when it is necessary. In this respect, we decrease the value of  $E_e - E_g$  down to 34 kcal/mol, while increasing the value of  $\epsilon_+ - \epsilon_-$  up to 19 kcal/mol.



### III. Results and Discussions

#### A. Uncatalysed Reaction

In the absence of enzymes that catalyze the reaction, the interaction between the nucleotide and two heat baths  $B$  and  $\tilde{B}$  is responsible for the spontaneous tautomerization  $|S\rangle \leftrightarrow |S^\ddagger\rangle \rightarrow |P\rangle$ . Such a tautomerization can occur only if each of the interactions  $H_N$ ,  $H_{BC}$ , and  $H_{\tilde{B}S}$  comes to the fore one by one in the order given in what follows: the initialization of the transformation from  $|S\rangle$  to  $|P\rangle$  requires the excitation of configuration  $C$  due to an energy absorption from the heat bath  $B$  through  $H_{BC}$ . The resultant state  $|E\rangle_C \otimes |10\rangle_{12}$  is a coherent superposition of  $|\epsilon_3\rangle = |S^\ddagger\rangle$  and  $|\epsilon_4\rangle$ . Immediately after this excitation, the self-Hamiltonian of the molecule drives the evolution towards  $S^\ddagger$  as  $\epsilon_3 < \epsilon_4$ . The transformation from this transition state to  $|P\rangle$  depends on (i) the destruction of the quantum correlations of the pseudo-spins through  $H_{\tilde{B}S}$  and (ii) the loss of energy from the configuration atoms/groups through  $H_{BC}$ . These two interactions in arbitrary order lead to a mixture of  $|S\rangle$  and  $|P\rangle$ .

As the configuration state represents the whole atoms/groups in nucleotide (except for the proton of the H atom whose locations are regarded as pseudo-spins), the occurrence of its excitation is expected to be quite rare. Since the spontaneous inter-conversion of tautomers requires this excitation to be initialized, its occurrence is expected to be rare also. We show this mathematically here.

The master equation approach introduced above relies on the assumption that the configuration energy  $E_g$  or  $E_e$  dominates the total energy of the nucleotide (see Sec. II B 3). This allows us to first investigate the configuration state dynamics alone and then explore the pseudo-spin state dynamics for the predetermined configurations in time.

The initial state in an uncatalysed reaction is  $|S\rangle = |G\rangle_C \otimes |10\rangle_{12}$ . The steady-state solution of the master equation of the configuration state does not depend on the initial state and equals  $P_g|G\rangle_C\langle G|_C + P_e|E\rangle_C\langle E|_C$  where  $P_{g/e} = e^{-\beta E_{g/e}} / (e^{-\beta E_g} + e^{-\beta E_e})$ . When the configuration state is fixed to  $|G\rangle_C$ , there isn't any coupling between the pseudo-spins and so the interaction  $H_{BC}$  leads to decoherence. Hence, the initial pseudo-spin state  $|\psi(t_0)\rangle_{12} = |10\rangle_{12}$  that does not carry any quantum coherence remains the same during the open system dynamics described by the Eq. (9). On the other hand, there is a non-vanishing coupling between the pseudo-spins when the configuration state is fixed to  $|E\rangle_C$ . As long as the initial pseudo-spin state  $|\psi(t_0)\rangle_{12}$  lives in a subspace spanned by  $\{|01\rangle, |10\rangle\}$ ,  $H_{BC}$  drives the evolution to a detailed balance between  $|\epsilon_-\rangle_{12}$  and  $|\epsilon_+\rangle_{12}$  according to the chosen master equation, i.e., the pseudo-spins' state relaxes to the athermal attractor state  $\rho_{12}^{eq} = P_-|\epsilon_-\rangle\langle\epsilon_-| + P_+|\epsilon_+\rangle\langle\epsilon_+|$  where  $P_\pm = e^{-\beta\epsilon_\pm} / (e^{-\beta\epsilon_+} + e^{-\beta\epsilon_-})$ . Hence, the open system dynamics bring the state  $|S\rangle$  towards

$$\begin{aligned} \rho_N^{eq} &= P_g|G\rangle\langle G|_C \otimes |10\rangle\langle 10|_{12} + P_e|E\rangle\langle E|_C \otimes \rho_{12}^{eq} \\ &= P_g|S\rangle\langle S| + P_e P_-|S^\ddagger\rangle\langle S^\ddagger| + P_e P_+|\tilde{S}^\ddagger\rangle\langle \tilde{S}^\ddagger|, \end{aligned} \quad (12)$$

in the stationary state. It means that we will observe the molecule in the substrate state with a probability of  $p(S) = P_g$  at equilibrium. This probability is approximately equal to unity at physiological temperatures for the choice of  $E_e - E_g = 42$  kcal/mol. Similarly, the equilibrium probability of the occurrence of transition state becomes  $p(S^\ddagger) = P_e P_-$ . This probability is equal to  $2.84 \times 10^{-30}$  for  $E_e - E_g = 42$  kcal/mol and  $\epsilon_+ - \epsilon_- = 14$  kcal/mol at  $T = 37.5^\circ\text{C}$ . Increasing the temperature enhances it slightly but never exceeds the order of  $10^{-30}$  at physiological temperatures. On the other hand, the molecule cannot be converted to the product state in this approximation, even if the environment reaches extremely high temperatures as the final state  $\rho_N^{eq}$  is orthogonal to the  $|P\rangle$ , i.e.,  $p(P) = \text{tr}[\rho_N^{eq}|P\rangle\langle P|] = 0$ .

#### B. Water-Mediated Reaction

Before moving on to the role of quantum H-bonds in enzyme-catalyzed tautomerization, we investigate first this role in water-mediated tautomerization. To do so, we take into account the formation of two H-bonds between the nucleotide and one or more water molecules. Allowed proton locations on the opposite sides of pseudo-spins 1 and 2 are also regarded as pseudo-spins and respectively labeled by  $\bar{1}$  and  $\bar{2}$ .

We assume that the intermolecular H-bonds described by  $H_{HB}^{(1\bar{1})}$  and  $H_{HB}^{(2\bar{2})}$  generate quantum correlations between the nucleotide and the water molecule(s) as:

$$|\psi\rangle_{1\bar{1}2\bar{2}} = (\alpha|10\rangle + \sqrt{1-\alpha^2}|01\rangle)_{1\bar{1}} \otimes (\beta|01\rangle + \sqrt{1-\beta^2}|10\rangle)_{2\bar{2}}. \quad (13)$$

We consider the open system dynamics just after the generation of these intermolecular correlations. First, we eliminate the water's degrees of freedom  $\bar{1}$  and  $\bar{2}$  by taking a partial trace over them and focus on the reduced

system dynamics of the nucleotide. In this case, the initial state of the nucleotide is an incoherent superposition state:

$$|\psi(t_0)\rangle_N = |G\rangle_C \otimes \{\alpha^2\beta^2, |10\rangle; (1-\alpha^2)\beta^2, |00\rangle; \alpha^2(1-\beta^2), |11\rangle; (1-\alpha^2)(1-\beta^2), |01\rangle\}_{12}. \quad (14)$$

Open system dynamics of this incoherent superposition ends up in the following state:

$$\begin{aligned} \rho_{N|H_2O}^{eq} = & \alpha^2\beta^2 P_g |S\rangle\langle S| + (1-\alpha^2)(1-\beta^2) P_g |P\rangle\langle P| \\ & + (1-\alpha^2)\beta^2 P_g |S_-^\dagger\rangle\langle S_-^\dagger| + \alpha^2(1-\beta^2) P_g |S_+^\dagger\rangle\langle S_+^\dagger| \\ & + (1-\alpha^2)\beta^2 P_e |\tilde{S}_-^\dagger\rangle\langle \tilde{S}_-^\dagger| + \alpha^2(1-\beta^2) P_e |\tilde{S}_+^\dagger\rangle\langle \tilde{S}_+^\dagger| \\ & + (1-\alpha^2-\beta^2) P_e (P_- |S^\dagger\rangle\langle S^\dagger| + P_+ |\tilde{S}^\dagger\rangle\langle \tilde{S}^\dagger|). \end{aligned} \quad (15)$$

If the intermolecular H-bonds generate maximal entanglement between the nucleotide and the water molecule(s), i.e.,  $\alpha = \beta = 1/\sqrt{2}$ , the nucleotide reaches an equilibrium such that  $p(S) = p(S_-^\dagger) = p(S_+^\dagger) = p(P) = P_g/4$  that equals to 0.25 for the chosen model parameters. The balance between these four tautomers can be driven through S or P by changing the values of  $\alpha$  and  $\beta$  corresponding to a decrease in the amount of total entanglement generated through the H-bonds.

The values of  $\alpha$  and  $\beta$  depend on the geometric parameters of the interaction which is totally random, i.e., although the tautomeric conversion of S to P may be mediated by means of the quantumness of water - nucleotide H-bonds, there is a very little chance for the molecules in aqueous solution to show the right orientations that provide the required values of  $\alpha$  and  $\beta$ .

### C. Enzyme Catalyzed Reaction

Before the interaction, the nucleotide and the enzyme both exist in their ground states:

$$\begin{aligned} |\psi(t_0)\rangle_{NE} &= |S\rangle \otimes |E\rangle \\ &= |G\rangle_C |10\rangle_{12} \otimes |G'\rangle_{C'} |01\rangle_{34}. \end{aligned} \quad (16)$$

The pseudo-spin term of this state can be thought as the ground state of the interaction Hamiltonian  $H_I = H_{HB}^{(13)} + H_{HB}^{(24)}$  with large pseudo-spin separations and vanishing hopping constants. When  $R_{13}$  and  $R_{24}$  become sufficiently small, a small amount of entanglement is generated through the weak  $X_1-H\cdots X_3$  and  $X_2\cdots H-X_4$  bonds:

$$|\psi(t_1)\rangle_{NE} = |G\rangle_C \otimes |G'\rangle_{C'} \otimes (\alpha|10\rangle + \sqrt{1-\alpha^2}|01\rangle)_{13} \otimes (\beta|01\rangle + \sqrt{1-\beta^2}|10\rangle)_{24}. \quad (17)$$

This weak interaction then induces a classical and gradual conformational change in the binding site of E according to the induced-fit mechanism and the bond angles  $\phi_{13}$  and  $\phi_{42}$  become smaller. As explained in Sec.s IIA and IIB 4, this process occurs on a relatively large time-scale  $\tau_1$  and the pseudo-spins stay in the ground state of the time-dependent interaction Hamiltonian  $H_I$  at every instant of time. Hence, this conformational motion not only strengthens the binding interaction in ES complex due to a decrease in the energy, it also increases the quantum correlations of the intermolecular H-bonds.

In the meantime, the angle  $\phi_{43}$  and the inter-spin separation  $R_{43}$  both change during the binding stage (see Fig. 2). Hence, the intramolecular interaction between  $X_3$  and  $X_4$  gains a quantum character as well. In this respect, the total pseudo-spin interaction Hamiltonian  $H_I(t)$  should be taken as  $H_{HB}^{(13)} + H_{HB}^{(24)} + H_{HB}^{(34)}$  when  $t_2 > t_1$ .

When the interaction-induced conformational change stops at time  $t_3 > t_2$ , the binding site of the enzyme should end up in its highest excited state  $|E'\rangle$ , whereas the pseudo-spins should be in the ground state of  $H_I(t_3)$ :

$$\begin{aligned} |\psi(t_3)\rangle_{NE} &= |G\rangle_C \otimes |E'\rangle_{C'} \\ &\quad \otimes (a|0011\rangle + b|0101\rangle + c|0110\rangle + d|1001\rangle + e|1010\rangle + f|1100\rangle)_{1234} \\ &\equiv |ES\rangle. \end{aligned} \quad (18)$$

It follows from the state of the reaction intermediate ES that the entanglement generated at the end of the binding stage is shared among all of the four pseudo-spins. Next, we show that the four-qubit entanglement generated in this way can be transferred to S when the configuration and pseudo-spins of E subsequently return their initial states, which can enable the conversion of S to P. We will also consider the case in which the four-qubit entanglement of the reaction intermediate ES decays rapidly before the next conformational change of the enzyme.

### 1. Quantum correlated H-bonds

We assume without any loss of generality that the quantum correlations of each three H-bonds in Fig. 2-b is sustained until E undergoes a conformational change that converts it back to the initial state. In other words,  $\tau_2$  is assumed to be small compared to the decoherence time  $\tau_D$  enforced by the heat bath  $\tilde{B}$ . This is quite reasonable as the H-bonded atoms/groups are partially isolated from their environment until the detachment of the ES complex.

As explained in Sec.s II A and II B 4, the second conformation motion of interest drives  $C'$  from  $|E'\rangle$  to  $|G'\rangle$  and is governed by the interaction Hamiltonian  $H_{BC'}$ . During the course of this relatively fast motion, the pseudo-spins of E should detach from the pseudo-spins of S and return back to the initial product state  $|01\rangle_{34}$ . We describe this conformation-induced process by a sudden post-selection measurement  $\mathbf{M} = \mathbf{I}_{12} \otimes |01\rangle_{34}\langle 01|$  and find that some of the four-qubit entanglement of the reaction intermediate ES can be transferred to the pseudo-spins of S when  $\mathbf{M}$  converts the pseudo-spins of E back to their initial state:

$$\begin{aligned} \mathbf{M} + H_{BC'} : |ES\rangle &\rightarrow |\psi(t_4)\rangle_{\text{NE}} = |G\rangle_C \otimes (b'|01\rangle + d'|10\rangle)_{12} \otimes |E\rangle \\ &= (b'|P\rangle + d'|S\rangle) \otimes |E\rangle \\ &\equiv |ES^\ddagger\rangle, \end{aligned} \quad (19)$$

where  $b' = b/\sqrt{b^2 + d^2}$  and  $d' = \sqrt{1 - b'^2}$ . We can analyze the open system dynamics of the nucleotide using the master equation approach introduced in Sec. II B 3, starting at  $t = t_4$ . The stationary solution becomes

$$\begin{aligned} \rho_{\text{N}|q\text{HB}}^{\text{eq}} &= d'^2 P_g |G\rangle\langle G|_C \otimes |10\rangle\langle 10|_{12} + b'^2 P_g |G\rangle\langle G|_C \otimes |01\rangle\langle 01|_{12} + P_e |E\rangle\langle E|_C \otimes \rho_{12}^{\text{eq}} \\ &= d'^2 P_g |S\rangle\langle S| + b'^2 P_g |P\rangle\langle P| + P_e P_- |S^\ddagger\rangle\langle S^\ddagger| + P_e P_+ |\tilde{S}^\ddagger\rangle\langle \tilde{S}^\ddagger|. \end{aligned} \quad (20)$$

This means that the enzyme converts the nucleotide into the product state with a probability of  $p(P) = b'^2 P_g$  at equilibrium. Also, neither  $p(S^\ddagger)$  nor  $p(\tilde{S}^\ddagger)$  changes when compared to equilibrium probabilities in the uncatalysed case.

$b'$  depends on the strength of the H-bonds formed in the enzyme-substrate interaction, as does the efficiency of the catalysis. If the three H-bonds shown in Fig. 2-b generate a maximal W-type four-qubit entanglement, i.e.,  $a = b = c = d = e = f = 1/\sqrt{6}$ , the nucleotide reaches an equilibrium such that  $p(S) = p(P) = P_g/2$  that equals 0.5 for our chosen model parameters.

We can compare this result with another obtained in water-mediated tautomerization. When the amounts of entanglement generated through each water - nucleotide H-bond are chosen to be maximal, the nucleotide reaches an equilibrium with  $p(S) = p(P) = 0.25$ . Here, when the overall four-qubit entanglement is chosen to be maximal, the pairwise entanglement generated through each enzyme - nucleotide H-bond is not maximal and the equilibrium probabilities corresponding to both tautomers are twice as high as 0.25. Moreover, the ionic transition states  $S_\pm^\ddagger$  do not emerge unlike the water-mediated case in which  $p(S_\pm^\ddagger) = 0.25$ . In the meantime, the equilibrium probability of the neutral transition state is still kept at the order of  $10^{-30}$  at physiological temperatures.

In this context, not only the conformational change induced in the enzyme increases the likelihood of the formation of quantum H-bonds with the nucleotide, but also the subsequent conformational change that brings the enzyme back to its initial state makes quantum H-bonds a more efficient resource for the tautomerization process.

### 2. Classically correlated H-bonds

The assumption of  $\tau_2 < \tau_D$  isn't necessary to derive our insight into the possible role of proton tunneling in an induced-fit model of enzyme catalysis. Once the quantum correlations are created by proton tunneling events through H-bonds, the enzyme can use them as a resource to convert S to P by the same mechanism under consideration even if these correlations rapidly decay to classical correlations during decoherence.

In the case of  $\tau_2 > \tau_D$ , the final state of the pseudo-spins of ES at the end of the binding stage should be a classically correlated state rather than a four-qubit entangled state:

$$\begin{aligned} \rho_{1234}(t_3) &= a^2 |0011\rangle\langle 0011| + b^2 |0101\rangle\langle 0101| + c^2 |0110\rangle\langle 0110| \\ &\quad + d^2 |1001\rangle\langle 1001| + e^2 |1010\rangle\langle 1010| + f^2 |1100\rangle\langle 1100|. \end{aligned} \quad (21)$$

After the pseudo-spins of E are detached from the pseudo-spins of S and returned back to their initial state by the post-selection measurement induced by the second conformational change, the nucleotide ends up in a mixture of S

and P as below:

$$\begin{aligned}
\rho_{NE}(t_4) &= |G\rangle\langle G|_C \otimes (d'^2|10\rangle\langle 10|_{12} + b'^2|01\rangle\langle 01|_{12}) \otimes |E\rangle\langle E| \\
&= (d'^2|S\rangle\langle S| + b'^2|P\rangle\langle P|) \otimes |E\rangle\langle E| \\
&\equiv |ES^\ddagger\rangle\langle ES^\ddagger|,
\end{aligned} \tag{22}$$

where  $b'$  and  $d'$  are the re-normalized  $b$  and  $d$ , as before. If we feed master equation (9) with this incoherent superposition state instead of the coherent superposition state  $|\psi(t_4)\rangle_N$  given in (19), the steady state solution  $\rho_{N|cHB}^{eq}$  obtained is the same density matrix with  $\rho_{N|qHB}^{eq}$  in (20). Hence, the equilibrium probabilities remain the same in both cases. Our conclusion still holds even if the quantum correlations of H-bonds found in the reaction intermediate ES are converted to classical correlations by strong decoherence just at the beginning of the catalytic stage.

### 3. Activation energy

A state transformation from  $\rho$  to  $\rho'$  is said to be thermodynamically favorable only if the free energy  $F$  goes down, i.e.,  $\Delta F = F[\rho'] - F[\rho] \leq 0$ . Biological systems can carry out thermodynamically unfavorable state transformations by coupling them to favorable ones. However, even thermodynamically favorable biochemical state transformations generally involve the formation of transition states with higher free energies than initial states. Enzymes lower these activation barriers but are not expected to remove them completely. The difference in the free energy between the transition and initial (or final) states guarantees that this catalyzed transformation is sufficiently slow for the organism inside which it takes place.

It is worth remembering that the tautomerization process of interest is not assumed to be the ultimate catalytic function of the multifunctional enzyme, but rather supports a secondary catalytic function required for the ultimate one. In this respect, an interesting question to ask is whether all enzyme-catalyzed reactions have a rate-limiting step between the initial and final states. In other words, can an enzyme provide the formation of a transition state with a free energy lower than the free energy of the initial (or final) state in specific cases? The simple model investigated in this study points to a surprising possible answer to this question in what follows.

The free energy of the nucleotide can be calculated by:

$$F[\rho] = \langle E \rangle - RT S[\rho] = \text{tr}[\rho H_N] + RT \text{tr}[\rho \log_2 \rho] \tag{23}$$

where  $R$  is the universal gas constant, 1.987 cal/(mol K). As the states of S, P, and  $S^\ddagger$  are pure states, i.e., as  $\text{tr}[\rho^2] = 1$  for these tautomers, their von Neumann entropies vanishes. These states are also eigenstates of  $H_N$  which means that average energies taken over them are nothing but the corresponding eigenenergies. Hence, we end up with

$$F[|S\rangle\langle S|] = \epsilon_1 < F[|P\rangle\langle P|] = \epsilon_2 < F[|S^\ddagger\rangle\langle S^\ddagger|] = \epsilon_3. \tag{24}$$

We consider the free energy of the transition state  $ES^\ddagger$  that appears after the binding stage of enzyme catalysis and study the case in which quantum correlations that are generated through the H-bonds of ES is preserved until the start of the catalytic stage, i.e.,  $\tau_2 < \tau_D$ .  $|ES^\ddagger\rangle$  is separable (see Eq. (19)) and the reduced state of the nucleotide equals  $|ES^\ddagger\rangle_N = |G\rangle_C \otimes (b'|01\rangle + d'|10\rangle)_{12}$  where  $d' = \sqrt{1 - b'^2}$ . The expected value of the energy over this state is  $\text{tr}[|ES^\ddagger\rangle\langle ES^\ddagger|_N H_N] = b'^2 \epsilon_2 + (1 - b'^2) \epsilon_1$ . As it is a pure state, its von Neumann entropy vanishes and its free energy becomes

$$F[|ES^\ddagger\rangle\langle ES^\ddagger|_N] = b'^2 \epsilon_2 + (1 - b'^2) \epsilon_1, \tag{25}$$

which corresponds to a free energy just in-between the free energy of S and P, a value much lower than expected in biochemical reactions (Fig. 4).

In the case of  $\tau_2 \not< \tau_D$ ,  $|ES^\ddagger\rangle$  is separable again (see Eq. (22)) but the reduced state of the nucleotide equals  $|ES^\ddagger\rangle_N = |G\rangle_C \otimes ((1 - b'^2)|10\rangle + b'^2|01\rangle)_{12}$ . As  $\text{tr}[|ES^\ddagger\rangle\langle ES^\ddagger|_N H_N]$  is also equal to  $b'^2 \epsilon_2 + (1 - b'^2) \epsilon_1$ , the expected value of the energy between S and P along the reaction coordinate is not affected by decoherence. However, unlike the previous case, the reduced state of the nucleotide is not a pure state, which means that its von Neumann entropy does not vanish:  $S[|ES^\ddagger\rangle\langle ES^\ddagger|_N] = -b'^2 \log_2 b'^2 - (1 - b'^2) \log_2 (1 - b'^2) > 0$ . The free energy then drops further by the loss of quantumness of correlations in the H-bonds as below:

$$F[|ES^\ddagger\rangle\langle ES^\ddagger|_N] = b'^2 \epsilon_2 + (1 - b'^2) \epsilon_1 + RT (b'^2 \log_2 b'^2 + (1 - b'^2) \log_2 (1 - b'^2)). \tag{26}$$

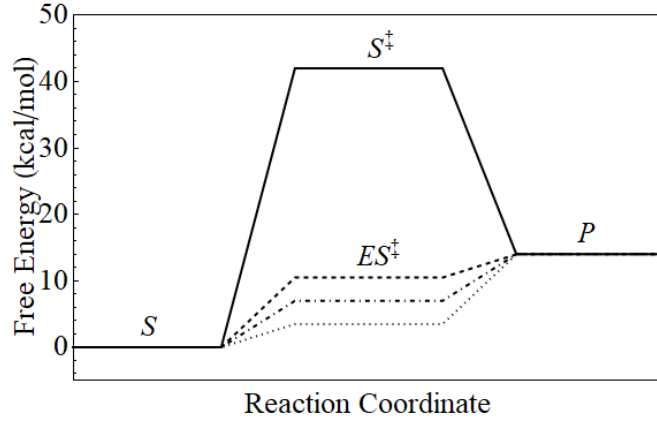


FIG. 4. Alternative reaction pathways from S to P. Uncatalysed S (solid line) requires a high activation energy to reach  $S^\ddagger$ . Here,  $E_e - E_g = 42$  kcal/mol,  $\epsilon_+ - \epsilon_- = 14$  kcal/mol and  $F[|S\rangle\langle S|]$  is set to zero as explained in the text. E is found to lower the activation energy by leading the reaction into an alternative chemical pathway ( $ES^\ddagger$ ). Quantum correlations generated through H-bonds enable E to lower the activation energy down to a much lower value in-between the energies of S and P.  $T = 37.5^\circ\text{C}$ ,  $\tau_2 < \tau_D$  and  $b'^2$  is fixed to 3/4, 2/4 and 1/4 respectively for the dashed, dot-dashed, and dotted lines.

However, this entropy-based decrease is not likely to be significant as  $RT < 1$  kcal/mol at physiological temperatures and  $S[|ES^\ddagger\rangle\langle ES^\ddagger|_N] \leq 1$ . Thus,  $F[|ES^\ddagger\rangle\langle ES^\ddagger|_N]$  is expected to be in-between  $F[|S\rangle\langle S|]$  and  $F[|P\rangle\langle P|]$  once again.

We can numerically compare the activation energies in the catalyzed and uncatalyzed reactions using the model parameters that we chose above (Fig. 4). Let's fix  $F[|S\rangle\langle S|]$  to zero for simplicity. To do so, both of the conformation and pseudo-spin terms of  $\epsilon_1$  are equated to zero, i.e.,  $E_g = 0$  and  $W_1 + \lambda_{12} = 0$ . Furthermore, we assume without any loss of generality that  $((W_1 - W_2)^2 + 4J_{12}^2)^{1/2} \approx W_2 - W_1$ . Then we end up with  $F[|P\rangle\langle P|] \approx 14$  kcal/mol and  $F[|S^\ddagger\rangle\langle S^\ddagger|] \approx 42$  kcal/mol. When we take  $T = 37.5^\circ\text{C}$  and  $b'^2 = 1/2$  (or equivalently  $b = d = 1/\sqrt{6}$ ) as before,  $F[|ES^\ddagger\rangle\langle ES^\ddagger|_N]$  becomes 7 kcal/mol if  $\tau_2 \leq \tau_D$ , and 6.38 kcal/mol otherwise. When  $b'^2$  is raised to 3/4, these values change to 10.5 and 10 kcal/mol respectively. On the other hand, a decrease in  $b'^2$  to 1/4 also lowers  $F[|ES^\ddagger\rangle\langle ES^\ddagger|_N]$  to 3.5 for  $\tau_2 < \tau_D$  and 3 kcal/mol for  $\tau_2 > \tau_D$ . Hence the rate enhancement the enzyme brings about is in the range of 22 to 27 orders of magnitude for  $1/4 \leq b'^2 \leq 3/4$  and  $T = 37.5^\circ\text{C}$ , based on the first-order rate equation  $k = \frac{k_B T}{h} e^{-\frac{\Delta F^\ddagger}{RT}}$ , where  $k_B$  is the Boltzmann constant and  $h$  is the Planck constant. The lower limit of this rate enhancement can be decreased down to  $5 \times 10^{19}$  by increasing the upper limit of  $b'^2$  up to unity. Both limits can be pulled down by squeezing the energy levels of the Hamiltonian given in (5), e.g. when  $1/4 \leq b'^2 < 1$ ,  $T = 37.5^\circ\text{C}$ ,  $E_e - E_g = 34$  kcal/mol, and  $\epsilon_+ - \epsilon_- = 19$  kcal/mol, the enzyme leads to a rate enhancement in the range of 10 to 20 orders of magnitude. Note that although this enhancement is more reasonable when compared to the experimentally estimated upper limits, it does not change our main proposition that the free energy of the transition state is smaller than the free energy of the product in the enzyme catalyzed reaction.

#### IV. Conclusions

We showed that the quantum correlations generated through H-bonds can be used as a resource in an induced-fit mechanism that leads generic nucleotide tautomerization into an alternative chemical pathway. This increases the occurrence of the minor tautomeric form P even if the conversion of the major tautomeric form S to P isn't possible in the absence of the enzyme. Moreover, the advantages of this scenario go beyond that. As the new transition state that emerges in this pathway corresponds to the quantum superposition of S and P, the free energy for the new transition state is found to be between the individual free energies of S and P. Hence, the enzyme provides an alternative reaction pathway with a dramatically smaller activation energy (Fig. 4). Moreover, such a reactive pathway doesn't require anything more than a passive transformation of the enzyme's configuration in the catalytic stage.

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