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Dynamics of proton tunneling in Hydrogen-bonded systems through Green's function formalism

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ABSTRACT

This study proposes a new theoretical model based on Green's function formalism for studying proton tunneling via hydrogen bonding. This approach allows calculating the tunneling probability and the tunneling energy that proton transfer occurs along a given path inferred a priori. The method is extended to multiple protons tunneling, characterizing the behaviour of some biological molecules. Specifically, the cases of the proton transfer in the Fujicurin A molecule and the double proton tunneling in the Guanine-Cytosine base-pair are investigated. The new approach is an alternative to those present in the literature. It allows straightforwardly predicting the mechanisms of intramolecular and intermolecular proton transfers involving the rearrangement of conjugated electrons.

Keywords:
Green function; path integral method; proton tunneling; hydrogen bonding

Introduction

Proton tunneling is a quantum tunneling involving the transfer of a proton from one site to an adjacent site of a given molecule separated by a potential barrier (Klinman & Kohen, 2013; Meng et al., 2015; Pinotsi et al., 2016). This model is equivalent to a double-well potential, whose geometry depends on the chemical nature of the donor and acceptor and the chemical-physical properties of the environment. According to the Wentzel-Kramers-Brillouin approximation (WKB), the probability for a particle to tunnel is inversely proportional to its mass and the width of the potential barrier (Bountis, 1992). A proton is about 2000 times more massive than an electron, so it has a much lower tunneling probability. Nevertheless, proton tunneling still occurs, especially in molecules where the proton participates in a hydrogen bond (Butenhoff & Moore, 1988; Fillaux et al., 2007; Jana & Ganguly, 2018; Marais et al., 2018). The latter contributes to a decrease in both the width and the height of the potential barrier, above all if its covalent character is predominant to the purely electrostatic one. Proton transfer via hydrogen bond plays a crucial role in the tautomerism phenomena of biological molecules and is at the basis of the mechanisms governing many reactions involving proteins (Golo & Volkov, 2003; Horsewill et al., 2001; Matsui, 2022; McMahon, 2003; Slocombe et al., 2022). For this reason, proton tunneling has always attracted the attention of experimental and theoretical chemists to understand its dynamics and find the variables governing it. The study has been conducted in the last decades using the most disparate approaches, from DFT (density functional theory) (Sapse, 1998; Sarai & DeVault, 1986) to HH/DD KIE (kinetic isotope effects) (Cheng et al., 2022; Hans-Heinrich Limbach et al., 1982; Limbach et al., 2006), passing through machine learning force fields (Unke et al., 2021) and QM/MM (Quantum Mechanics/Molecular Mechanics) methods (Faulder et al., 2001; Ranaghan et al., 2017; Sole et al., 2020). However, none of these methods suggests the reaction pathway inside the potential barrier because tunneling is a quantum phenomenon fuzzy by Heisenberg's uncertainty principle (the potential barrier separating the two reaction sites is classically forbidden and cannot be investigated experimentally).

In this study, the proton tunneling via hydrogen bonding is investigated using the Green function (GF) formalism (Barton, 2005; Seremet, 2022; Setten et al., 2015). This method, widely used in quantum field theory (Herrera et al., 2021), makes it possible to calculate the probability by which a given physical phenomenon occurs according to a possible path predetermined a priori. In our case, the reaction pathway is constructed using a set of atomic and molecular orbitals arbitrarily chosen among those potentially involved in the proton transfer. This makes it potential to construct different reaction paths and calculate their probabilities to predict on a theoretical foot what happens mechanistically inside the potential barrier. We addressed the study through GF formalism since it is more general than the wavefunction. GF carries information about the history of the particle, from the initial state (in our case, the proton bonded to the donor group and interacting via hydrogen bond with the acceptor site) to the final state (the proton bonded to the acceptor group and interacting via hydrogen bond with the donor site), and is governed by an equation of motion (the Dyson equation) that is simpler to solve than Schrodinger's (Lambert, 2021; Sieber, 2007).

The paper is organized as follows: in section 2, the motivation for using the GF formalism and its physical meaning is briefly discussed to facilitate reading and understanding of the following sections. In section 3, the theoretical model that leads to calculating the tunneling probability and the tunneling energy associated with a predetermined reaction pathway is formulated. Section 4 discusses some examples of how the proposed method works. The cases of single proton tunneling via intramolecular hydrogen bond and double proton tunneling via intermolecular hydrogen bond are investigated.

Motivation and GF Formalism

Let us consider a donor group D, belonging to a generic molecule, to which hydrogen is chemically bonded. This group interacts with an acceptor site A via hydrogen bonding (intramolecular, if A belongs to the same molecule, intermolecular if A belongs to another molecule). Suppose proton transfer from the donor site to the acceptor site is chemically allowed (from a thermodynamics and kinetics point of view). The model we are considering is shown in Figure 1.

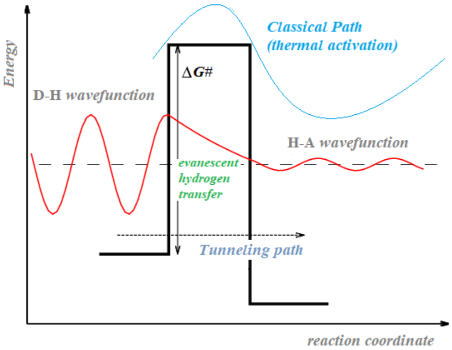

Figure 1. schematic model of proton tunneling via hydrogen bond.

The height $\Delta G^{\#}$ and the length of the potential barrier separating the energy well of the D-H bond from that of the H-A bond depend on the nature of the hydrogen bond (depending on the geometry, the environment, and the nature of the specific donor and acceptor atoms, the hydrogen bond energy varies between some Kcal/mol to about 60 Kcal/mol). In principle, the stronger the hydrogen bond and the lower are height and length of the potential barrier. If the donor group is thermally activated, i.e. the energy of the reaction site is higher than $\Delta G^{\#}$, then the proton transfer takes place according to a classical pathway. Otherwise, the reaction can only occur by quantum tunneling. This last process is the one that characterizes almost all of the tautomerism in biological molecules, given that the vital processes take place at temperatures of the order of tens of degrees Celsius (Krishtalik, 2000; Scheiner et al., 1986).

Studying the dynamics of proton transfer in the classically forbidden region (where the proton behaves like an evanescent wave) means calculating the tunneling matrix, which maps the left boundary values of the solution of the Schrodinger equation, represented by the D-H bond, onto the right ones, represented by the H-A bond. This can be done by solving the Schrodinger equation in which the potential energy operator is represented by the double well's energy profile, which defines the proton tunneling between the initial state, the D-H bond, and the final one, the H-A bond. Analytically solving such a problem involves using unusual mathematical tools for the chemist (the solution leads to fifth-degree algebraic equations) and laborious calculations (Vshivtsev et al., 1998). Since the tunneling matrix describes the propagation of the analytical solution across the potential barrier, it can be expressed as a GF. The latter is the mathematical form of the Feynman propagator, used to study scattering phenomena in quantum field theory, which describes the probability amplitude of a physical phenomenon. Notably, for the problem being studied, it represents the probability of proton tunneling along the direction of the hydrogen bond connecting the donor and acceptor groups. This probability depends on the path through the classically forbidden region (reaction mechanism). This path is not unique, and in principle, it is constructed arbitrarily, even if coherently with the chemical-physical properties that define the problem. All possible reaction pathways are obtained by varying one or more steps composing it. As we will see shortly, the steps are represented by molecular and atomic orbitals. This is the rationale on which the theory we propose in this study is based.

We need to know the Hamiltonian operator within the potential barrier to compute the tunneling matrix. The equation relating the Hamiltonian operator with the GF is (Seremet, 2022)

$$i\hbar G(\boldsymbol{r},t;\boldsymbol{r}',t') = \Theta(t-t')\left\langle \Psi_0(t)\middle|\widehat{\Psi}(\boldsymbol{r})e^{-iH(t-t')/\hbar}\widehat{\Psi}^{\dagger}(\boldsymbol{r}')\middle|\Psi_0(t')\right\rangle, \tag{1}$$

where $G(\boldsymbol{r},t;\boldsymbol{r}',t')$, $\Theta(t-t')$ and $H(t-t')$ are the GF, Heaviside function and Hamiltonian, respectively. The term $\widehat{\Psi}^{\dagger}(\boldsymbol{r}')|\Psi_0(t')\rangle$ is the state with an added electron in $\boldsymbol{r}'$ to the N-electron ground-state at time t'. The operator $e^{-iH(t-t')/\hbar}$ propagates the state $\widehat{\Psi}^{\dagger}(\boldsymbol{r}')|\Psi_0(t')\rangle$ from the time t' to the time t. The term $\langle\Psi_0(t)|\widehat{\Psi}(\boldsymbol{r})$ denotes the state where one electron is added in $\boldsymbol{r}$ to the N-electron ground-state at time t. In time domain, the GF is represented by (Seremet, 2022)

$$G(\boldsymbol{r},t;\boldsymbol{r}',t') = \sum_n \varphi_n(\boldsymbol{r})\varphi_n{}^*(\boldsymbol{r}')e^{-iH_n(t-t')/\hbar}. \tag{2}$$

where $\varphi_n(\boldsymbol{r})$ are wavefunction describing the nth step of the path (this aspect of the theory will be clarified in the next section). Eq. 2 is the GF obtained by summing all the propagators associated with each step forming the whole path. Applying the Laplace-Fourier transform to Eq. 2, the GF representation in the frequency (energy) domain is obtained (Seremet, 2022)

$$G(\boldsymbol{r},\boldsymbol{r}';E) = \int_0^{\infty} G(\boldsymbol{r},t;\boldsymbol{r}',t')e^{-iH/\hbar}dt = i\hbar\sum_n \frac{\varphi_n(\boldsymbol{r})\varphi_n{}^*(\boldsymbol{r}')}{E-E_n}, \tag{3}$$

where $E = \hbar\omega$. Let us now introduce the Dyson equation. For this purpose, we denote by U a perturbative potential, which is small compared to the energy of the unperturbed system. If G_0 is the GF of the unperturbed system, then the propagator within the perturbed region is given by (Seremet, 2022)

$$G = G_0 + G_0UG. \tag{4}$$

This equation is fundamental for the formulation of the proton tunneling theory being proposed. Indeed, the height of the potential barrier is small compared to the energy of the D-H and H-A bonds, and, therefore, the GFs describing the system in the wells' regions can be considered free propagators. Their value within the potential barrier is easily calculated using Eq. 4. The same holds for the GFs associated with the molecular and atomic orbitals forming the reaction pathway, as demonstrated in the next section. We now have the necessary and sufficient mathematical tools to develop the theory.

Proton Tunneling: The Governing Model

Let us consider a particle (hydrogen atom) in a one-dimensional symmetric double well. Analytically, the potential curve can be written as follows (Baradaran & Panahi, 2017)

$$U(x) = \Delta G_0{}^{\#}(x^2 - a^2)^2, \tag{5}$$

where $\Delta G_0{}^{\#}$ is the barrier heigh, a is the distance $a = |x_0 - x_1|$. The coordinates x_0 and x_1 are such that $U(x_0) = \Delta G_0{}^{\#}$ and $U(x_1) = min U(x)$, i.e. a is the distance between the centre of the potential barrier and the minimum of the well. The Schrodinger equation (SE) for this system reads

$$\left[-\frac{\hbar^2}{2m}\frac{d^2}{dx^2} + \Delta G_0{}^{\#}(x^2 - a^2)^2\right]\varphi(x) = E\varphi(x). \tag{6}$$

Eq. 6 provides a spectrum of discrete energies $E_n\left(\Delta G_0{}^{\#}, a\right)$ which depends on the geometry of the potential curve. Solving Eq. 6 allows for obtaining the energies and the tunneling probabilities but is a challenging task from a mathematical point of view. This difficulty is overcome if GF formalism is used. GF is a solution of the inhomogeneous differential equation

$$[z - L(x)]G(x, x'; z) = \delta(x - x'), \tag{7}$$

where $L(x)$ is a linear Hermitian time-independent operator, δ is the Dirac function, and $z \in \mathbb{C}$ is a parameter. Operator $L(x)$ satisfies to the following eigenvalue equation

$$L(x)\varphi_n(x) = \lambda_n\varphi_n(x). \tag{8}$$

Denoting by $\{\varphi_n(x)\}$ the complete set of solutions of Eq. 8, the following property holds

$$\sum_n \varphi_n(x)\varphi_n{}^*(x') = \delta(x - x'). \tag{9}$$

Substituting Eq. 9 in Eq. 7 one gets

$$[z - L(x)]G(x, x'; z) = \sum_n \varphi_n(x)\varphi_n{}^*(x'), \tag{10}$$

from which, supposing all eigenvalues of operator $[z - L(x)]$ are different from zero, is obtained

$$G(x, x'; z) = \sum_n \frac{\varphi_n(x)\varphi_n{}^*(x')}{\lambda - \lambda_n} \quad z \neq \lambda_n, \tag{11}$$

where, for clarity, we set $z = \lambda$. We need to define $G(x, x'; z)$ at $z = \lambda_n$. To do this we use the limiting procedure, forming a branch cut along certain part of the real axis (Beardon & Minda, 2003)

$$G(x, x'; \lambda) = \lim_{\varepsilon \to 0^{\pm}} G(x, x'; \lambda \pm i\varepsilon), \tag{12}$$

where $z = \lambda \pm i\varepsilon$. In such a way Eq. 11 becomes

$$G(x, x'; \lambda) = \sum_n \frac{\varphi_n(x)\varphi_n{}^*(x')}{\lambda - \lambda_n \pm i\varepsilon}, \tag{13}$$

which holds whatever the value λ_n is. The GF of Eq. 13 is meromorphic with a finite number of poles, and represents the explicit form we will use in the continuation, with λ assuming the role of energy. For this reason, $G(x, x'; E)$ is called the GF in the energy (frequency) representation.

Let us apply what has been obtained to Eq. 6. Denoting by $\mathcal{H} = \left[-\frac{\hbar^2}{2m}\frac{d^2}{dx^2} + \Delta G_0{}^{\#}(x^2 - a^2)^2\right]$ the Hamiltonian, is obtained

$$[E - \mathcal{H}]G(x, x'; E) = \delta(x - x'), \tag{14}$$

whose solutions are

$$G_n(x, x'; E) = \sum_n \frac{\varphi_n(x)\varphi_n{}^*(x')}{E - E_n \pm i\varepsilon}. \tag{15}$$

The wavefunctions $\varphi_n(x)$ and eigenvalues E_n are obtained by applying the self-consistent field method (SCF). Eq. 15 suggests that proton tunneling can occur through a finite number of possible pathways, each with its energy. All these paths lead from the initial state, in which the proton is chemically bonded to the donor group D, to the final state, in which the hydrogen is chemically bonded to the acceptor group A. We denote by $G_{D-H}(x, x'; E_{D-H})$ the free GF of the initial state and by $G_{A-H}(x, x'; E_{A-H})$ that of the final state. These GFs are calculated using Eq. 15 and related by the Dyson equation

$$G_{A-H}(x, x'; E_{A-H}) = G_{D-H}(x, x'; E_{D-H}) + G_{D-H}(x, x'; E_{D-H}) U G_{A-H}(x, x'; E_{A-H}), \tag{16}$$

where U is the perturbation related to the tunneling process. Eq. 16 holds since the energy $\Delta G_0{}^\#$ is small compared to the A-H and D-H bond energies. Using some simple algebra, from Eq. 16 one gets

$$U = [G_{D-H}(x, x'; E_{D-H})]^{-1} - [G_{A-H}(x, x'; E_{A-H})]^{-1}. \tag{17}$$

The potential given by Eq. 17 allows calculating the explicit form of the GFs relating to all possible reaction pathways and the associated probabilities. Each path is formed by single steps represented by suitable molecular orbitals. It should be clarified that by pathway, we mean the steps that take place strictly within the classically forbidden region, i.e, within the potential barrier. We will apply the proposed method to two examples in the following section to clarify how it works. The first is related to a proton tunneling via an intramolecular hydrogen bond, and the second concerns a double proton tunneling via an intermolecular hydrogen bond.

Proton Tunneling: How the Model Works

Let us consider the proton tunneling via an intramolecular hydrogen bond occurring in a Fujicurin A molecule. The system to be studied is shown in Figure 2

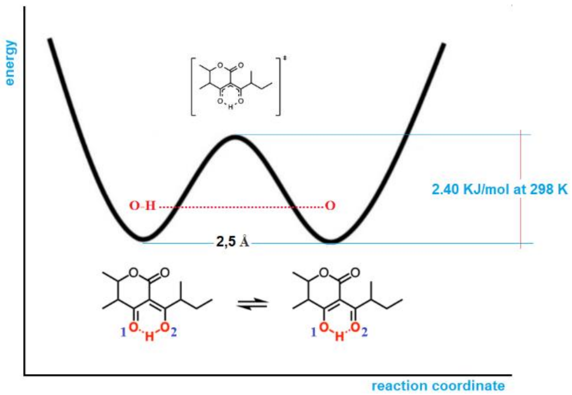

Figure 2. proton tunneling via intramolecular hydrogen bond in Fujicurin A molecule. The double well potential is supposed to be symmetric.

A symmetrical double well was chosen even if the hydroxyl groups 1 and 2 are bonded to different molecule fragments. This approximation is legitimate as we investigate proton tunneling by limiting the region where the proton transfer between the donor and acceptor groups occurs. Furthermore, proton tunneling involves a rearrangement of the π-electrons of the six-atom ring closed by the intramolecular hydrogen bond, so it is reasonable to consider the molecular orbital energies of carbonyl 1 and hydroxyl 2 of the initial state equal to those of the carbonyl 2 and hydroxyl 1 of the final state. We now have to choose the orbitals that form the pathway from the initial state to the final one. Therefore, we must conjecture a reaction mechanism consistent with the chemical-structural characteristics of the molecular region involved in the proton transfer. For example, the first step of the pathway is represented by an increase in the average length of the O(2)-H bond, which means assuming that the electrons of this bond is described by a parametrized molecular orbital. The parametrization is performed through a numerical parameter μ added to the bond distance $d_{O(2)-H}$. This means using molecular orbital obtained in non-adiabatic fashion, where the Born-Oppenheimer approximation does not more hold. The computation of the parametrized molecular orbital can be done using MOLPRO quantum chemistry program package (Werner et al., 2011). Due to this distance increases, the proton is more affected by the interaction with the carbonyl's oxygen 2. So, the second step is represented by an independent hydrogen atom, where the interactions with oxygens 1 and 2 cancel each other. This leads to choosing the 1s orbital as the second reaction step. Finally, as a third step, we can assume that the hydrogen is chemically bonded to oxygen 1 by forming an H-O(1) bond. This means choosing the molecular orbital in the ground state of the H-O(1) bond as the third step. The set that characterizes this reaction pathway (proton tunneling) is given by

$$path\ I\colon \left\{\varphi_{O(2)-H}{}^{(par.\ orbital)}, \varphi_{1s}, \varphi_{O(1)-H}\right\}. \tag{18}$$

where the apex $(par.\ orbital)$ denotes the parametrized molecular orbital. A second possible pathway is obtained by assuming that the third step consists of a parametrized molecular orbital $\varphi_{O(1)-H}{}^{(par.\ orbital)}$. The set of orbitals forming the reaction pathway then becomes

$$path\ II\colon \left\{\varphi_{O(2)-H}{}^{(par.\ orbital)}, \varphi_{1s}, \varphi_{O(1)-H}{}^{(par.\ orbital)}\right\}. \tag{19}$$

A third path could be the one that involves the formation of independent hydrogen whose 1s orbital is highly polarized along the direction of the hydrogen bond. This path, therefore, will be equal to pathway I but with the φ_{1s} orbital replaced with a polarized $\varphi_H{}^{(pol.)}$ Orbital (Fiedler et al., 2011). The latter can be obtained preliminarily as a weighted linear combination between the 1s orbital and one of the 2p orbitals (as a function of the directionality of the hydrogen bond). The obtained path is

$$path\ III\colon \left\{\varphi_{O(1)-H}{}^{(par.\ orbital)}, \varphi_H{}^{(pol.)}, \varphi_{O(1)-H}\right\}. \tag{20}$$

A further pathway is obtained by combining path II and path III, and so on. This clarifies the arbitrariness in constructing the possible reaction pathways, which must remain consistent with the chemical-structural characteristics of the atoms involved in the hydrogen bond. These pathways are characterized by their associated energy and GFs. As we will see, the latter carries the information on the probability that proton tunneling occurs along that given path. We specify that if the pathway's energy is more significant than $\Delta G_0{}^{\#}$, it must be discarded as the proton transfer will not take place by tunneling but by thermal activation. We also point out that the goodness of the chosen path does not necessarily increase as the set orbitals increase.

We now have to calculate the GF associated with each step of the chosen paths. To do this, we must first calculate the perturbation potential (or tunneling potential) using the Dyson equation. In this regard we note that the value of $\Delta G_0{}^{\#}$ is 2.40 Kcal/mol (Tanaka et al., 2022), i.e., much lower than the energy of the O-H bond, which is greater than 400 Kcal/mol. This makes it possible to apply Dyson's equation to the case being investigated. Using Eq. 17, we get

$$U = \left[G_{O(1)-H}\right]^{-1} - \left[G_{O(2)-H}\right]^{-1}, \tag{21}$$

where the free propagators are

$$\begin{cases} G_{O(1)-H} = \dfrac{\varphi_{O(1)-H}\varphi_{O(1)-H}{}^{*}}{E - E_{O(1)-H} + i\varepsilon} \\ G_{O(2)-H} = \dfrac{\varphi_{O(2)-H}\varphi_{O(2)-H}{}^{*\cdot}}{E - E_{O(2)-H} + i\varepsilon} \end{cases} \tag{22}$$

We recall that the single molecular wave functions and the related energies are preliminarily calculated by the SCF method. Such information is already available in the literature for many organic molecules involved in proton tunneling via hydrogen bonding (Stuke et al., 2020; Takaya et al., 2021). Substituting Eq. 22 in Eq. 21 and calculating the limit $\varepsilon \to 0$, we obtain a real function of the energy E, which has the value $\Delta G_0{}^{\#}$ as its maximum and the energies of the O(1)-H and O(2)-H bonds as a minimum (the latter in the example being considered are supposed to be equal). Let us consider the path I. The free propagators of the three steps forming the reaction path are

$$\begin{cases} G_{O(2)-H}{}^{(par.\ orbital)} = \dfrac{\varphi_{O(2)-H}{}^{(par.\ orbital)}\varphi_{O(2)-H}{}^{(par.\ orbital)^*}}{E - E_{O(2)-H}{}^{(par.\ orbital)} + i\varepsilon} \\ G_H = \dfrac{\varphi_{1s}\varphi_{1s}{}^*}{E - E_{1s} + i\varepsilon} \\ G_{O(1)-H} = \dfrac{\varphi_{O(1)-H}\varphi_{O(1)-H}{}^*}{E - E_{O(1)-H} + i\varepsilon} \end{cases} . \tag{23}$$

The full propagator $G_{path\ I}$ is the sum of the three free propagators of Eq. 23. We need to compute the GFs in the classically forbidden region; using Eq. 16 and some simple algebra, one gets

$$\begin{cases} G_{O(2)-H}{}^{(tun.)} = G_{O(2)-H} - U \\ G_H{}^{(tun.)} = G_H - U \\ G_{O(1)-H}{}^{(tun.)} = G_{O(1)-H} - U \end{cases} , \tag{23}$$

where U is given by Eq. 21. As usual, the full $G_{path\ I}{}^{(tun.)}$ is the sum of the three propagators of Eq. 23. Let us now define the decay factor η (Onuchic et al., 1991)

$$\eta_i = \frac{G_i{}^{(tun.)}}{G_0}, \tag{24}$$

where i denotes the i^th^ step of the path, and G_0 is the GF of the first step not included in the classically forbidden region (in our case $G_{O(2)-H}$). The meaning of decay coefficient derives from the fact that the wave function inside the barrier behaves like an evanescent wave (referring to Figure 1) and decays in the direction of the final state. The total decay coefficient associated to the pathway is the product of all η_i coefficient, and its probability is given by

$$\mathfrak{P}(path) = \prod_i^n \eta_i \cdot \left(\prod_i^n \eta_i\right)^* . \tag{25}$$

Eq. 25 must be used carefully as the GFs are generalized functions, and their product suffers from arbitrariness in the space of the Schwartz distributions (Nanni, 2022). Notably, GF can be written as

$$G_n(x, x'; E) = \lim_{\varepsilon \to 0} \frac{\varphi_n(x)\varphi_n{}^*(x')}{E - E_n + i\varepsilon} = P.V. \left[\frac{\varphi_n(x)\varphi_n{}^*(x')}{E - E_n}\right] - i\pi\delta(E - E_n), \tag{26}$$

where $P.V.$ is the Cauchy principal value and δ is the Dirac function. Both are Schwartz distribution and the product with other distribution must be performed using the Hörmander approach (Kumar & Sevilla, 2009). The term $-i\pi\delta(E - E_n)$ in Eq. 26 represents the dissipation of the wave function within the barrier: the greater the E_n and the smaller the $\Delta G_0{}^{\#}$, the faster it is. Returning to the case being investigated, the probability associated to path I is

$$\mathfrak{P}(path\,I)=\frac{G_{O(2)-H}{}^{(tun.)}G_{H}{}^{(tun.)}G_{O(1)-H}{}^{(tun.)}}{\left(G_{O(2)-H}\right)^{3}}\left(\frac{G_{O(2)-H}{}^{(tun.)}G_{H}{}^{(tun.)}G_{O(1)-H}{}^{(tun.)}}{\left(G_{O(2)-H}\right)^{3}}\right)^{*}. \quad (27)$$

The same procedure should be applied to the other paths. The larger $\mathfrak{P}(path)$ value indicates which mechanism is more likely for proton tunneling. Since we use a parametrized molecular orbital, the function $\mathfrak{P}(path\,I)$ also depends on μ. This allows the parameter μ to be found by solving the equation $(\partial\mathfrak{P}/\partial\mu)=0$. The μ value must range in the set $\left(0,R^{\#}-d_{O(2)-H}\right)$, where $R^{\#}$ is the position of the barrier's peak along the reaction coordinate. If the μ value exceeds $\left(R^{\#}-d_{O(2)-H}\right)$, then the considered path must be discarded. To compute the energy associated with the path I, we have to add the GFs of Eq. 23. Substituting Eq. 22 in Eq. 23, and with simple algebra, in the limit $\varepsilon\rightarrow 0$, we get

$$\begin{aligned}
&G_{path\,I}{}^{(tun.)}\\
&=\frac{(E-E_{1s})\left(E-E_{O(1)-H}\right)\varphi_{O(2)-H}{}^{(par.\ orbital)}\varphi_{O(2)-H}{}^{(par.\ orbital)^{*}}}{E^{2}\left(E-E_{O(1)-H}+E_{1s}-E_{O(2)-H}{}^{(par.\ orbital.)}\right)}\\
&+\frac{\left(E-E_{O(2)-H}{}^{(par.\ orbital)}\right)\varphi_{1s}\varphi_{1s}{}^{*}}{E^{2}\left(E-E_{O(1)-H}+E_{1s}-E_{O(2)-H}{}^{(par.\ orbital.)}\right)}\\
&+\frac{(E-E_{1s})\left(E-E_{O(2)-H}{}^{(par.\ orbital)}\right)\left(E-E_{O(1)-H}\right)\varphi_{O(1)-H}\varphi_{O(1)-H}{}^{*}}{E^{2}\left(E-E_{O(1)-H}+E_{1s}-E_{O(2)-H}{}^{(par.\ orbital.)}\right)}\\
&--3U.
\end{aligned} \quad (28)$$

The term U is given by Eq. 21, and its explicit form is (at the limit $\varepsilon\rightarrow 0$)

$$U=\frac{\left(\varphi_{O(2)-H}\varphi_{O(2)-H}{}^{*}\right)\left(E-E_{O(1)-H}\right)-\left(\varphi_{O(1)-H}\varphi_{O(1)-H}{}^{*}\right)\left(E-E_{O(2)-H}\right)}{\left(\varphi_{O(2)-H}\varphi_{O(2)-H}{}^{*}\right)\left(\varphi_{O(1)-H}\varphi_{O(1)-H}{}^{*}\right)}. \quad (29)$$

A closer look at Eq. 28 discloses that $G_{path\,I}{}^{(tun.)}$ contains the electron density that characterizes proton transfer. It appears at the numerator and is a weighted linear combination of the electron densities associated with the single steps forming the reaction paths and those associated with the initial and final states of the proton transfer (whose contributions are given by the explicit form of U). Denoting by $\rho^{(tun.)}{}_{(path\,I)}$ the tunneling density, which, as usual, is given by $\left[\varphi^{(tun.)}{}_{(path\,I)}\left(\varphi^{(tun.)}{}_{(path\,I)}\right)^{*}\right]$, and by $H^{(tun.)}$ the tunneling Hamiltonian, one gets the tunneling energies $E^{(tun.)}{}_{(path\,I)}$ as

$$H^{(tun.)}\varphi^{(tun.)}{}_{(path\,I)}=E^{(tun.)}{}_{(path\,I)}\varphi^{(tun.)}{}_{(path\,I)}. \quad (30)$$

As already stated, if $E^{(tun.)}{}_{(path\,I)}>\Delta G_{0}{}^{\#}$, the chosen pathway is not a tunneling path but rather a path of thermal activation.

The proton transfer of Figure 2 can also take place in the opposite direction to the one we have just considered. More precisely, the intramolecular proton transfer is in equilibrium. To evaluate the opposite tunneling with the same pathway, applying Eq. 27 by changing the denominator is sufficient. The latter will be, as mentioned above, the first propagator not involved in the classically forbidden region. Since for pathway I we have chosen the ground state of the O(1)-H bond as the final step, then as G_0 we must choose the free propagator of the C-O(1) bond. Therefore, one obtains

$$\begin{aligned}
&\mathfrak{P}(path\,I)^{(backforward)}\\
&=\frac{G_{O(2)-H}{}^{(tun.)}G_{H}{}^{(tun.)}G_{O(1)-H}{}^{(tun.)}}{\left(G_{C-O(1)}\right)^{3}}\left(\frac{G_{O(2)-H}{}^{(tun.)}G_{H}{}^{(tun.)}G_{O(1)-H}{}^{(tun.)}}{\left(G_{C-O(1)}\right)^{3}}\right)^{*}.
\end{aligned} \quad (31)$$

The energy corresponding to the back-forward tunneling pathway remains unchanged since we supposed (as an approximation) a symmetric double well. We conclude that the sum of $\mathfrak{P}(path\ I)$ and $\mathfrak{P}(path\ I)^{(backforward)}$ gives the function describing the probability of proton tunneling at equilibrium (for pathway I). The same must be computed for the other possible pathways.

The proposed treatment is based on the approximation that the free propagator preceding the classically forbidden region is associated with the O(2)-H bond. In reality, proton tunneling involves rearranging the conjugated π-electrons, regardless of the tunneling direction. The dynamics by which this rearrangement occurs affect the tunneling probability. More precisely, the lower the rearrangement energy, the higher the likelihood that proton tunneling occurs, whatever the inferred reaction pathway. Therefore, the most rigorous approach is substituting the propagator at the denominator of Eq. 31 with free GF associated with the delocalized molecular orbital along the molecular ring that goes from oxygen O(1) to oxygen O(2).

Let us now consider the case of two molecules connected by two concomitant hydrogen bonds. Specifically, we investigate the proton transfer dynamics in the Guanine-Cytosine base-pair, which is of fundamental importance in studying DNA structure. The system is shown in Figure 3

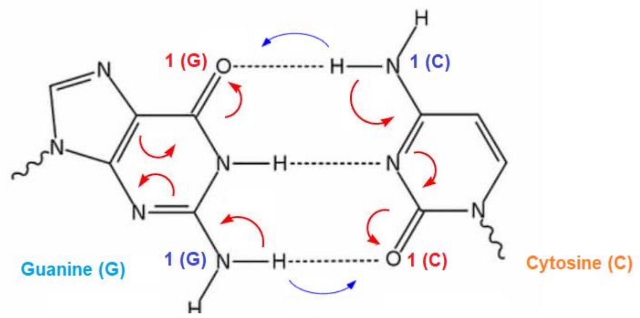

Figure 3. Double proton transfer in Guanine-Cytosine base-pair.

As can be seen, the proton transfer activation along one of the two hydrogen bonds systematically involves the activation of the other. Therefore, the double proton transfer is a concerted reaction mechanism that affects the entire intermolecular loop in which the σ and π electrons rearrangement occurs. Since Guanine and Cytosine are different molecules, the wells of the donor and acceptor groups have different depths (asymmetric double wells). Let us apply the GF's approach. Specifically, we calculate the possible pathways and related tunneling energies for each proton transfer, proceeding as done for the previous example. In this case, the GFs of the initial and final states must also consider the rearrangement of the π-electrons. This means using the LCAO-SCF method to compute the delocalized molecular orbitals along the two fragments of the loop of the intermolecular concerted reaction mechanism. We thus obtain the single probabilities of proton tunneling, which are denoted by $\mathfrak{P}^{(1)}(path\ J)$ and $\mathfrak{P}^{(2)}(path\ J')$, where (1) and (2) denote the two hydrogen-bonds, whereas J and J' denote the inferred pathways. Through these probabilities, we can straightforwardly calculate those corresponding to the double proton transfer, which will be given by all the possible permutations of the products between the probabilities $\mathfrak{P}^{(1)}(path\ J)$ and $\mathfrak{P}^{(2)}(path\ J')$

$$\mathfrak{P}^{(double\ proton\ tun.)}(J,J') = \wp\left(\mathfrak{P}^{(1)}(path\ J), \mathfrak{P}^{(2)}(path\ J')\right), \tag{32}$$

where $\wp$ denotes the permutation. For instance, supposed to have constructed three proton transfer paths via hydrogen bonds 1 and three via hydrogen bond 2. In that case, we have the following double proton transfer probabilities, each characterized by a given energy

$$\begin{cases} \mathfrak{P}^{(double\ proton\ tun.)}(I,I')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(I,I'')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(I,III') \\ \mathfrak{P}^{(double\ proton\ tun.)}(II,I')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(II,II')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(II,III') \\ \mathfrak{P}^{(double\ proton\ tun.)}(III,I')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(III,II')\ ;\ \mathfrak{P}^{(double\ proton\ tun.)}(III,III') \end{cases} . \tag{33}$$

Eq. 33 holds if all proton transfer paths via hydrogen bond 1 differ from those that occur via hydrogen bond 2. The more considerable value obtained for $\mathfrak{P}^{(double\ proton\ tun.)}(J, J')$ indicates the most probable mechanism for double proton tunneling. This approach is innovative compared to what is documented in the literature (Angiolari et al., 2023; Kumar & Sevilla, 2009; Soler-Polo et al., 2019). The proposed method can potentially be used to study multiple proton transfers in complex systems such as biological ones.

Conclusion

The GF method has been introduced in theoretical chemistry only recently, mainly for studying the electronic structure of periodic many-body systems, especially when the electrons are strongly correlated (Linderberg, 2004). This paper proves that this formalism can also be applied to study other physicochemical phenomena. Specifically, we construct a theoretical GF's model to study proton tunneling in hydrogen-bonded systems. The approach consists of determining a priori a hypothetical tunneling mechanism, which takes place in the classically forbidden region of the potential barrier that separates the donor and acceptor groups, and calculating the probability of its occurrence and the associated energy. This mechanism is represented by a set of molecular and atomic orbitals, which are those involved in the breaking and forming of bonds along the direction of the hydrogen bond. This approach is innovative to those proposed in other works (Bountis, 1992; Fillaux et al., 2007; Jana & Ganguly, 2018; Marais et al., 2018; Pinotsi et al., 2016; Tikhonov, 2022) and has the advantage of using consolidated calculation programs, such as the LCAO-SCF, DFT, and MP2 ones. With this method it is possible to obtain the electron density within the classically forbidden region, and to predict how the strength of the hydrogen bond can facilitate or not the proton transfer. In particular, this method could be a useful and straightforward tool to study the dependence of the proton tunneling on the temperature and the environment. For example, increasing temperature allows access to excited vibrational levels of the donor group, making those higher energy reaction pathways more likely. The nature of the environment could instead modify the hydrogen bond strength, leading to reversals of the energies associated with the possible tunneling pathways (and, therefore, to a modification of the tunneling mechanism).

Furthermore, the proposed model is effective in studying the dynamics of multiple proton transfer, especially the one whose mechanism involves the rearrangement of electrons of the molecule or a part of it. In this case, it is possible to investigate how a chosen pathway for one of the proton transfers influences the other, thus establishing the rule to determine the most probable concerted mechanism. This application also suggests that this method could be helpful in the theoretical study of the proton tunneling domino, which has recently aroused the interest of chemists (Schreiner et al., 2015).

Conflicts of interest

The authors declare that there are no conflicts of interest.

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