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Theory of Electron Transfer in Biomolecular Systems

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INTRODUCTION

The kinetics of molecular electron transfer (ET) play a key role in the current nanoscale research, for its crucial importance both in biological reactions [1-3] and in the processes of nanoelectronics [3-6].

Various challenges are addressed in modern electronics. For example, organic thin films useful for optoelectronics were produced [7, 8]; possible implementations of molecular switches, rectifiers and transistors [9, 10] have been explored. Single-molecule junctions may help minimize the size of computer circuitries and enhance their performances [11]. Molecular electronics is developing mainly towards the possible exploitation of intermolecular reactions and intrinsic molecular functions. Along these lines, the most practicable implementation involves molecule-electrode junctions.

The outlined framework imposed an intensive theoretical and experimental research on the electronic transmission through molecules and molecular interfaces. Then, the traditional view of ET between donor and acceptor groups translates into a novel view of ET molecular systems as current-carrying conductors, where the involved ET rates determine the nanoscale conductivity. Moreover, much attention has been focused on biomolecules, because of their rich functionalities.

In these respects, computer electronics, bioengineering and medicine find common points. The rate and the structure dependence of intermolecular ET reactions are particularly important issues in the study of many vital processes in living cells [1], including catalysis and recognition phenomena, as well as in bioelectronics. Another common point is the nearly ubiquitous presence of water, which is the most important molecular environment for ET processes [4, 12], ranging from the reactions in biological solutions to those between organic layers or at the interface between solutions and nanodevices.

Well-known biomolecular functions need to be reexamined from a nanoelectronic point of view and, in the same sense, new functions have to be characterized and understood. From a theoretical point of view, this requires the development of existing analytical tools, but also the introduction of new theoretical models and approaches, with suitable versatility and predictive capabilities. In particular, an outstanding goal is to fill the gap between the methods
traditionally employed to study biological and inorganic (semiconductors, metals, etc.) systems. This is important for the long run objective of adequately treating interactions between the two kinds of systems in future bioelectronic applications. The present thesis fits in the latter context, focusing on the following issues.

Electronic structure and ET properties of selected biomolecular systems. Two molecular systems of interest in biology and bioelectronics are studied, i.e. the protein azurin (Az) from *Pseudomonas aeruginosa* (in the dimeric form) and a short piece of DNA (a dimer of two stacked guanine-cytosine base pairs). Most of the present thesis is focused on the Az system. The last chapter illustrates our work in progress on DNA.

Az is a redox-active protein, belonging to the family of cupredoxins [13]. It seems a promising candidate for the implementation of molecular electronic devices for several reasons [10, 14-18]. In fact, it performs ET in biochemical processes, has suitable structural properties (in particular, a solvent-exposed disulfide bridge exploitable for substrate binding) and preserves its functionality when attached to a substrate [17].

In general, the electron transfer between proteins is an essential step in biological energy production. ET reactions in living cells occur after the formation of short-lived protein complexes. In particular, the Az encounter complexes in solution are reasonably mimicked by covalently cross-linked Az dimers [19]. The study of the electron transfer in an Az dimer is valuable with reference both to biological processes and to nanodevices, where Az arrays may be usefully deposited upon suitable electrodes. In both cases, because of the tunneling nature of ET, the involved protein regions around the redox sites are relatively small [20]. Such circumstance helps the derivation of the relevant ET rates by means of electronic structure calculations (which are generally rather accurate, but computationally expensive and even more difficult for long-distance ET), because the latter can be usefully restricted to the ET relevant protein regions. A successful pruning of the protein system requires an appropriate analysis of the character and the position of its residues. In the present thesis we pay particular attention to the crucial role of some protein aminoacids in the determination of the ET rate. The protein regions more involved in ET were also identified by studying the features of the ET relevant electronic orbitals through density of states and isodensity surface plot analyses.
As to DNA, it is well-known that its fundamental biological role consists in information storage and transduction. On the other hand, its electrical properties are interesting in the fields of the dynamics, response and function of biosensors and nanostructures [21]. Experimental data are mainly available for positive charge (hole) hopping in DNA [22-23], which is expected to occur between G bases [24-26]. The electronic structure calculations presented in this thesis investigate the use of Koopmans’ theorem, and the relative merits of the Hartree-Fock and Density-Functional Theory approaches.

Electron transfer rates. Nowadays, the increasing availability of ET kinetic data and the development of powerful computational tools allow various comparisons between theory and experiment [15, 27-31]. Notwithstanding this, the accurate prediction of the rates of most biological ET reactions remains a long-standing challenge, and this is particularly true for long-distance tunneling, which is the main ET mechanism in proteins [20, 32]. As a matter of fact, several concomitant factors, subject of intensive investigations [2, 33-35], generally determine the rates of ET processes, including the structure and the energy of the donor and the acceptor groups, their distance, the structure and the thermal atomic motion of the intervening medium. Further factors affecting intermolecular ET are the docking of the involved molecules and the properties of the often interposed solvent [36]. On the other hand, within Marcus’ theory [33, 37, 38], the dependence of the ET rate on the electronic and nuclear degrees of freedom is reduced to a few main quantities (investigated in chapter 1): an effective frequency for the nuclear motion along the reaction coordinate (see chapter 1), the reaction free energy, the reorganization energy (the free energy change due to the nuclear rearrangement after the electron transfer), and the electron transfer matrix element, also called transfer integral [39], which measures the electronic coupling between the reactant states. The latter is a key quantity for many redox processes and provides a compact link between ET rates and electronic properties of the interacting systems. Thereby, considerable efforts have been recently devoted to compute transfer integrals through several quantum chemical methods [30, 39-45]. Nevertheless, transfer integrals are often very small and thus hardly computed with high accuracy. Moreover, the involved biomolecules are generally too large for exhaustive \textit{ab initio} calculations, so that approximate methods are required, such as semiempirical and protein-fragment approaches. In
this thesis we present a new method to compute transfer integrals [45], which is not free from approximations (illustrated in chapters 1, 2), but overcomes some common limitations. Indeed, it can use a complete multielectron scheme, thus including electronic relaxation effects; it does not require the knowledge of the transition-state coordinate; it can avoid the computation of excited state quantities (see chapters 2-5); and it does not make use of empirical parameters. This method has been implemented in a Density-Functional Theory (DFT) scheme, mainly because DFT is a good compromise between accuracy and computational feasibility for large metal-ion complexes, such as Az dimers. This choice also matches the aim of treating biological and inorganic components with the same method, in view of possible applications relevant to bioelectronics.

**Water-biomolecule interactions: effects on electron transfer.** Water is a nearly ubiquitous environment in biological ET and water molecules can be found also in other contexts. In particular, it has been shown [19] that Az dimers (similar to the wild type one) in the crystal structure trap two water molecules inside the protein-protein interface. Water can affect intermolecular ET by means of its electrostatic and quantum interactions with the protein redox sites. It can determine the best ET pathway and change the activation free energy [12, 33]. Many experimental [19, 32, 46-48] and theoretical [12, 49-52] studies aimed at understanding the role and the efficiency of water in mediating ET reactions, with particular attention to the rate dependence on the water thickness between the ET active sites. Several open questions still remain [46]. Both single-exponential [48] and multi-exponential [12] decays of the ET rate with the distance between the solvated sites were found. In some cases, water appeared to be a poor [48] or unimportant [53] ET mediator, while, in other cases, the possible ET efficiency of the water medium has been clearly illustrated [12] or conjectured [19].

In the present work we show (chapters 3-4) that the same water molecules between the redox sites of an Az dimer can promote or oppose electron transfer as a result of the interplay of two factors, i.e. the quantum mediation by water of the electron tunneling between the copper redox sites and the electrostatic interactions between the water and protein subsystems. After an appropriate modeling of the protein system, we have found a slower exponential decay of the ET rates with the copper-to-copper distance, in the presence of the water dimer [54]. Moreover, our analysis of the electronic structure (chapter 4) on an
extensive model, including all the residues around the protein active sites and the water dimer in between, agrees with the multiple ET pathways picture recently proposed [12, 55, 56] for other systems, and is able to read the interplay between ET pathways in terms of quantum-electrostatic effects. We believe that the methodology used in this work may be a useful approach for the predictive investigation of ET reactions in biochemical environments.

The thesis is organized as follows. Chapter 1 presents an overview of different features of ET theories, with particular attention to quantities and approximations exploited in the following treatment. Chapters 2-4 are based on (published or submitted) papers produced during the PhD activity; they also include additional analyses and details with respect to the articles. The new method to calculate transfer integrals is illustrated, compared to other methods and applied to the Az dimer, with and without water. Chapter 5 deals with a work in progress on ET between DNA base pairs. Bibliography is reported at the end of each chapter.

Bibliography


Chapter 1

THEORY OF ELECTRON TRANSFER

In this chapter we present an overview of some important features of electron transfer (ET) theories on which the ET formalism and data analyses in the following chapters rest. In section 1.1 we introduce some basic approximations and appropriate perspectives for describing and modeling the many-dimensional configuration landscape of the target systems. Then (section 1.2) useful concepts and achievements from the transition state theory are illustrated. Hence we present the essential features of ET reactions (section 1.3) and their involvement in the fundamental Marcus’ ET theory (section 1.4). After an analysis of the physical properties (in particular, the key quantity “transfer integral”) contributing to the rate of ET reactions (section 1.5), we provide a more specialized analysis of Marcus’ rate equation for ET (section 1.6). Finally, we outline a quantum mechanical treatment of nonadiabatic ET reactions, where the role of the transfer integral is fully appreciated (section 1.7).

The theory presented in this chapter introduces in a critical manner all the background aspects that are faced in the following chapters, which contain the original results of this thesis. We therefore emphasize, in the following presentation, the issues that will be faced to develop the original work.

1.1 Potential energy surface (PES)

1.1.1 Basic approximations and nuclear potential energy.

The quantum mechanical treatment of a redox system requires the solution of the wave equation for a “super-molecule” consisting of all nuclei and electrons in the reacting species and in the intervening medium. This would be an extremely difficult task even for most reactions in the gas phase. The usual approach invokes the Born-Oppenheimer (BO) approximation. It rests on the fact that the
mass of the electrons is much smaller than that of the nuclei, while both electrons and nuclei are submitted to forces of comparable intensity [1]. As a result, the motion of the nuclei is generally much slower than that of the electrons and the two motions may be treated separately. Such an approximation allows writing the total wave function \( \psi(Q, q) \) (\( Q \equiv \{ Q_i \} \) and \( q \equiv \{ q_i \} \) are the sets of nuclear and electronic coordinates, respectively) as a product of a nuclear wave function \( \chi(Q) \) and an electronic wave function \( \phi(q; Q) \). The latter depends parametrically on the set \( Q \). \( \phi \) is relatively insensitive to changes in the nuclear positions, so that it can adjust itself quasi-statically to the nuclear motion (adiabatic approximation). This amounts to neglect the effects of the nuclear momentum and kinetic energy operators on \( \phi \) [2]. In this picture, the electronic motion can be regarded as occurring in a potential field created by stationary nuclei. The energy corresponding to a given electronic state is thus evaluated for any fixed arrangement of nuclei, including all terms except the nuclear kinetic one [2]. The above energy appears as the potential energy in the dynamical equations of the nuclear motion, which is essentially affected by average electronic densities. Thus, it is called a potential energy, although including the kinetic energy of electrons. This potential energy, as a function of the nuclear coordinates, represents a multi-dimensional hypersurface (or energy landscape [3]) for any given electronic state. As we shall see, the BO approximation may not hold where different hypersurfaces are close to intersect, in that corresponding to quasi-degenerate electronic energies. In these cases, the terms neglected by the BO approximation behave (and can be indeed introduced) as perturbations, which may contribute to remove the degeneracy.

Let us now suppose that a system undergoes an essentially electronic process, e.g. an electronic transition described by a perturbation term \( V \) in the Hamiltonian operator \( H \). As a result of the transition, the wave function of the system changes from \( \psi_1(Q, q) = \phi_1(q; Q)\chi_1(Q) \) to \( \psi_\xi(Q, q) = \phi_\xi(q; Q)\chi_\xi(Q) \) (for the sake of simplicity, here we consider the coupling between just two vibrational levels. Introducing the electronic matrix element

\[
V^{(e)}_{\xi\eta}(Q) = \langle \phi_\xi | V | \phi_\eta \rangle = \int \phi_\eta^*(q; Q)V(Q, q)\phi_\xi(q; Q)\,dq ,
\]

the global matrix element is written as
\[ V_{IF} = \langle \psi_I | V | \psi_F \rangle = \int \chi_1^*(Q)V_{IF}^{(e)}(Q)\chi_F(Q)dQ. \]  

(1.2)

Hence, the transition probability is proportional to \( |V_{IF}|^2 \). In the spirit of the BO adiabatic approximation (but with a more specific aim), it can be assumed that the electronic transition takes place ‘instantaneously’ on the time scale of the nuclear motion. Thus, both the wave functions \( \chi_1(Q) \) and \( \chi_F(Q) \), as well as their product \( \chi_1^*(Q)\chi_F(Q) \), are appreciable only in a narrow range around a certain value \( Q \), where \( V_{IF}^{(e)}(Q) \equiv V_{IF}^{(e)}(Q) \), and \( V_{IF} \) can be written as

\[ V_{IF} = V_{IF}^{(e)}(Q)C_{IF}, \]  

(1.3)

with

\[ C_{IF} = \int \chi_1^*(Q)\chi_F(Q)dQ. \]  

(1.4)

The nuclear overlap \( C_{IF} \) or its square is called the Franck-Condon (FC) factor and Eqs. (1.3)-(1.4) express the well-known FC approximation [1, 2]. The latter is clearly useful whenever a process involving an electronic matrix element is considered. On the other hand, if the nuclear configuration of the system can change considerably, the process under study can, in general, occurs around very different coordinates \( Q \) (here we dropped the indication of a particular coordinate). As a consequence, even assuming the FC approximation for a single event, in principle \( V_{IF}^{(e)} \) can appreciably vary while the nuclear dynamics evolves. However, a stronger approximation can sometimes be made, completely neglecting the dependence of \( V_{IF}^{(e)} \) on \( Q \). This is often called the Condon approximation [4, 5], which broadly holds for allowed optical transitions and for many ET reactions [4].

In general, the transition between two given electronic states can involve different vibrational states, so that the nuclear term \( |C_{IF}|^2 \) in the transition probability is replaced by a density of states, weighted by the (square) Franck-Condon factor, here called \( \rho_{FC} \). Then, the relevant quantity for a system with significant nuclear motion is the mean square coupling
resulting from a thermal average on the nuclear modes. Eq. (1.5) is meaningful insofar as referred to a system in thermodynamic equilibrium, for which the indicated averages are well-defined. Moreover, it assumes the FC approximation (i.e., the matrix element was factorized into an electronic matrix element and a FC factor) but not the Condon approximation (in the sense that the electronic matrix element can yet depend on the nuclear coordinates and is not taken away from the average). At any time, each nuclear overlap generally depends on a narrow range of $Q$, so that $\rho_{\text{FC}}$ fluctuates around its own mean value much more rapidly than $V_{\text{IF}}^{(e)}$ does. Thereby, Eq. (1.5) can often be restated as

$$< |V_{\text{IF}}|^2 > \equiv < |V_{\text{IF}}^{(e)}|^2 > \rho_{\text{FC}} > .$$

Detailed analyses of non-Condon effects, with particular reference to charge transfer reactions can be found in Refs. 5, 6.

1.1.2 From the nuclear potential energy to the partial free energy.

Several processes (e.g. protein folding, long-distance ET reactions, etc.) occur on time scales slower than the relaxation times of the environmental modes. Moreover, many chemical reactions can be followed along one or a few “reactive coordinates”, because the essential features of the PESs just depend on these coordinates [7]. In such cases, it is useful to “average” on the faster degrees of freedom and to take the projection of the resulting energy landscape onto the chosen reactive coordinates. Further, it is possible to average on all the “non-reactive” modes. Consider, for example, the intermolecular ET in solvated dimers of the blue copper protein Azurin (Az) (see Fig. 1.1). This long-range ET reaction mainly involves the redox sites (and, possibly, some water molecules in between), i.e. the protein regions around the copper ions (redox sites). Furthermore, the dielectric relaxation time of bulk water (which is usually the solvent) in standard conditions is above $10^{-11}$ s [8], that is much faster than the long-range ET rate (see below). Thus, it may be adequate to consider the free energy coming out from an energy average on the degrees of freedom of bulk water and possibly of the protein matrices around the redox sites.
Fig. 1.1. Idealized drawing of the quaternary structure of an azurin dimer. The stick representation illustrates the protein regions around the Cu ions (purple spheres) and the water dimer in between, to which the ab initio calculations of next chapters are applied. The MD simulation runs in chapter 4 include the solvation water surrounding the protein system.

The averaging procedure converts a PES into a ‘potential’ (effective potential) free energy surface (here abbreviated as PFES). To show this, we separate the nuclear generalized coordinates of a system into two interacting subsets: the reactive coordinates $\mathbf{R} \equiv \{R_j\}$ and the non-reactive ones $\mathbf{r} \equiv \{n_k\}$, with respective momenta $\mathbf{P} \equiv \{P_j\}$ and $\mathbf{p} \equiv \{p_k\}$. Limiting the formalism to classical statistical mechanics, we introduce the ‘partial’ partition function

$$Z_{r,p}(\mathbf{R}) = \frac{1}{h^\nu} \int \exp \left[ -\frac{E(\mathbf{r},\mathbf{p};\mathbf{R})}{k_B T} \right] d\mathbf{r} d\mathbf{p}, \quad (1.7)$$

where $E(\mathbf{r},\mathbf{p};\mathbf{R})$ is the potential energy for the reactive modes, $h$ is the Planck’s constant, $\nu$ is the number of non-reactive degrees of freedom, $k_B$ is the Boltzmann’s constant, $T$ is the temperature. Hence a partial free energy can be defined as

$$G_{r,p}(\mathbf{R}) = -k_B T \ln[Z_{r,p}(\mathbf{R})]. \quad (1.8)$$

Eq. (1.8) represents a Helmholtz free energy or a Gibbs free energy, depending
on whether a canonical (NVT) ensemble or an isothermal-isobaric (NPT) ensemble is used, respectively. \( G_{r,p}(R) \) has the following significant properties (see Appendix A):

(i) It includes an entropic term \( S_{r,p}(R) \), which measures the disorder in the set \((r, p)\) (e.g. describing the bulk solvent and part of the solute species) for a given \( R \) (e.g. defining the reactive nuclear coordinates of the solute and solvent species).

(ii) The probability density of the reactive coordinate configurations can be recast as a free energy distribution, given by

\[
f(R) = \frac{\exp\left[-G_{r,p}(R)/k_{B}T\right]}{\int \exp\left[-G_{r,p}(R)/k_{B}T\right] dR}.
\]  

(iii) \( G_{r,p}(R) \) represents a potential of mean force [9]; in fact the component of the force along the \( k \)th reactive mode, averaged on the \((r, p)\) configurations is simply given by

\[
< F_k >_{r,p} = -\frac{\partial G_{r,p}(R)}{\partial R_k}.
\]  

In other terms, Eq. (1.10) describes the thermodynamic driving force acting on the point representative of the system, while it moves on the PFES.

1.1.3 PFESs for typical electron transfer (ET) systems.

The previous procedure can be adopted for systems involved in electronic processes and, in particular, in electron transfer reactions. The overall set of nuclear coordinates is given by \( Q \equiv \{R, r\} \), while \( q \equiv \{q_i\} \) and \( \mu = \{\mu_i\} \) denote the sets of electronic coordinates and momenta, respectively. The electronic energies \( \varepsilon_n(Q) \) (where \( n \) stands for the appropriate set of quantum numbers) are solutions of the eigenvalue equations

\[
\left[ \sum_{i} \frac{\mu^2_i}{2m_i} + V(R, r, q) \right] \phi(q; R, r) = \varepsilon_n(R, r)\phi(q; R, r),
\]  

\( 1.11 \)
where $m_e$ is the electron mass and the potential energy term $V(R, r, q)$ mainly includes all the electrostatic interactions. Then, the partial free energies can be defined through Eqs. (1.7) and (1.8), with

$$E_n(r, p; R) = e_n(R, r) + \sum_{j=1}^{\nu} \frac{P_j^2}{2m_j}, \quad (1.12)$$

in such a way that one PFES $G_n(R)$, with its own entropy $S_n(R)$, corresponds to each electronic eigenstate. Analogously, a PFES can be constructed for any electronic state (also if not an eigenstate).

ET reactions involve the transfer of an electronic charge between a donor and an acceptor trapping sites. In this context, only some nuclear modes are directly coupled to the electron motion with appreciable interaction and are thus identified as the reactive modes. In particular, it has been shown [10] how, under suitable approximations (one-electron picture, quadratic potential wells along the nuclear coordinates, linear coupling between electron and nuclear modes), an ET Hamiltonian can be defined by

$$H_{ET} = H^e + H^{N_e} + H^N + H^{Nh}, \quad (1.13)$$

where $H^e$ is the one-electron Hamiltonian, $H^{N_e}$ describes the coupling between the reactive coordinates and the electron, $H^N$ is the Hamiltonian for the reactive coordinates and $H^{Nh}$ includes the energy terms of the bath plus its coupling with the reactive coordinates. By using the Hamiltonian (1.13), the expression (1.12) for the effective potential energy of the reactive modes can be recast as

$$E_n(r, p; R) = \bar{e}_n(R) + U_N(R, r) + \sum_{j=1}^{\nu} \frac{P_j^2}{2m_j}, \quad (1.14)$$

where $\bar{e}_n(R)$ includes the electronic kinetic energy and the energy of interaction between the electron and the reactive modes, while $U_N(R, r)$ essentially consists of the electrostatic interactions between the reactive and non-reactive modes. From Eqs. (1.7), (1.8) and (1.14) it is seen that, at a given point $R$, the free energy
difference between any two PFESs, corresponding to arbitrarily chosen quantum numbers \( m \) and \( n \), is just \( \tilde{E}_n(R) - \tilde{E}_m(R) \). Thus, the same partial entropy \( S_{\text{r.p.}}(R) = S_{\text{r.p}}(R) \) is associated to any PFES (see Appendix A). In other words, since the electron subsystem does not appreciably interact with the non-reactive nuclear modes, it does not contribute to their partial entropy. Then, mean potential-energy surfaces (MPESs) \( U_{\text{r.p}}(R) = \langle E_n(r,p;R) \rangle_{r.p} \) may be usefully introduced (see sections 1.3-1.6). In fact, the vertical distances between any two MPESs are the same as for the corresponding PFESs, as far as the involved electronic levels have the same degeneracy. In such a case, it is particular useful to follow two MPESs along the reaction path (i.e. along the reaction coordinate, defined as the curvilinear abscissa along the reaction path). The reaction path can be described by a set of parametric equations, expressing the reactive coordinates as functions of the reaction coordinate, that is the parameter. Thus, at any given value of the reaction coordinate (that is, at the corresponding set of values for the reactive coordinates), the difference between the two MPESs equals that between the two corresponding PFESs.

1.2 Transition state theory (TST)

The TST derives an expression for the rate of chemical reactions, by applying statistical mechanics to key quantities defined in kinetics theories. In such a way, it provides a theoretical model to explain the temperature and concentration dependence of observed reaction rates.

![Fig. 1.2](image) A typical portion of PFES. The minima correspond to stable states. The reaction path connecting such states is represented by a trajectory that passes through the saddle point (thick line).
1.2.1 The transition state and the reaction coordinate.

Fig. 1.2 shows a typical portion of PFES for two reactive modes. In many chemical reactions in solution, $R_1$ and $R_2$ may be identified as a solute and a solvent reactive coordinates, the latter approximately describing the solvent reorganization [11]. The energy minima correspond to stable molecular species. They appear as valleys in the PFES for the reactants and the products of a reaction. Since the free energy (or the mean potential energy) reflects a multitude of configurations, it acquires a simple quadratic form near a minimum. This can be ascribed to the usually normal distribution of the energy contributions from the large number of non-reactive modes. For slow processes characterized by high free energy barriers, Fig. 1.2 represents a PFES upon which a vibrationally equilibrated system moves in a nearly frictionless way [7]. The potential of mean force in Eq. (1.8) represents the driving force that leads the system towards equilibrium configurations. ‘Diffusive’ or 'stochastic’ effects become, instead, important for processes fast enough that the reaction rate approaches the rate of the environmental relaxation [7]. During a reaction, the passage from one minimum to the other requires the transit through regions of higher free energy. The ridge between the two minima has a lowest point, that is a saddle. The most probable reaction trajectory (thick line in Fig. 1.2) passes through the saddle point, corresponding to the transition state, along a minimum-energy path [12]. This path, named the reaction path, matches the direction of the gradient at any point of the potential energy surface [13]. In this manner, the reaction path is a steepest descent path from the transition state to both reactant and product minima and the thermodynamic driving force, given by Eq. (1.8), acts always in the direction of extremum partial free energy change. The curvilinear length of the displacement along this path defines the reaction coordinate, that can be often used for an unidimensional picture of the reaction. The lowest saddle point is a maximum versus the reaction coordinate and an extremum with respect to the other coordinates. It defines the height of the activation barrier that must be overcome for the process to occur.

When mass-weighted Cartesian coordinates (proportional to the square root of the inherent nuclear masses or mode effective masses) are used, an “intrinsic” reaction coordinate [13] is obtained from the solution of the equation of motion for ‘classical’ nuclei, that move on the PES in such a way to approach with an
infinitesimal velocity to the minima and to the transition state (from which the feature of “intrinsic motion” or quasi-static nuclear displacement [14]). From a geometrical point of view, the intrinsic reaction coordinate describes the shortest path on a PES for going from reactants to products via the transition state [15]. It is worthy of note that, despite the complexity of most chemical reactions, their description in terms of a reaction pathway has often a reliable foundation on empirical observations.

The above discussion in this section rests on a classical view of the nuclear modes. On the other hand, it is worth mentioning that, at sufficiently low temperatures, the quantum nature of the nuclear modes become important. In such cases, the nuclear modes (in particular, the more effective high-frequency modes) are reorganized by activationless tunneling [4, 16, 17] between the vibrational levels in the reactant and product states. Marcus’ theory has been extended to included such effects (see [4, 18] and references therein).

1.2.2 TST rate equation.

Let us consider the scenario for a chemical reaction in solution. At first the reactant molecules A and B are far away. Hence they diffuse together to form a precursor complex (initial complex, named I) [18], which is an equilibrium state for the internal coordinates of the solutes. In this encounter complex the potential energy for all the internal degrees of freedom is at a minimum. The solutes are, thus, in a stable reactant structure. Moreover, such a structure is utterly stable (just at the bottom of a valley in Fig. 1.2) if also the solvent (hence the whole solution) is at a minimum of free energy. Starting from this point, the interaction with the fluctuations of the environment can lead to I-configurations with higher energy, up to the transition state. Indeed, the latter includes the configurations at the top of the activation barrier within a small but otherwise arbitrary distance \( \delta \) along the reaction coordinate [12]. Any configuration that belongs to the transition state defines a so-called activated complex (\( M^\dagger \)). The (unstable) transition state can give back the reactants or can evolve towards the equilibrium (product) state of the successor complex (final complex, named F). Then, a last diffusive step generally follows, if the products consist of separated molecules.

A typical (ground) PFES along the reaction coordinate is shown in Fig. 1.3. The forward reaction from I to F can be sketched as
where the transit through the transition state has been explicitly shown. Let us suppose that the overall reaction is of the first order [19], so that its rate is given by

\[ v = k[I], \]  

(1.16)

where \( k \) is the rate constant for the reaction and \([I]\) is the concentration of the species I.

Only activated complexes moving along the reaction coordinate \( x \) from left to right in Fig. 1.3 contribute to the forward reaction. Thus, based on the assumptions that such a motion can be described within classical mechanics and that the kinetic population of the transition state follows the Maxwell distribution, the mean velocity of \( M^\dagger \) is given by

\[ <\dot{x}> = \frac{\int_{-\infty}^{\infty} u(x) \exp\left(-\frac{m\dot{x}^2}{2k_BT}\right)\dot{x} \, d\dot{x}}{\int_{-\infty}^{\infty} \exp\left(-\frac{m\dot{x}^2}{2k_BT}\right) \, d\dot{x}} = \left(\frac{k_BT}{2\pi m}\right)^{1/2}, \]  

(1.17)
where \( m \) is the effective mass of the reacting system for the motion along \( x \), the Heaviside function \( u(\dot{x}) \) (\( u = 1 \) for \( \dot{x} > 0 \) and \( u = 0 \) for \( \dot{x} < 0 \)) has been introduced to select the activated complexes moving towards \( x_p \). The first assumption is fulfilled for reactants with sufficiently high molar mass (as the ones considered in the following chapters). The second hypothesis (which is a good approximation for thermal reactions [12]) rests on the fact that the reactants obey the Maxwell-Boltzmann distribution too; this is indeed the case if the energy redistribution among their degrees of freedom, due to “collisions” (in general, effective encounters), is much faster than the reaction rate. According to Eq. (1.17), a rough estimate (as rough as the definition of \( \delta \) ) of the average time for crossing the transition state is

\[
\frac{\delta}{<\dot{x}>} = \delta \left( \frac{2\pi m}{k_B T} \right)^{1/2}.
\]  

(1.18)

At this point, it is assumed that all the activated complexes crossing the transition state reach the product state. Then, the rate of the reaction is given by the number of complexes that overcome the transition state per unit volume and unit time, namely

\[
v = \frac{[M^2]}{\delta (2\pi m/k_B T)^{1/2}}.
\]  

(1.19)

By comparison of Eqs. (1.16) and (1.19), we derive that the TST rate constant of a reaction is given by

\[
k = \frac{[M^2]}{[I]} \frac{1}{\delta (2\pi m/k_B T)^{1/2}}.
\]  

(1.20)

The ratio of concentrations in the right-hand side of Eq. (1.20) is equal to the ratio of the probabilities of the two species, which, in turn, is given by the ratio \( Z_m / Z_1 \) of the corresponding partition functions. The dominating contribution to \( Z_1 \) comes from the bottom of the free energy well, described by

\[
G(x) = G(x_i) + \frac{1}{2} m \omega^2 (x - x_i)^2,
\]  

(1.21)
where $\omega$ is an effective frequency for the motion along the reaction coordinate. Thus, neglecting the non harmonic behavior of $G(x)$ when the transition state is approached, it is

$$Z_1 \equiv \frac{1}{h} \exp[-G(x_1)/k_BT] \times \int_{-\infty}^{\infty} \exp[-m\omega^2(x-x_1)^2/2k_BT]dx \int_{-\infty}^{\infty} \exp(-m\dot{x}^2/2k_BT)m\dot{x} \, dx$$

$$= \frac{k_BT}{\hbar \omega} \exp[-G(x_1)/k_BT]. \tag{1.22}$$

As to activated complexes, if $\delta$ is small enough, the change of $G(x)$ within the transition state is negligible and

$$Z_{m'} \equiv \frac{1}{h} \exp[-G(x^+)/k_BT] \int_{-\delta/2}^{\delta/2} dx \int_{-\infty}^{\infty} \exp(-m\dot{x}^2/2k_BT)m\dot{x} \, dx$$

$$= \frac{\delta}{h} (2\pi mk_BT)^{1/2} [-G(x^+)/k_BT], \tag{1.23}$$

where $x^+$ is named the transition coordinate and corresponds to the maximum of the activation barrier. By combing Eqs. (1.20), (1.22) and (1.23), we obtain the rate constant

$$k = \frac{\omega}{2\pi} \exp(-\Delta G^+/k_BT), \tag{1.24}$$

where the quantity

$$\Delta G^+ = G(x^+) - G(x_1) \tag{1.25}$$

is the free energy of activation. Note that the hardly known $m$ and the somewhat indeterminate quantity $\delta$ have canceled out in the derivation of Eq. (1.24). Let us note also that Eq. (1.22) can be recast in the form

$$Z_1 = \exp(-G_1/k_BT), \tag{1.26}$$

with

$$G_1 = G(x_1) + k_BT \exp(h\omega/k_BT). \tag{1.27}$$

Here $G_1$ is the overall free energy for the reactant super-molecule, weighing the
probability to find the reactants anywhere in the corresponding basin. By insertion of Eq. (1.27), the expression (1.24) for the reaction rate constant acquires the Eyring form [20]

\[ k = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^*}{k_B T}\right), \quad (1.28) \]

with

\[ \Delta G^* = G(x^+) - G_1. \quad (1.29) \]

Eq. (1.24) [or Eq. (1.28)] does not contemplate that the activated complex, after exploring the top of the barrier, may come back to the reactant state. To account for this possibility, a transmission coefficient \( \kappa \) is introduced in Eq. (1.24), thus acquiring the form

\[ k = \kappa \frac{\omega}{2\pi} \exp\left(-\frac{\Delta G^*}{k_B T}\right). \quad (1.30) \]

\( \kappa \) is defined as the fraction of forward crossings that lead to products. From the point of view of TST, when the energy of the incoming complex is only slightly larger than the height of the activation energy, only the lowest path at the top of the barrier is allowed, there is a little chance for dissipation upon it and \( \kappa \) is close to unity. On the other hand, larger energies imply greater possibilities to go around at the top of the barrier, taking various return paths (in the PES picture) and thus reducing \( \kappa \) [12]. Note also that, whereas different PFESs are associated to a system (each corresponding to a given electronic state), TST limits itself to adiabatic processes, \(^1\) for which the point representative of the system explores only the ground PFES. In this respect and beyond, the introduction of \( \kappa \) provides a link to the treatment of nonadiabatic reactions, also from a quantum mechanical point of view. In particular, specializing the TST to ET reactions, \( \kappa \) should include an electronic factor \( \kappa_e \), which is the electronic transmission coefficient. As a matter of fact, in the following study of the rates of ET processes, we will focus on \( \kappa \), referring to it simply as the “transmission coefficient”.

\(^1\) Let us remark that the term ‘adiabatic’ is here used with an acceptance which matches also visually its Greek etymology [from \textit{adiabatos} (not able to go through): \textit{a-} (not) + \textit{dia-} (through) + \textit{batos} (passable)].
1.3 Essential features of ET reactions.

A process can be qualified as an ET reaction if it involves a displacement of localized electronic charge at nearly fixed nuclear coordinates. The scenario for a bimolecular ET reaction in solution is, e.g., the following [7]. At first, the donor molecular group $D$, on which the transferring electron is initially localized, and the acceptor group $A$, receiving the transferred electron, diffuse together. Once the reactant state or precursor complex has been formed (with the electron essentially in $D$), the increasing interaction between the two molecules may distort their electronic levels up to a suitable intermediate configuration where ET can occur. Hence, the electron transfer, leading to the product state or successor complex, is followed by a suitable nuclear relaxation and later diffusion away. In the present thesis we will be interested only in the very ET reaction, from the precursor to the successor complex.

An ET reaction is a time-dependent phenomenon and its exact quantum-mechanical description, indeed, requires the solution of the time-dependent Schrödinger equation for the time-dependent wave function of the overall ET system. The complete Hamiltonian operator of the system is given by

$$\mathcal{H} = H + U_N + T_N,$$  \hspace{1cm} (1.31)

where $H$ is an electronic Hamiltonian [i.e. $H^e + H^{Ne}$ in the scheme of Eq. (1.13)], $U_N$ includes the interactions between the nuclear degrees of freedom and $T_N$ is the nuclear kinetic energy operator. The application of $T_N$ to a factorized wave function gives

$$T_N \phi(q, Q) \chi(Q) \equiv -\sum_k \frac{\hbar^2}{2m_k} \nabla_k^2 \phi(q, \{Q_k\}) \chi(\{Q_k\})$$

$$= -\sum_k \frac{\hbar^2}{2m_k} \left[ \phi(q, \{Q_k\}) \nabla_k^2 \chi(\{Q_k\}) + 2\nabla_k \phi(q, \{Q_k\}) \cdot \nabla_k \chi(\{Q_k\}) + \chi(\{Q_k\}) \nabla_k^2 \phi(q, \{Q_k\}) \right].$$ \hspace{1cm} (1.32)

The BO adiabatic approximation neglects the last two terms (named nonadiabatic
terms [2]). When considering the PESs of a given system, an improvement to this approximation consists in keeping the nonadiabatic diagonal term associated with the nuclear momentum and kinetic energy operators (diagonal nuclear coupling term) [19]. Therefore, for a system with initial and final electronic wave functions \( \phi_i(q, Q) \) and \( \phi_f(q, Q) \) respectively, the improved BO approximation corresponds to neglecting the non-diagonal nuclear coupling term

\[
T_{HF} = -\langle \phi_i(q, \{Q_k\}) | \sum_k \frac{\hbar^2}{2m_k} \nabla^2 \phi_k(q, \{Q_k\}) \rangle + \langle \phi_i(q, \{Q_k\}) | \sum_k \frac{\hbar^2}{m_k} \nabla \phi_k(q, \{Q_k\}) \cdot \nabla_k \rangle .
\]

(1.33)

The general form of the system wave function is (apart from a normalization factor)

\[
\psi(Q, q, t) = \sum_i \phi_i(Q, q, t) \chi_i(Q, t),
\]

(1.34)

where \( \phi_i(Q, q, t) \) and \( \chi_i(Q, t) \) are the wave functions for the electronic and nuclear subsystems respectively. In molecular ET theory the expansion of Eq. (1.34) is, in general, limited to two static electronic states (two-state approximation) [4, 7, 19]: an initial state \( \phi_i(q, Q) \) representing the reactants surrounded by the solvent and a final state \( \phi_f(q, Q) \) for the products surrounded by the solvent. Moreover, only the reaction nuclear coordinate \( x \) (or a few reactive coordinates) is often used. Thus, Eq. (1.34) is truncated to two terms, by writing

\[
\psi(x, q, t) = \chi_i(x, t) \phi_i(q, x) + \chi_f(x, t) \phi_f(q, x).
\]

(1.35)

In Eq. (1.35) the (explicit) time dependence is limited to the nuclear coefficients,\(^\text{2}\) which take explicitly into account the nuclear motion and weigh the contributions of the two electronic wave functions in the instantaneous wave function of the

\(^{\text{2}}\) Let us observe that the indexes \( I \) and \( F \) in the nuclear wave functions refer to the fact that \( \chi_i \) (\( \chi_f \)) provides the nuclear wave function whenever the overall state is factorized and \( \phi_i \) (\( \phi_f \)) describes exactly the state of the electronic subsystem.
system. Note that the state in Eq. (1.35) has the paradigmatic form of the “not separable” or “mixed entangled” states [21, 22], thus implying quantum correlations between the nuclear and electronic degrees of freedom. This circumstance is, however, lost whenever the nuclei are treated as classical particles, so that both nuclear coefficients (and thus the overall wave function) are proportional to the delta function \( \delta[x - x(t)] \), and Eq. (1.35) becomes

\[
\psi(x, q, t) = [C_i(t)\phi_i(q, x) + C_f(t)\phi_f(q, x)]\delta[x - x(t)].
\]  

(1.36)

More generally, the wave function in Eq. (1.35) can be written in a factorized (hence separable) form whenever \( I \chi \) and \( F \chi \) differ for a factor depending only on \( t \). \( \phi_i \) and \( \phi_f \) can be chosen as a set of states that diagonalize the electronic Hamiltonian (named adiabatic) or a set (diabatic) that does not, the latter being a very convenient zeroth-order basis set for weakly interacting systems [23].

---

**Fig 1.4** (Adapted from Fig. 1 of Ref. 59) Energy (PFESs or MPESs) versus reaction coordinate \( x \) for the initial (I) and final (F) states in a typical ET reaction. The adiabatic (solid lines) and diabatic (dashed lines) curves are represented. \( \lambda \) is the reorganization free energy, \( U_{IF} \) is the transfer integral (section 1.5), \( \Delta G^0 \) (\( \Delta U^0 \)) is the PFE (MPE) of reaction (section 1.4) and \( \Delta G^\lambda \) (\( \Delta U^\lambda \)) is the adiabatic activation PFE (MPE). The diabatic activation energy reach the crossing seam point \( P \), but it is nearly equal to the corresponding adiabatic quantity in nonadiabatic ET.

Typical PFESs or MPESs for the two kinds of electronic states are illustrated in
Fig. 1.4. The solid lines refer to the adiabatic states, describing the energy eigenvalues of the ground and first excited electronic states as a function of nuclear position. In the adiabatic representation, only $T_{\text{IF}}$ couples the states [19, 23]. $T_{\text{IF}}$ has a minor role in the diabatic picture, because the coupling is dominated by the electronic coupling matrix element, named also tunneling matrix element [6, 19] or transfer integral, that, for negligible overlap between the diabatic states $\phi_i$ and $\phi_F$, is given by [23]

$$H_{\text{IF}} = \langle \phi_i (q, x) | H | \phi_F (q, x) \rangle .$$

(1.37)

It is worthy of note that, in principle, the event that the nonadiabatic matrix elements are much smaller than the electron tunneling matrix element does not assure the adequacy of the BO approximation, because of possible upstream errors in the functional forms of the BO wave functions [24]. As a matter of fact, the failure of this basic approximation is rarely important in chemical and biological ET, where commonly the electronic mixing is not directly due to the nuclear kinetic energy and to the mixing of the electronic and nuclear states [4]. However, the BO approximation can fail in some cases, particularly in bridge-mediated electron transfer at very long distances [4, 6, 24, 25]. Indeed, the bridge-nuclear relaxation gives rise to inelastic tunneling pathway channels that can lead to a breakdown of the BO approximation [6, 25].

Eq. (1.37) expresses the coupling between the diabatic states which produces the increasing separation between the adiabatic states near the transition coordinate $x^*$. In other words, the adiabatic states already include the effects of such coupling in their construction. If the diabatic states are orthogonal, the minimum separation between the adiabatic states (also called tunneling splitting [19]) is just $2|H_{\text{IF}}|$.

Ref. 24 provides a quantitative study on the failure of the BO and FC approximations for an exactly solvable model, made of an electron in a contrived potential well, coupled to one nuclear degree of freedom. There, it is shown that the more energy the electron can carry away, at the expense of the vibrational energy on the donor site, the further it can tunnel (in agreement with the general fact that particles tunnel better at higher energies). This circumstance is an expression of the coupling between the electronic and nuclear degrees of freedom, that introduces terms related to the nuclear dynamics to what in the uncoupled scheme was a purely electronic (long distance) decay constant.
\( \phi_i(q, x_i) \) and \( \phi_p(q, x_p) \) describe the states of the electronic subsystem in the equilibrium (global) states of reactants and products, respectively. In the simplest diabatic representation, \( T_{ip} \) is exactly zero (although such an approximation is not possible when \( H_{ip} \) is very small or zero [23, 26]), because the dependence of the diabatic wave functions on \( x \) is completely neglected, by assuming that \( \phi_i(q, x) = \phi_i(q, x_i) \) and \( \phi_p(q, x) = \phi_p(q, x_p) \) at any \( x \). Actually, such a small dependence is generally expected [19, 23, 27], e.g. if \( \phi_i \) and \( \phi_p \) are chosen as the (single) valence bond structures corresponding to the reactants and products, which are little affected when nuclear coordinates change. This is also the case for the choice made in this thesis.\(^4\) We study the electron transfer between the copper redox sites of an Az dimer, with some reference to recent experiments on covalently linked Az dimers in solution [28]. The large Cu-to-Cu distance allowed us to define the diabatic states as the direct products between the ground electronic state of one reduced Az and that of the other oxidized Az (after suitable pruning around the ET active sites, as described in the next chapter). Indeed, it is well-known that generally, in a molecular system, the displacements of the nuclei about their equilibrium positions have little effect on the ground electronic wave function. [1, 2]. From the above it is clear that each diabatic state describes a state with the charge always (i.e. for any \( x \)) localized in one of the ET partners.

Some essential features of the ET reactions can be caught from Fig. 1.5 [29], which shows on the left a series of effective one-electron potential energy curves for the electronic motion and on the right the corresponding diabatic MPESs for the nuclear motion. In the left side figures, the abscissa is the electron coordinate \( q \), each well corresponds to the possible localization of the moving electron in one of the reacting molecules and the horizontal bars represent the corresponding electronic levels. In the right side figures, the abscissa is instead the nuclear reaction coordinate \( x \). The filled circle in Fig. 1.5a indicates that initially an electronic orbital localized in the D group is occupied. The

\(^4\) However, the method for calculating transfer integrals presented in this thesis is not constrained to this choice of the diabatic states. Moreover, the independence of the diabatic wave functions on the nuclear coordinates is not assumed; rather, the (anyway related) Condon approximation is employed, in its strict form (chapters 2 and 3) or in the relaxed form that comes out from Eq. (1.6).
Effective one-electron potential-energy curves (on the left) and corresponding nuclear MPES (on the right). $q$ is the electronic coordinate, $x$ is the (nuclear) reaction coordinate. The bars (left) indicate electronic levels in the wells. Filled circles represent localized electronic orbitals that are occupied first [in (a)] or after [in (e)] the electron transition, at the corresponding equilibrium $x$. Open circles denote the involved virtual levels. The dots in (c) refer to the electronic level degeneration at $x^\dagger$. The tunneling splitting is disregarded.

Fig. 1.5 (adapted from Fig. 2 of Ref. 29) Corresponding equilibrium configuration of nuclei is $x_1$ (Fig. 1.5b). Instead, the open circle in Fig. 1.5a indicates that, after an electron transition, an orbital localized in the A group is occupied. According to the FC principle, the nuclei cannot appreciably change their momenta and rearrange to new equilibrium positions during the electronic transition. Thereby, in Fig. 1.5b the electronic transition is represented by a vertical line connecting the two MPESs. The energy gap between the two electronic levels cannot be compensated through energy exchange between electrons and nuclei, so that the transition can be assisted only by an external radiation field. On the other hand, fluctuations of the nuclear positions can lead to the transition configuration $x^\dagger$ (Fig. 1.5d), for which the two relevant electronic levels are degenerate (Fig. 1.5c). In this case, ET can occur without any external field, because it meets both the FC principle, that requires a vertical transition, and the energy conservation, that implies a horizontal transition. After the ET process, the rearrangement of the nuclear positions
generally leads to the equilibrium configuration $x_f$ for the product electronic state (see Figs. 1.5e, f). Now the level in A is lower, while the virtual one in D has been raised.

A suitable understanding of ET processes requires the analysis of the crucial interplay between the electronic coupling and the coupling to the nuclear motion, especially near the crossing of the diabatic curves, namely (within the adiabatic representation) in the region of the avoided crossing between the adiabatic curves. The first fruitful theoretical approach to ET was provided by Marcus, who treated classically the nuclear motion and obtained parabolic diabatic curves under reasonable hypotheses [29-31].

1.4 ET reactions: Marcus’ Theory. I

From this section onward, we will deal with some models for the study of ET reactions [7, 29, 32, 33]. The attention will be primarily focused on outer-sphere ET reactions, where major structural changes (e.g. bond breakage or formation) are not entailed, thereby allowing more manageable theoretical approaches. This is often the case when the redox partners do not share any atom or group, or more generally, when their relevant electronic orbitals interact weakly. Indeed, a weak electronic interaction, characterized by a slight overlap between such orbitals, may suffice to electronically couple the reactant molecules in such a way to allow an appreciable ET.

Marcus’ theory of electron transfer can be set within the unidimensional framework of Fig. 1.4. The energy features of the nuclear dynamics, which assists the electron transition between the ET partners, can be described in terms of a few free energy quantities, listed below.

(a) The free energy of activation, defined by Eq. (1.25), is the free energy barrier that the system must overcome in order to reach the transition state. It is determined by the values of the potential free energy at the coordinates $x_i$ and $x^\dagger$, apart from the (often neglected) correction due to the avoided crossing.

(b) The reorganization free energy $\lambda$ is the free energy required to rearrange the nuclear coordinates from the equilibrium configuration of a given electronic
state to that of the other one, while remain in the same electronic state.

(c) The (work-corrected) free energy of reaction describes the free energy change of the system in the whole ET process. It is given by [29]

\[ \Delta G^0 \equiv G_f(x_f) - G_i(x_i) = G(x_f) - G(x_i) = \Delta G^0 + w_f - w_i, \quad (1.38) \]

where \( G_i(x) \) and \( G_f(x) \) are the diabatic free energy curves, \( \Delta G^0 \) is a “standard” free energy of reaction, defined as the difference between the configurational free energy of labeled reactant molecules, when they are fixed in far away positions (virtually infinitely far apart), and the corresponding quantity for the product molecules. \( w_i \) is the work necessary to bring the reactants from fixed positions infinitely far apart to the configuration where ET occurs; \( w_f \) is the analogous term for the products. Note that \( \Delta G^0 \) equals zero for an electron self-exchange reaction, where the reacting molecules differ only in the respective oxidation states (exchanged by the reaction).

A useful relation among the above ET quantities can be easily found under the following fundamental Marcus’ assumption [35, 36]:

Any possible change in the charge distribution of the reacting molecules is followed by a proportional change in the dielectric polarization of the solvent (linear-response approximation), which is a thermal bath with Gaussian statistics.

Then, on the further assumption that the solvated reactants and products have the same polarization properties, such hypothesis implies that the reactant and product (diabatic) free energy curves along the reaction coordinate are parabolas with the same curvature \( m \omega^2 \) [36], that is

\[ G_i(x) = G_i(x_i) + \frac{1}{2} m \omega^2 (x - x_i)^2 \quad (1.39a) \]

\[ G_f(x) = G_f(x_f) + \frac{1}{2} m \omega^2 (x - x_f)^2. \quad (1.39b) \]

\[ ^5 \text{The meaning of the attribute “standard” in the present context is elucidated in Ref. 34.} \]
Thus, imposing the intersection condition $G_i(x^+) = G_e(x^+)$ and neglecting the
splitting $G_i(x^+) - G(x^+)$ with respect to the activation free energy $\Delta G^\dagger$, the
sought relation turns out to be [29]

$$\Delta G^\dagger = \frac{\left(\lambda + \Delta G^0\right)^2}{4\lambda}. \quad (1.40)$$

The possibility to observe effects ascribable to distorted parabolas or to parabolas
with different curvatures has been recently explored [36-38], but we do not
consider it in the present treatment.

Due to the topological definitions of the initial, transition and final states and
to the environmental Gaussian statistics, also the MPESs are generally assumed
to be parabolas with the same curvature. This is indeed the case if the vibrational
frequencies associated with the reactive coordinates are not appreciably changed
by the ET reaction. In such cases, the initial and final equilibrium states have the
same entropy, and the same is true for the transition state, defined as a
combination of the initial and final states [32]. Then, Eq. (1.40) can be restated in
terms of the corresponding average energy quantities. This simplifying
assumption is employed in the remainder of this chapter.

Under the hypotheses and approximations leading to Eq. (1.40) (but working
on a multi-coordinate model), Marcus obtained the following equation for the
rate constant of redox reactions in solution [29, 34], expressing the combined
effects of the electronic coupling and of the coupling to the nuclear motion on
the ET rate:

$$k = \kappa \nu \exp\left(-\frac{\Delta G^\dagger}{k_B T}\right), \quad (1.41)$$

where $\kappa$ is the electronic transmission coefficient or electronic factor, $\nu$ is the liquid
phase collision frequency or, generally, an effective frequency for the motion
along the reaction coordinate, and the exponential is the nuclear factor, describing
the probability that the system reaches the transition state. Eq. (1.41) is similar to
the ad hoc corrected Eq. (1.30), and $\nu$ can be identified with $\omega/2\pi$.\(^6\) On the other

\(^6\) Indeed, in the oversimplified picture of TST, a “collision” in a bimolecular reaction
could be identified with the transit through the top of the activation barrier, with
which a frequency $\omega/2\pi$ could be associated.
hand, in general $\kappa$ cannot be identified with $\kappa'$. Moreover, Eq. (1.41) rests upon an appropriate equation for the electrostatic free energy of non-equilibrium states and on statistical mechanical relations that allow a specific definition of each included quantity, well-suited to ET reactions. In the next section we will analyze the factors that appear in the Eq. (1.41). If, as a consequence of the ET process, the frequencies of the nuclear modes change and/or anharmonic effects become important, the fundamental Eq. (1.41) still formally holds and the electronic factor preserves its crucial role (see below), but the involved nuclear quantities acquire more complicated expressions or need to be obtained numerically [4, 39-43].

1.5 **Electron tunneling vs ET: transfer integral and transmission coefficient**

The passage from the situation in Fig. 1.5a to that in Fig. 1.5c shows that the electron transfer involves a redistribution of the electronic charge, across a barrier that changes in response to the nuclear motion. Therefore, ET is in general an electron tunneling phenomenon [4, 19, 32] and the tunneling can indeed occurs when the two relevant electronic levels approximately coincide. This is the core of an ET reaction, in which the electron actually transfers from one reactant molecule to the other. Moreover, when the reacting species are characterized by activated complexes with a very small electronic coupling (as it is the case in long-distance ET), the electron tunneling is a kinetically crucial step. Therefore, we review a few elements of the theory of tunnelling, in conjunction with their application to ET theories.

1.5.1 **Electron tunneling and transfer integral: nonadiabatic and adiabatic limits.**

In chemical and biological ET, electron tunneling generally occurs between two bound states. We start our brief analysis from the simplest (but conceptually useful) model, that is a symmetric double-well potential energy. It can be related to two single wells with identical energy levels, as depicted in Fig. 1.6a. For
Fig. 1.6 (a) Electronic potential energy at \( x^\parallel \). The two degenerate localized levels (blue horizontal bars) are split by tunnel effect into orbitals diffuse on both ET sites (black bars). (b) Nuclear MPESs. The electronic coupling \( |H_{\parallel}| \) (half-splitting at \( x^\parallel \)) is shown. (c) Asymmetric electronic potential energy at a nuclear coordinate \( x \) far from \( x^\parallel \). The further splitting induced on the localized levels by tunnel effect is negligible (in comparison, the transfer integral has been exaggerated for better visibility). Black bars do not correspond to orbitals equally diffuse on the ET sites.

example, each well could model the potential energy seen by the transferring electron (or, in general, by the valence electronic distribution, if a multi-particle picture were adopted) in the redox site of an Az molecule, if the latter were isolated, fixing its coordinates to the ones corresponding to \( x^\parallel \). Indeed, the usefulness of such a model rests on the fact that, within the BO separation scheme, tunneling occurs only when the ET relevant levels in the two wells are (nearly) degenerate.

Within the approximations of section 1.3, the localized wave functions \( \phi_I \) and \( \phi_F \) correspond to eigenlevels of the (instantaneous) separated wells, with a suitable energy \( E \). At present, their overlap \( S_{IF} = \langle \phi_I | \phi_F \rangle \) is assumed negligible. Moreover, the double well is assumed fixed, thus abstracting from the actual ET process and getting some useful information.

The behavior of the potential energy near the top of the barrier expresses the presence of an interaction between the reactants, that couples and so alters the states corresponding to their separated wells. The tunnel effect (i.e. the resonant
probability of back-and-forth tunneling between the two confined isoenergetic levels) is reflected in a quantum resonance of the two electronic configurations. Thereby, the two resultant electronic eigenstates are delocalized in both the wells. One of them is lower and the other is higher in energy than the localized levels. Consequently, within each well, the unperturbed level is split into a doublet. In relation to the electronic coupling, the half-splitting is given by [44]

\[ \Delta E/2 = |H_{\text{IF}}| = |\langle \phi_i | H | \phi_f \rangle|. \] (1.42)

Instead, in relation to the properties of the barrier, the splitting can be written as [4]

\[ \Delta E = \frac{\hbar \omega_e}{\pi} \exp(-\sigma/2), \] (1.43)

with the Gamov factor [45]

\[ \sigma = \frac{2}{\hbar} \int_{-a}^{a} \sqrt{2m_e[V(q) - E]} \, dq, \] (1.44)

where \(-a\) and \(a\) are the barrier limits, \(V(q)\) is the electronic potential energy and \(\omega_e\) is an electronic vibrational frequency for the single well. Actually, \(\omega_e\) depends on the energy, because of the anharmonicity of the distorted wells, although it changes appreciably only for levels close to the top of the barrier. Note also that the tunneling probability and thus the splitting is larger for higher levels, for which the barrier is lower. From a dynamical point of view, if the electron is initially confined in the well on the left, the probability that it is trapped in the well on the right after a given time interval \(\tau\) is, from Rabi’s formula [44],

\[ P = \sin^2 \left( \frac{|H_{\text{IF}}| \tau}{\hbar} \right). \] (1.45)

In the short time limit, when reverse transitions have not yet begun, it is

\[ P \equiv |H_{\text{IF}}|^2 \left( \frac{\tau}{\hbar} \right)^2 \propto \exp(-\sigma). \] (1.46)
It is useful to express $P$ or $|H_{\text{IF}}|^2$ as a function of the barrier width, i.e. $R = 2a$, which is a measure of the distance between the redox sites in the actual system (e.g., the copper-to-copper distance in azurin dimers). If the height of the barrier with respect to $E$ is nearly constant in most of the relevant range of the electronic coordinate (as may well be the case for long distances between the reactants), Eq. (1.46) gives

$$|H_{\text{IF}}(R)|^2 \equiv |H_{\text{IF}}(R_0)|^2 \exp[-\beta(R - R_0)], \quad (1.47)$$

where we have introduced a suitable decay constant $\beta$ and a range $R_0$ to which the steep variations of the barrier are limited. These two quantities depend on the properties of the reactants and of the intervening medium, if any. Eq. (1.47), which was expressly derived above for a single reaction coordinate, provides in many cases a reasonable approximation to the behavior of the (square) electronic coupling matrix element for long-range ET, and the same decay with the distance between the reactants is reflected in the global ET rate (see below).

Within the above simplified picture, Fig. 1.6b shows that the splitting of the electronic levels relevant to ET gives the minimum separation between the two MPESs, that occurs at the transition coordinate $x^\perp$. The latter is thereby defined as the value of the reaction coordinate that marks the crossing of the diabatic curves. In the many-dimensional PES landscape, $Q^\perp$ is the nuclear coordinate corresponding to the lowest energy on the crossing seam surface [33, 46].

Fig. 1.6c shows the effective one-electron potential energy at a generic coordinate $x$, different from $x^\perp$. At this nuclear coordinate, the separation $\Delta E$ between the adiabatic curves is composed of both the energy difference $\Delta E_{\text{IF}}$ between the diabatic levels and the further splitting $2|H_{\text{IF}}|$, due to their coupling, in such a way that

$$\Delta E = \sqrt{\Delta E_{\text{IF}}^2 + 4|H_{\text{IF}}|^2}. \quad (1.48)$$

Note that, if the coupling $|H_{\text{IF}}|$ is small enough and $x$ is far apart from $x^\perp$, then the diabatic levels are very close to the adiabatic ones.
From the above issues we argue that the transfer integral plays an essential role in ET reactions. In Fig. 1.7 two limiting cases are depicted. When the electronic coupling is weak (nonadiabatic regime), a “sudden” [23] ET process can happen virtually at $x^\dagger$, where the FC principle is fulfilled (Fig. 1.7a). On the other hand, when the electronic coupling is strong enough (adiabatic regime), the splitting at the avoided crossing is correspondingly large and the electron transfer occurs more gradually along the reaction coordinate. In such a case, the adiabatic representation can be conveniently used, following the process on the lower adiabatic curve; hence a TST treatment may be adequate.

![Diagram](image)

**Fig. 1.7** (Adapted from Fig. 2 of Ref. 23) Nuclear MPESs, illustrating (a) the weak electronic coupling (nonadiabatic) and (b) the strong coupling (adiabatic) limits.

Some remarks are in the order. (a) An accurate analysis of electron transfer reactions requires a combined treatment of nuclear dynamics and electronic state evolution. For example, the overall rate of a long-distance ET reaction depends not only on the shape of the symmetric double well, but also on the time of its persistence, due to the nuclear dynamics. (b) The transition probability in Eq. (1.45) or Eq. (1.46) refers to a static double-well potential, and thus relates in no way the time quantity to the nuclear dynamics. In its formulation, the nuclear kinetic energy is not taken into account and no information on the activation (free) energy is included. (c) Eq. (1.47) fails in a wide class of reactions, e.g. when $R_e = R_o$.

The value of the transmission coefficient $\kappa$ is strictly related to points (a)-(c). A theoretical formalism for the electronic transition step in ET reactions, treating
the various $\kappa$-regimes in an unified way and allowing a thermal average of the
transition probability, was independently provided by Landau [47], Zener [48]
and Stückelberg [49], with later refinements and extensions [50, 51]. In the next
subsection we will address points (b)-(c).

1.5.2 *Electron behavior in the transition state region: Landau-Zener model.*

In this section we discuss the Landau-Zener model, exploiting the MPESs
along the reaction coordinate. The probability of transition in the region of the
avoided crossing depends on the splitting between the MPESs and on the energy
associated with the nuclear dynamics. In the Landau-Zener formalism, the total
electronic wave function is written as a linear combination of the diabatic wave
functions, with time dependent coefficients. Inserting it into the time dependent
Schrödinger equation, the equations of motion for the expansion coefficients are
obtained. Finally, such equations are solved under the following simplifying
assumptions: (i) The nuclear motion is classical, with a constant velocity $\dot{x}$ in the
crossover region, where the potential energy is approximately constant. (ii) The
diabatic potential curves are linear in either side of the transition coordinate. (iii)
The energy of the system is high enough that the classical turning points upon
the abovementioned curves are well above their intersection.

The resultant probability $\bar{F}$ that, in traversing the crossing, the system
remains on the initial potential curve (see arrow 1 in Fig. 1.8) is given by [47, 48]

$$\bar{F} = \exp(-\gamma),$$  \hspace{1cm} (1.49)

with

---

**Fig. 1.8** Multiple passage at the crossing seam of the initial and final MPESs in the non-
adiabatic ET.
\[ \gamma = \frac{2\pi}{\hbar} U_{2}^{2} \frac{1}{x \Delta F}, \]  

(1.50)

where \( \Delta F \) is the difference in slope of the curves \( I \) and \( F \) at the transition coordinate, i.e.

\[ \Delta F = \frac{d \mid U_I(x) - U_F(x) \mid}{dx} = \frac{d \mid G_I(x) - G_F(x) \mid}{dx} |_{x = \xi^I}. \]  

(1.51)

Therefore, the probability for a successful transition on a single attempt is

\[ P = 1 - \overline{P} = 1 - \exp(-\gamma). \]  

(1.52)

Note that, contrary to usual perturbation schemes, Eq. (1.49) holds independently of the \( U_{IF} \) value, for both strong (\( \gamma >> 1 \)) and weak (\( \gamma << 1 \)) interactions. The total probability \( P_{IF} \) of electronic transition from the state \( I \) to the state \( F \) is obtained by adding up all the attempts on the upper adiabatic curve. To this end, let us consider the composite process 1-3 in Fig. 1.8: step 1 stays on the curve \( I \), corresponding to a probability \( \overline{P} = 1 - P \); step 2 jumps from \( F \) to \( I \) on the upper adiabatic MPES, with a probability \( P \) (equal to the probability for the inverse transition, because of the symmetry in Fig. 1.6a); finally, step 3 ends on the \( F \)-portion of the lower MPES, with a probability \( 1 - P \). Assuming statistical independence among the three steps, the overall probability for the composite event is \( (1 - P)P(1 - P) \). Along these lines, the total probability for a forward transition is

\[ P_{IF} = P + (1 - P)P(1 - P) + ... = P + (1 - P)^2 \sum_{k=0}^{\infty} P^{2k+1} = \]

\[ = P + (1 - P)^2 P \frac{1}{1 - P^2} = \frac{2P}{1 + P} = \frac{1 - \exp(-\gamma)}{1 - \frac{1}{2} \exp(-\gamma)}. \]  

(1.53)

Finally, the transmission coefficient \( \kappa \) is given by the thermal average \( <P_{IF}>_T \) over the vibrations able to reach the transition coordinate. Two limiting cases are particularly important.

(i) Sufficiently strong electronic couplings between the initial and final diabatic
states (i.e., \( U_{IF} \) large enough that \( \gamma \equiv \gamma_T \gg 1 \)) define the adiabatic limit, where the system is not able to reach the upper PES (\( \bar{P} \equiv 0 \)). The ET reaction proceeds through a smooth shift on the lower PES and the electronic transition certainly occurs (\( \kappa \equiv 1 \)), as the system oversteps the top of the activation barrier.

(ii) Instead, in the opposite (nonadiabatic) limit of weak coupling (i.e., \( \gamma_T \ll 1 \)), the relations \( \bar{P} \equiv 1 - \gamma \equiv 1 \), \( P \equiv \gamma \) and \( P_{IF} \equiv 2\gamma \) hold. They express the fact that, every time the system reaches the top of the activation barrier, it almost certainly crosses the gap twice (back and forth) proceeding along the I curve, each time with a small probability \( \gamma \) to transit on the F curve. In this event,

\[
\kappa \equiv 2\gamma_T = \frac{4\pi}{h\Delta F} \frac{U_{IF}^2}{< \gamma >},
\]

so that the transmission coefficient results proportional to the square transfer integral.

The expression of \( P_{IF} \) is clearly suitable for a thermal average, because it gives the transition probability as a result of the interplay between the electronic coupling and the nuclear dynamics. In fact, Eq. (1.54) can be explained with another key. To this end, let us observe that the passage from Eq. (1.53) to Eq. (1.54) implies a small transition probability, generally as a consequence of a fast nuclear dynamics and of a small coupling between the involved electronic states. The quick nuclear motion determines a little time of persistence \( \tau_N \) of the symmetric electronic potential. Then, the small electronic coupling (corresponding to a high and/or wide potential energy barrier for the electronic motion) entails an increased lifetime \( \tau_{el} = h/2U_{IF} \) of the localized electronic states, at the expense of the transition probability. Indeed, \( \kappa \) may be roughly expressed as the ratio of \( \tau_N \) and \( \tau_{el} \) [4]. From the geometry of the MPESs in a sufficiently small region (of width \( \Delta x \); see Fig. 1.4) around the transition nuclear coordinate it results

\[
2U_{IF} \approx \frac{\Delta x}{2} \left| \frac{dU_{el}}{dx} \right|_{x=x^0} + \frac{\Delta x}{2} \left| \frac{dU_{el}}{dx} \right|_{x=x^0} = \frac{\Delta x}{2} \Delta F.
\]

(1.55)
Hence,
\[
\tau_N \sim \frac{\Delta x}{\dot{x}}_T \approx \frac{4U_{IF}}{\Delta F} < \frac{1}{\dot{x}}_T
\]  
(1.56)
and
\[
\frac{\tau_N}{\tau_{el}} \sim \frac{4U_{IF}^2}{\hbar \Delta F} < \frac{1}{\dot{x}}_T,
\]  
(1.57)
to be compared with the expression (1.54) for \( \kappa \).

In conclusion, the transmission coefficient effectively appears in Eq. (1.41) for the ET rate constant when the electronic coupling is sufficiently small and the nuclear motion is fast. In such conditions, a single-exponential decay of the ET rates with the distance between the redox sites, as indicated in (Eq. 1.47), can be observed, although multi-exponential behavior was also found, e.g. in some protein ET reactions through an increasing water thickness [53].

1.6 ET reactions: Marcus’ Theory. II

1.6.1 Transfer integral effects in the specialized Marcus’ equation for ET rates: adiabatic and nonadiabatic regimes.

The pre-exponential factor \( \kappa \nu \) in Eq. (1.41) can be easily evaluated, using the quantum-mechanical formula provided by Landau-Zener for \( P_{IF} \) and treating the nuclear motion according to classical statistical mechanics. When the electron subsystem is in the initial diabatic state, the nuclear subsystem, having a reduced mass \( m \), oscillates in the MPES I with an angular frequency \( \omega \) and an amplitude \( x_0 = (2E/m \omega^2)^{1/2} \), where \( E \) is the total nuclear energy [32].

Let us first consider the adiabatic limit (Fig. 1.7a). The nuclear system can reach the transition coordinate only if its kinetic energy is at least equal to the activation (free) energy \( \Delta U^\ddagger \equiv U^\ddagger = \Delta G^\ddagger \), that is with a probability (nuclear factor)
\[
p = \frac{\int_{-\infty}^{-\Delta U^\ddagger} \exp(-E/k_B T) \ dE}{\int_{-\infty}^{\infty} \exp(-E/k_B T) \ dE} = \exp(-\Delta U^\ddagger/k_B T).
\]  
(1.58)
Whenever the activation barrier is mounted (if it is the case, with a frequency \( v = \omega/2\pi \)), the electron transition certainly occurs (\( k_{ad} = < P_{\text{ad}} >_\gamma = 1 \)). Thus, Eq. (1.41) for the ET rate becomes

\[
\kappa_{ad} = \frac{\omega}{2\pi} \exp(-\Delta G^\ddagger/k_B T) = v \exp(-\Delta G^\ddagger/k_B T). \tag{1.59}
\]

In the nonadiabatic limit (Fig. 1.7b), \( p \) preserves its expression (1.58). Whenever \( E \) exceeds the activation energy, the system passes through the transition coordinate \( x^\ddagger \) with a velocity

\[
\dot{x} = \omega \sqrt{x_0^2 - x^2} = \frac{2}{\sqrt{m}} (E - U^\ddagger). \tag{1.60}
\]

Moreover, it is easy to show that

\[
\Delta F = m\omega^2 (x_F - x_i) = \omega \sqrt{2\lambda m}. \tag{1.61}
\]

Inserting the Eqs. (1.60) and (1.61) into Eq. (1.54), we obtain the transmission coefficient

\[
\kappa = 2\pi \frac{U_{W}^2}{h\omega} \frac{1}{\sqrt{\lambda}} \int_{U_\gamma}^{\infty} (E - U^\ddagger)^{-1/2} \exp(-E/k_BT) \, dE = \frac{2\pi}{h\nu} \frac{U_{W}^2}{\sqrt{\lambda}} \sqrt{\frac{\pi}{\lambda k_B T}}. \tag{1.62}
\]

Hence, the expression for the nonadiabatic ET rate is

\[
k_{\text{nonad}} = \frac{U_{W}^2}{\hbar} \sqrt{\frac{\pi}{\lambda k_B T}} \exp(-\Delta G^\ddagger/k_B T), \tag{1.63}
\]

as given by Marcus in Ref. 54.

Ultimately, an enlightening scheme for the various regimes can be obtained in

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7 This equation can be equivalently derived (see Ref. 32) by considering the transition probability upon a single attempt, \( P \equiv \gamma \), and the fact that the system crosses the transition coordinate nearly twice per cycle.
terms of the transfer probability $P$ on a single attempt (which is a function of $E$ through the nuclear velocity) and of the inherent frequency of transit through $x^\ddagger$, $f(E)$. In fact,

$$
\kappa v = <P_i^{\omega \omega}_T> = <P(E)\left[\frac{2}{1 + P(E)} \frac{\omega}{2\pi}\right]>_T \equiv <P(E)f(E)>_T, \quad (1.64)
$$

so that:

(i) **Adiabatic limit:** $P(E)$ is unity and the system crosses just one time per cycle $x^\ddagger$, that is $f(E) = \omega/2\pi$. In fact, in accordance with Eq. (1.52), when «$U_{if}$ becomes large enough, the electronic states are so strongly mixed that further increase in $U_{if}$ will not change the ET rate» (Ref. 19, p. 119). In this situation, the ET rate is determined by the effective frequency of the nuclear motion and by the nuclear factor (altogether, by the nuclear fluctuations leading to the crossing point along the reaction coordinate), as expressed by Eq. (1.59).

(ii) **Nonadiabatic limit:** $P(E) \equiv \gamma(E) \ll 1 \Rightarrow \bar{P}(E) \equiv 1 - \gamma(E) \equiv 1$, i.e. $P(E)$ is very small and thus $x^\ddagger$ is crossed nearly two times per cycle, that is $f(E) \approx 2(\omega/2\pi) = \omega/\pi$. As a matter of fact, the coupling between the two ET relevant states is so weak that the electron transfer may not occur even for favorable nuclear geometries that satisfy the FC requirements for ET [55]. In other terms, «if the electronic interaction causing the splitting is very weak, a system initially on curve I will tend to stay on I as it passes to the right across the intersection» (Ref. 34, p. 681) up to the turning point. In such a case, both the electronic and the nuclear factors affect the ET rate constant. In particular, the ET rate increases with the transfer integral, as expressed by Eq. (1.63). Then, the dependence of the electronic coupling on the distance between the ET sites, e.g. described by Eq. (1.47) and observed in many long-range reactions, is reflected in the behavior of the ET rate. This has been indeed found for the (suitably pruned) Az dimer considered in chapters 2 and 3.
(iii) **Intermediate case:** \( P(E) \) and \( f(E) \) have intermediate values, as generally expressed by Eq. (1.64). Correspondingly, the electron and nuclear factors conjunctly affect the ET rate constant as in Eq. (1.41), but the transmission coefficient has not the simple expression (1.62).

In fact, a single theory that rigorously treats and connects the different regimes is not available. Generally, the preexponential factor into Eq. (1.41) depends on both \( U_{IF} \) and the dynamic motion along the reaction coordinate, related to the value of the inherent friction [56]. Here we limit ourselves to note that, in the adiabatic limit and for very large values of the friction, the reaction is controlled by the diffusion to the crossing point along the reaction coordinate [57], so that the preexponential factor has not the free-vibration expression of Eq. (1.59).

### 1.6.2 Generalized transfer integral and small overlap approximation.

In the previous sections, we widely appreciated the crucial role of the transfer integral in determining ET rate constants. Thereby, it is opportune to consider that, when the overlap \( S_{IF} \) between the diabatic electronic states cannot be neglected, an evaluation of the transfer integral more accurate than in Eq. (1.37) is required. Within the two-state approximation, this is accomplished by writing the (adiabatic) electronic ground state as a linear combination of the diabatic states\(^8\) and applying the Ritz method, which gives the secular equation

\[
\begin{vmatrix}
H_{II} - E & H_{IF} - ES_{IF} \\
H_{IF} - ES_{IF} & H_{FF} - E
\end{vmatrix} = 0,
\]

(1.65)

where \( E \) is the generic energy eigenvalue, \( H_{II} = \langle \phi_i | H | \phi_i \rangle \), \( H_{FF} = \langle \phi_f | H | \phi_f \rangle \) and the wave functions are normalized. The eigenvalues of Eq. (1.65) are\(^9\)

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\(^8\) This can be done with reference to Eq. (1.36) or, more generally, when the wave function of Eq. (1.35) can be factorized. In both cases, the time (and thus the nuclear coordinate) is treated as a parameter, hardly ever explicitly indicated.

\(^9\) In Eq. (1.66), \( H_{IF} \) is reasonably assumed real; otherwise, \( H_{IF} \to \text{Re}(H_{IF}) \) in the second term under the root and \( H_{IF}^2 \to |H_{IF}|^2 \).
The energy separation at the generic $x$ is then given by

$$E_{\pm}(x) = \frac{1}{1 - S_{IF}^2} \left[ \frac{H_{II} + H_{IF} - 2H_{IF}S_{IF} \pm \sqrt{1 + 4\Delta E_{IF}^2 - (H_{II} + H_{IF})H_{IF}S_{IF} + H_{II}H_{IF}S_{IF}^2 + H_{IF}^2} }{2} \right]. \hspace{0.5cm} (1.66)$$

The energy separation at the generic $x$ is then given by

$$\Delta U(x) \equiv E_+(x) - E_-(x) = \sqrt{\Delta E_{IF}^2 + 4V_{IF}^2}, \hspace{0.5cm} (1.67a)$$

with

$$V_{IF}(x) = \frac{1}{1 - S_{IF}^2} \left| H_{IF} - S_{IF} \frac{H_{II} + H_{IF}}{2} \right|. \hspace{0.5cm} (1.67b)$$

When $S_{IF}^2 << 1$, Eqs. (1.67a, b) can be rewritten as

$$\Delta U(x) = \sqrt{\Delta E_{IF}^2 + 4V_{IF}^2} \hspace{0.5cm} (1.68a)$$

and

$$V_{IF}(x) = \left| H_{IF} - S_{IF} \frac{H_{II} + H_{IF}}{2} \right|. \hspace{0.5cm} (1.68b)$$

respectively. Eqs. (1.67a, b) or (1.68a, b) extend Eq. (1.48) to cases in which $S_{IF}$ is not negligible. Due to the localized character of the initial and final states, the condition $S_{IF}^2 << 1$ is fulfilled in many ET reactions. This approximation is also employed in the next chapter, where we develop a novel method for calculating transfer integrals, which does not resort to Eq. (1.68b). In general, $V_{IF}$ is referred to as the (generalized) transfer integral [23] (or ET matrix element [33]). Within the Condon approximation (even in its relaxed form; see subsection 1.1.1), a suitable simplified definition is

$$U_{IF} = \frac{\Delta U(x^\dagger)}{2} = V_{IF}(x^\dagger). \hspace{0.5cm} (1.69)$$

On the other hand, if some part of the ET system undergoes signification
motion, generally the expression (1.69) no longer gives the right quantity to be inserted in the ET rate equation. In fact, in such a case, a picture resting exclusively on the reaction coordinate is not adequate. Rather, significant changes in $V_{I\bar{F}}$ can arise from displacements along coordinates orthogonal to $x$. Then, a suitable classification of nuclear modes is needed, as described in the following subsection.

1.6.3 Transfer integral and mode classification.

For MPESs as, e.g., that in Fig. 1.7a, the electronic transition is dominated by a narrow range of configurations for which the electronic coupling is nearly constant, i.e. $V_{I\bar{F}}(x) \equiv V_{I\bar{F}}(x^\dagger) \equiv U_{I\bar{F}}$. Consequently, the Condon approximation can be safely applied to the given mode, by attributing the value $U_{I\bar{F}}$ at $V_{I\bar{F}}(x)$ independently of $x$. Such a mode is named an accepting mode [5, 52], in that it supports the energy exchanges needed both to induce electron (virtual) level degeneration and to properly relax the nuclear structure after the electron transition. The reaction coordinate, introduced to describe the global reaction, depends just on the accepting modes. As a matter of fact, the identification of a reaction coordinate in a system with many degrees of freedom is a very difficult task. Thus, it is common practice to make recourse to intuition for defining an “ad hoc reaction coordinate”.

New features arise generally for ET systems with wide nuclear motions. Suppose, for example, that the donor and acceptor groups are separated by a liquid water medium. The effects of its disordered motion may be negligible on the energies of the localized donor and acceptor states, but considerable and probably fluctuating on the coupling between the two states. For example, if the barrier in Fig. 1.6a is sufficiently high, its variation may have a large relative effect on level splitting even if it does not significantly change the localized states. In other terms, the weak (or “flat”) dependence of the $D$ and $A$ states on such water modes does not limit the electron transfer to small ranges of configurations along them. Since these modes can strongly influence the electronic coupling and thus the ET rate, they are named inducing modes [5].

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10 In the absence of large nuclear motions important for the ET process, the Condon approximation may be actually extended to the entire $x$ axis.
The presence of inducing modes limits the applicability of the Condon approximation or even determines its breakdown. Consider, in particular, the case of an Az dimer in solution. Experimental data [28] revealed the presence of two water molecules, relevant to ET, accommodated in the gap between the copper redox sites of the two molecules. By modeling the configurational space of the nuclear system by means of a reaction coordinate $x$ and of an orthogonal inducing coordinate $r$ (on which the ET significant displacements of the water dimer are described), we can evaluate the transfer integral $U_{IP}(r)$ for different $r$ values along a MD trajectory. Then, assuming the Condon approximation in the relaxed form of Eq. (1.6), we take the mean square value $<U_{IP}^2(r)>$ as the quantity to be inserted in the ET rate. The original results of this thesis relative to such a procedure are presented in chapter 4, for a complex system made of an Az dimer with bridging water molecules. For our target system, the MD sampling is limited to the water subsystem, also for the chief purpose of isolating the water effects on ET.

1.7 Quantum mechanical description of nonadiabatic ET

In the vibronic state representation, a nonadiabatic ET reaction is a non-radiative transition from an initial set of vibronic states

$$\left\{ |\psi_{1v}\rangle\right\} = \left\{ |\phi_{1}(q;Q)\chi_{1v}(Q)\rangle\right\}$$

(1.70)

to a final set

$$\left\{ |\psi_{Fw}\rangle\right\} = \left\{ |\phi_{F}(q;Q)\chi_{Fw}(Q)\rangle\right\},$$

(1.71)

where $\phi_{1}(q;Q)$ and $\phi_{F}(q;Q)$ are the diabatic electronic wave functions, while $\chi_{1v}(Q)$ and $\chi_{Fw}(Q)$ are the vibrational functions associated with the D and A diabatic energy surfaces, respectively [6, 19, 33]. Then the transition probability per unit time for a reaction from a single level of the reactant basin to the product manifold, $|\psi_{1v}\rangle \rightarrow \left\{ |\psi_{Fw}\rangle\right\}$, is given by the Fermi’s golden rule [44] as
\[ k_v = \frac{2\pi}{\hbar} \sum_w \left| \langle \psi_{1v} | V | \psi_{Fw} \rangle \right|^2 \delta(E_{1v} - E_{Fw}) \]
\[ = \frac{2\pi}{\hbar} |V_{1w}|^2 \sum_w \left| \langle \chi_{1v} | \chi_{Fw} \rangle \right|^2 \delta(E_{1v} - E_{Fw}) \]  \hspace{1cm} (1.72)

where \( E_{1v} \) and \( E_{Fw} \) are the unperturbed energies of the vibronic states \( |\psi_{1v}\rangle \) and \( |\psi_{Fw}\rangle \), respectively. The Dirac \( \delta \)-function ensures energy conservation,\(^\text{11}\) \( V \) is the effective electronic Hamiltonian and the electronic coupling matrix element \( V_{1w} = V_{1w}(Q) = \langle \phi_v | V | \phi_{Fw} \rangle \) has been introduced. Within the Condon approximation, the latter is identified with \( U_{1w} = V_{1w}(Q) \) and factored out of the sum in Eq. (1.72). Finally, when the Boltzmann distribution is assumed over the initial vibronic manifold, the thermal average of \( k_v \) gives

\[ k = \frac{2\pi}{\hbar} |U_{1w}|^2 \frac{1}{Z} \sum_v \rho_{\text{FC}} \exp\left(-\frac{E_{1v}}{k_B T}\right) = \frac{2\pi}{\hbar} |U_{1w}|^2 < \rho_{\text{FC}} > \]  \hspace{1cm} (1.73)

where \( Z \) is the partition function for the reactant basin and

\[ \rho_{\text{FC}} = \sum_w \left| \langle \chi_{1v} | \chi_{Fw} \rangle \right|^2 \delta(E_{1v} - E_{Fw}) \]  \hspace{1cm} (1.74)

is the Franck-Condon density of final states for a given initial state. Corrections for non-Condon effects [5, 58], directly applicable to the classical Marcus' rate, are discussed in subsection 1.1.1 and chapter 4. A treatment of non-Condon effects in the time domain is provided in Ref. 6, on the assumption that the vibrations affecting the D and A energies (accepting modes) are independent of (i.e. orthogonal to) those modulating the D-A tunneling barrier and hence the tunneling matrix element (inducing modes).

We wish to emphasize that the transfer integral preserves its crucial role (also quantitatively) in the quantum-mechanical determination of ET rates.\(^\text{12}\) It

\(^\text{11}\) Indeed, the rigorous conservation imposed by the Dirac \( \delta \)-function is an approximation (virtually always a good approximation), as may be seen in Ref. 44.

\(^\text{12}\) As a matter of fact, this might be reasonably expected, since the difference between classical and quantum-mechanical theories rests on the respective treatment of nuclear motions.
provides a compact link between the ET rate and the electronic structural properties of the D-A interactions. Indeed, the present thesis focuses on the development of a fruitful method for calculating transfer integrals (chapter 2 or Ref. 59) and on its application to derive ET rate behaviors of biological and bioelectronic interest (chapters 2-3 or, in the order, Refs. 59-60, and chapters 4-5). Particular attention is also devoted to some aspects of water-biomolecule interactions affecting ET processes (see Ref. 60 and chapter 4).

References


(1986).


Chapter 2

ET RATES IN AZURIN DIMERS, BY COMPUTING TRANSFER INTEGRALS THROUGH A NEW METHOD

In this chapter we present a new method to calculate transfer integrals and apply it to the electron self-exchange reaction in Az dimers. The decay of the inherent rate constant with the distance between suitably modeled Az redox sites is also studied, by using (and comparing) both the developed method and an energy-splitting method. The latter derives electronic couplings from one-particle quantities (obtained in a self-consistent way) and turned out to be valuable for determining the rates of ET reactions inside Ru-modified azurins \[1\]. The effects of various basis sets and exchange-correlation functionals on transfer integrals are also analyzed. Finally, we inserted the computed transfer integrals, along with an independent estimate of the reorganization free energy \[2-4\], in Marcus’ rate equation for nonadiabatic ET. Hence, the resultant rate constants were compared to available experimental data.

2.1 One-electron and many-electron schemes

In the previous chapter we exploited an effective one-electron picture to catch some typical aspects of ET reactions. The simplest formalization of such a picture rests on a suitable use of the orbital wave functions, under the assumption that the electronic Hamiltonian can be approximated as an independent-particle operator. Some more sophisticated methods for defining one-electron models \[5-7\] make use of Koopmans’ theorem (in the Condon Approximation) \[8, 9\], which involves self-consistent field approximations to the many-electron interactions, thus going beyond the naive independent particle model \[10\]. Within the Hartree-Fock (HF) scheme, Koopmans’ theorem states that the change in the total energy...
of a system due to the removal of the electron occupying a given unrelaxed or “frozen” spin-orbital (i.e. the inherent first ionization potential or inner-shell ionization potential, by neglecting the electron reorganization upon the ionization of the system), is exactly the negative energy of the corresponding spin-orbital. Whenever the errors arising from the HF scheme (that does not take into account electron correlation) and from the above theorem (disregarding electron relaxation) cancel each other [9] or, at any rate, are small enough, the difference between the HOMO (highest occupied molecular orbital) and HOMO-1 energies of the system with an extra electron (approximately) equals the splitting between the energies of the ground and first excited states of the ET system [1, 5-7]. The above error cancellation works well in various cases, although a weak point may be the application of Koopmans’ theorem to inner-shell ionization potentials.

The method presented in the next section can use any many-electron scheme, although this is not required. As a matter of fact, both a complete multi-electron scheme and a partial many-electron implementation, defined by Eqs. (23a-b) and (24) in the next section, were employed here. In this respect, our method allowed us to test the effectiveness of the latter implementation, thus reducing the computational cost of part of our analysis. Furthermore, the method has been developed within both the two-state model and the complete state model, but neglecting the overlaps between the employed diabatic states in the latter case. The Condon approximation is exploited [see the Eq. (A3) in the Appendix A of the following paper] and its relaxed form is allowed (chapters 1, 4).

The proposed method has been implemented in a Density-Functional Theory (DFT) scheme (by employing a PW91 exchange-correlation functional). In reality, any DFT implementation may be exposed to self-interaction errors (SIEs), due to the wrong asymptotic behavior of the available (approximate) exchange-correlation functionals [11-14]. On the other hand, the here adopted implementation does not resort to excited state quantities, thus limiting possible SIEs. Moreover, our comparison between energy-splitting calculations using the PW91 functional and the hybrid B3LYP functional altogether supports a minor role of SIEs for the system under study.

13 The overlap approximation in the two-state case is fully discussed in chapter 1, in the reported paper and in the next section.
2.2 First-principles density-functional theory calculations of electron-transfer rates in azurin dimers

This section consists of the article


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Virtual Journal of Biological Physics Research 15-02-2006 issue

2.3 Overlap approximation within the two-state model

The long distance between the redox sites and the localized character of the defined diabatic states make the overlap $S_{IF}$ negligibly small for all the model systems introduced in the previous section.\(^1\) On the other hand, in this section we show that Eq. (10) goes well beyond the rightmost (approximate) equality (5). To this end, we rewrite the eigenvalues of the secular equation (1.65) in the exact implicit form

\[
E_z = \frac{1}{2} \left[ H_{II} + H_{IF} \pm \sqrt{d^2 + 4(H_{IF} - E_z S_{IF})^2} \right]
\]  

(2.1)

(\text{where } d \equiv \Delta E_{IF}), \text{ from which we obtain}

\[
\Delta = \frac{1}{2} \left[ \sqrt{d^2 + 4(H_{IF} - E_z S_{IF})^2} + \sqrt{d^2 + 4(H_{IF} - E_z S_{IF})^2} \right].
\]

(2.2)

For sufficiently small overlaps,\(^2\) exploiting the same definition of $\Delta$, we find

\[
\Delta \approx \frac{1}{1 + 2S_{IF}/\sigma} \sqrt{d^2 + 4(H_{IF} - E_z S_{IF})^2},
\]

(2.3)

with

\[
\sigma = \sqrt{\frac{d^2}{4(H_{IF} - E_z S_{IF})^2}}.
\]

(2.4)

In particular, for

\[
S_{IF} \ll \sigma/2,
\]

(2.5)

\(^{1}\) This was also verified through an in-house developed code [16].

\(^{2}\) As a matter of fact, here it may be reasonably assumed that both terms in Eq. (2.2) are of the order of magnitude of $\Delta$, as it is in most cases, although it can be shown that this condition is not essential when the relation (2.5) is fulfilled.
\[ \Delta \equiv \sqrt{d^2 + 4(H_{IF} - E_{IF})^2}. \]

(2.6)

Note that the condition (2.5) is not prominently different from the condition \( S_{IF}^2 \ll 1 \) introduced in section 1.6.3 (in particular, sufficiently far from the transition coordinate, it is \( \sigma >> 1 \), so that the relation (2.5) is always satisfied and only the condition \( S_{IF}^2 \ll 1 \) is required). At this point, a comparison between Eqs. (1.68a) and (2.6) gives\(^3\)

\[ V_{IF}(Q) \equiv H_{IF} - E_{IF}. \]

(2.7)

Then, the equations for the components of the ground state vector are written as

\[
\begin{align*}
\left[ d + \sqrt{d^2 + 4(H_{IF} - E_{IF})^2} \right] \alpha + V_{IF} \beta &= 0 \\
V_{IF} \alpha - \sqrt{d^2 + 4(H_{IF} - E_{IF})^2} \beta &= 0
\end{align*}
\]

(2.8)

where Eq. (2.1) has been exploited to recast the diagonal terms of the secular matrix. Finally, subtracting the second equation multiplied for \( \alpha \) to the first one multiplied for \( \beta \), the Eq. (10) of the previous article is found. Thereby, for an overlap \( S_{IF} \) small enough with respect to unity and \( \alpha^2 + \beta^2 \equiv 1 \), the Eq. (10) provides a good estimate of the transfer integral, also if the latter is appreciably different from \( |H_{IF}| \).

2.4 Transfer integral: beyond the two-state model

As pointed out in the article, the three expressions (9a), (9b) and (10) for the transfer integral are not equivalent (also for a negligible overlap \( S_{IF} \)) if the two-state approximation is not exactly fulfilled. In such a case, by using the complete state model, under the simplifying assumption of vanishing overlaps between the involved electronic states, we found...
\[
V_{\text{IF}} \equiv \frac{\alpha \beta d}{\alpha^2 - \beta^2} + \left[ r(Q) - r(Q^+) \right] H_{\text{IT}}, \quad (2.9)
\]

with
\[
r \equiv \frac{\gamma \text{sgn}(\alpha)}{\alpha + \beta}. \quad (2.10)
\]

Eq. (2.9) makes a clear connection between the relevant electronic coupling \( H_{\text{IF}} \) (or \( V_{\text{IF}} \), since \( S_{\text{IF}} \) is completely neglected in this section) and the interfering coupling \( H_{\text{IT}} \), and points to Eq. (10) as the best estimate of the transfer integral when the two-state assumption is approximately satisfied. Furthermore, the complete-state treatment allows a physical distinction between Eqs (9a-b) and Eq. (10). To illustrate this point, in Appendix B we derive the following approximate expressions for the components \( \alpha \) and \( \beta \):

\[
\alpha \equiv e^{i\theta} \sqrt{\frac{1}{2} \left( 1 - \frac{d}{\Delta_0} \right) \frac{1}{1 + Ax^2}}, \quad \beta \equiv -se^{i\theta} \sqrt{\frac{1}{2} \left( 1 + \frac{d}{\Delta_0} \right) \frac{1}{1 + Ax^2}}, \quad (2.11)
\]

where
\[
A = \frac{\Delta_0^2 + 2H_{\text{IT}}^2}{4H_{\text{IT}}^2 \Delta_0 (\Delta_0 + 2|H_{\text{IF}}|)}, \quad \Delta_0 = \sqrt{4H_{\text{IF}}^2 + d^2}, \quad (2.12)
\]

\( \theta \) is chosen as a multiple of \( 2\pi \) (so that \( \alpha \) and \( \beta \) are real) and \( x \) is a small correction term to the separation energy between the adiabatic PESs. As found in the same appendix, \( Ax^2 \) is the leading term due to the interfering electronic coupling \( H_{\text{IT}} \). Eqs. (2.11) show how \( H_{\text{IT}} \) intervenes to determine the inequality \( \alpha^2 + \beta^2 < 1 \). In particular, for a small enough correction \( x \), it is

\[
Ax^2 \equiv \frac{\gamma^2}{\alpha^2 + \beta^2} = \frac{1}{\alpha^2 + \beta^2} - 1 \quad (2.13)
\]

and Eqs. (2.11) can be recast as
\[
\frac{\alpha}{\sqrt{\alpha^2 + \beta^2}} \equiv e^{i\theta} \sqrt{\frac{1}{2} \left[ 1 - \frac{d}{\Delta_0} \right]}, \quad \frac{\beta}{\sqrt{\alpha^2 + \beta^2}} \equiv -se^{i\theta} \sqrt{\frac{1}{2} \left[ 1 + \frac{d}{\Delta_0} \right]}.
\]  

(2.14)

Finally, inserting the rightmost Eq. (2.12) and Eq. (2.13) into Eqs. (2.14), and rearranging, the formula (10) for \( H_{IF} \) can be obtained. Thus, Eq. (10), unlike Eqs. (9a-b), provides an estimate of the electronic coupling that rightly takes into account the leading effect of the interaction \( H_{IT} \), which renormalizes the coefficients \( \alpha \) and \( \beta \) in the way described by Eqs. (2.11)-(2.12).

In this chapter, we developed and tested a method for calculating transfer integrals. Then, we exploited the computed transfer integral to evaluate the rate of the electron self-exchange reaction in the (wild type) Az dimer. Our next step consists in introducing a fixed water dimer (with the oxygen atoms in crystallographic positions [17]) between the protein redox sites, to evaluate its effects on the electron transfer process.

References


In this chapter we investigate the effects of a water dimer at the interface between the Az sites (see Fig. 1.1 and Fig. 1 in section 3.2) on the inherent ET process. We show that water can either enhance or suppress the ET rate, ascribing this twofold behavior to the interplay of two factors: the electrostatic interaction between proteins and water, and the “bridge” role of the latter. In the analysis, we held the water and protein molecules in fixed reciprocal orientations. This allowed us to better distinguish some aspects of their interactions relevant to ET.

In section 3.1 we present our preliminary study on the convergence of the procedure employed to evaluate electrostatic interactions and on basis set effects. In section 3.2 we report our main results, with reference to two protein models: (i) a small model (Fig. 1a in section 3.2) was exploited to investigate, at a convenient computational cost, the behavior of the transfer integral with the distance between the Copper redox sites; (ii) a larger model was used for a more accurate estimate of the transfer integral at crystallographic coordinates (drawn from Ref. 1). The robustness of our results is supported by the fact that we compare two situations for the same basic system (the azurin dimer with and without interfacial water) within the same computational scheme.

### 3.1 Refined calculation of the energy difference between the diabatic states

The asymmetric arrangement of the two water molecules with respect to the Az dimer required a more careful evaluation of the energy difference between the initial and final states than in Eq. (20) of section 2.2. Such a quantity can be generally written as in the Eq. (19) of the cited section, i.e.

\[
 d \equiv \Delta E_{IF} = (E_D + E_A^-) - (E_D^+ + E_A^+) + U_{D-A} - U_{D^+-A^-},
\]

\[
 = \Delta E_{IF}^{(0)} + U_{D-A} - U_{D^+-A^-}, \tag{3.1}
\]
where $E_D$ ($E_{D^+}$) is the ground-state energy of the isolated donor group $D$ in the reduced (oxidized) state of charge, $E_A$ ($E_{A^-}$) is the same for the acceptor group $A$ in the oxidized (reduced) state; $U_{D-A}$ and $U_{D^+-A^-}$ are the energies of interaction (here evaluated as electrostatic interaction) between the donor and acceptor groups in the initial diabatic state $|\phi_I\rangle = |D\rangle|A\rangle$ and in the final diabatic state $|\phi_F\rangle = |D^+\rangle|A^-\rangle$, respectively. $\Delta E_{IF}^{(0)}$ does not include the interaction terms, as in Eq. (20) of section 2.2. In the analyses of this chapter and of the next one, $U_{D-A}$ and $U_{D^+-A^-}$ are computed after multipole expansion of the involved charge distributions, by using the NWChem package [2].

Fig. 3.1 shows the decay of the transfer integral with the $D$-to-$A$ distance $R$ (as measured by the Cu-to-Cu distance), for the minimal protein model of Fig. 2a in section 2.2. Squares were obtained by employing $\Delta E_{IF}^{(0)}$, dark squares by using $\Delta E_{IF}$ and including the electrostatic interactions up to dipole-dipole terms. The difference between the two sets of theoretical points is negligible with respect to the usual errors in transfer integral evaluation. Therefore, Fig. 3.1 clearly indicates that electrostatic terms can be safely neglected to treat Az dimers without interfacial water, thus justifying the approximation chosen in the article of section 2.2 [Eq. (20) there].

At this point, two questions arise. What happens to electrostatic effects in the system investigated here, that contains water molecules between the redox centers? Can the electrostatic terms be still neglected to compute transfer integrals?

![Fig. 3.1 Transfer integrals vs the Cu-to-Cu distance $R$ for the minimal protein model, without interfacial water. Empty squares were obtained as in section 2.2 (they are the same as the circles in Fig. 7 of section 2.2). Filled squares include the effects of the electrostatic interactions between $D$ and $A$ (calculated through NWChem, using an Ahlrichs pVDZ basis set), up to dipole-dipole terms.](image)
In the presence of water, we define the D and A groups by incorporating each water molecule in the adjacent Az site. The water configuration makes the donor and acceptor groups asymmetric, so that the difference between their interactions in the initial and final states can significantly affect the value of $\Delta E_{\text{IF}}$.

In computing $U_{\text{D-A}}$ and $U_{\text{D'-A'}}$ through NWChem, the electronic wave functions are expanded on standard basis sets. We preliminarily tested the ability of a few common basis sets to reproduce the electric dipole moments of the isolated water molecules (with fixed geometry), for which we found the following mean values: 2.21D (using a 6-31++G basis set), 1.97D (Ahlrichs pVDZ), 1.85D (aug-cc-pVDZ), 1.83D (aug-cc-pVTZ), to be compared with an expected value of about 1.86D [3]. Further analysis on basis sets is included in Fig. 3.2, which shows the computed transfer integrals for the minimal protein model with the water dimer. The electrostatic interactions were calculated up to dipole-dipole

![Fig. 3.2](image-url)
terms for all sets of points. From Fig. 3.2 we draw the following main conclusions: (i) the different electrostatic interactions between D and A in the initial and final diabatic states appreciably contribute to $\Delta E_{\text{ie}}$. (ii) A suitable multipole expansion of the donor and acceptor charge distributions requires the use of distinct expansion centers for the water and Az subunits. (iii) It is virtually equivalent to use the diffuse Ahlrichs pVDZ or aug-ccpVTZ basis set for the water molecules (the latter cannot be utilized for the Az sites, due to the presence of the Cu ions). (iv) It is conceivable to adopt an independent multipole expansion for the water and protein subunits to the end of the $\Delta E_{\text{ie}}$ evaluation. In fact, as suggested by the square at $R = 14.6 \, \text{Å}$, the same transfer integral is virtually obtained when the electric dipole moment of each molecule is independently calculated and when the dipole moment of each Az is derived by subtracting the separately computed dipole moment of the adjacent water molecule to the total moment of the respective redox group (the converse was also verified).

At last, we verified the convergence of the multipole expansion procedure (see Fig. 3.3), thus obtaining the results described in the next section. From Fig. 3.3 it is clear that the inclusion of the electrostatic interactions up to quadrupole-dipole terms in $\Delta E_{\text{ie}}$ does not provide significant further changes of the transfer integrals. Therefore, quadrupole-quadrupole and higher order electrostatic interactions can be safely neglected.

![Graph](image)

**Fig. 3.3** Transfer integrals vs the Cu-to-Cu distance $R$ for the minimal protein model with the interfacial water. Dots and triangles as in Fig. 3.2. Circles were obtained as triangles, but including the quadrupole-dipole electrostatic interactions in the evaluation of $d$. 

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As to the larger protein model of Fig. 2b in section 2.2, the use of $\Delta E_{\text{IF}}$, including electrostatic interactions up to the quadrupole-dipole terms, produced a negligible change of the transfer integral value ($\approx 0.5\%$). On the contrary, in the presence of the water molecules, our estimate of the transfer integral is $0.69 \times 10^{-3}$ eV by using $\Delta E_{\text{IF}}^{(0)}$, $3.14 \times 10^{-3}$ eV by employing $\Delta E_{\text{IF}}$ (electrostatic interactions up to dipole-dipole terms) and $3.22 \times 10^{-3}$ eV including also quadrupole-dipole interactions. Ultimately, the described procedure appears suitable for evaluating the quantity $\Delta E_{\text{IF}}$, to be inserted in the formula (2.2) for transfer integrals.

We believe that our refined method, in which the description of electrostatic terms is included, can be effectively applied to other inter-molecular ET processes. Moreover, a further refined calculation of electrostatic interactions, presented in chapter 5, extends the applicability of the method to situations in which the above multipole expansion is not appropriate.

### 3.2 Water effects on electron transfer in azurin dimers.

This section consists of the article


available on publisher’s site [http://pubs.acs.org/](http://pubs.acs.org/).
References


Chapter 4

COMPETING WATER EFFECTS ON ELECTRON TRANSFER. AZURIN DIMERS. II

It is generally recognized that water can play a crucial role in determining the rates of ET reactions, because its quantum and electrostatic interactions with the protein system can affect both the activation free energies and the most effective ET pathways [1, 2]. On the other hand, the efficiency of water in mediating ET is still largely debated, because diverse behaviors showed up in theoretical and experimental studies [3-7]. The work presented here fits into this context. In fact, it aims to disentangle different features of the water-protein interactions, in such a way to provide a unitary picture of concurring (and sometimes opposed) water effects on ET. In this chapter, we go beyond the static picture of chapter 3, by inspecting the effect of different water configurations on transfer integrals. Configurational sampling is carried out by combining ab initio calculations to the results of classical molecular dynamics simulations.

The study of section 4.2, resulting from the combined application of various theoretical and computational tools, confirms and exceeds the conclusions of the previous chapter. Our ab initio multi-electron calculations point to a slightly enhanced ET kinetics, in the presence of the water dimer between the Az Cu sites, dominated by a few strongly favorable water arrangements. Furthermore, through electrostatic calculations on ab initio electronic wave functions, we show that the ET rate can also be instantaneously decreased, if the water arrangement does not provide an efficient quantum bridging and concurs to determine an electron distribution on the protein matrix unfavorable to ET. Our results are consistent with the multiple ET pathways picture recently proposed [5, 8] for other systems, and allows a description of the interplay between ET pathways in terms of quantum-electrostatic effects.

4.1 Molecular dynamics (MD) simulations

Transfer integrals were computed for a number of selected configurations, taken from a MD run.
MD simulations were performed on the system of Fig. 1.1, surrounded by the water medium, by means of the NAMD program [9]. The protein configuration was held fixed at the crystallographic coordinates, while moving the solvent, for isolating and evaluating the ET role of the latter. The external water has been obviously included in MD simulations. It may indirectly influence the geometry of the interfacial water dimer, due to interactions essentially mediated by the protein matrix. On the other hand, the external water is far from the regions between the redox sites and does not directly intervene in the relevant ET processes. Thus, it was excluded from transfer integral \textit{ab initio} calculations.

Simulations (see Fig. 4.1) started from a 30 ps equilibration dynamics at a

\begin{figure}[h]
\centering
\begin{subfigure}{0.4\textwidth}
\includegraphics[width=\textwidth]{fig1a.png}
\caption{(a) Energy vs time in the \(T\)-equilibration dynamics.}
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\caption{(b) Temperature vs time in the \(T\)-equilibration dynamics.}
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\caption{(c) Temperature vs time in the \(p\)-equilibration dynamics.}
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\begin{subfigure}{0.4\textwidth}
\includegraphics[width=\textwidth]{fig1d.png}
\caption{(d) Pressure vs time in the \(p\)-equilibration dynamics.}
\end{subfigure}
\caption{Fig. 4.1 Equilibration MD at the temperature \(T = 298\) K and constant \(V\). (a) Energy vs time in the \(T\)-equilibration dynamics. (b) Temperature vs time in the \(T\)-equilibration dynamics. (c) Temperature vs time in the \(p\)-equilibration dynamics. (d) Pressure vs time in the \(p\)-equilibration dynamics. (e) Root mean square deviations of the interfacial water configurations with respect to their mean value.}
\end{figure}
temperature \( T = 298 \text{ K} \) and constant volume \( V \) (\( T \)-equilibration run), followed by a 50 ps equilibration (\( T \)-equilibration run) and a 0.5 ns production MD at the same \( T \) and with pressure \( p = 1 \) bar. The time step of the dynamics was 0.5 fs for all runs. The achievement of the desired equilibrium conditions was checked after each run, as shown in Fig. 4.1. Then, the analysis of the next section has been made.

### 4.2 Water-mediated electron transfer between protein redox centers

This section consists of the article

References

Chapter 5

TRANSFER INTEGRAL BETWEEN DNA BASE PAIRS

Charge transfer in DNA is currently the subject of intense experimental [1-3] and theoretical [4-10] research, because of its possible applications in the fabrication of nanostructures and biosensors. Most experimental results [11-13] concern the migration of positive charges (holes), which is expected to occur between guanine (G) bases [6, 14-16]. Thus, the electronic couplings for hole transfer between Watson-Crick pairs are fundamental quantities for studying charge transport along DNA duplexes [10]. Here we will deal with the electron transfer from a neutral guanine-cytosine (GC) pair to an adjacent radical cation (GC)\(^+\) (i.e. with the hole transfer in the opposite direction). This brief chapter describes the current state of a work in progress. Therefore, we draw some conclusions, but also leave open questions.

5.1 Atomic model and computational methods

5.1.1 Model structure of the \([(GC)^+, (GC)]\) dimer.

Fig. 5.1 illustrates the atomic model used in our electronic structure \textit{ab initio} calculations. It was constructed with the 3DNA package [17], using experimental idealized atomic coordinates of the bases [18] and the step parameters of regular B-DNA (i.e. a rise of 3.38 Å and a twist of 36°). The adopted model structure rests on two observations: (i) Previous calculations indicate that small changes of base geometries do not significantly affect the values of the
electronic couplings (differently from what happens for conformational changes) [10]. In particular, couplings computed [19] for the experimental structures and for B3LYP/6-31G* optimized geometries differed at most 5%. Thus, we relaxed only saturating H atoms, by using the PWSCF program of Quantum-ESPRESSO [20]. (ii) The backbone negligibly affects the couplings between base pairs [8, 21]. Consequently, we took away the sugar-phosphate backbone for our calculations.

5.1.2 Methods.

The general approach to the computation of the transfer integrals proceeds as for the Az dimer in the previous chapters. On the other hand, some peculiar features of the present system require particular attention when the transfer integral evaluation is implemented. Donor (D) and acceptor (A) are not symmetry-equivalent planar structures and are off resonance. As a consequence, the energy difference \( d \) between the initial and the final diabatic states is expected to be relatively large. Moreover, it cannot be computed through electric multipole expansion. In fact, the dimer of base pairs is characterized by a stacking of aromatic rings and their reciprocal distance is smaller than their mean size.

Taking into account the above considerations, we applied our method to calculate transfer integrals along the following lines, by suitably exploiting the NWChem package [22]:

(i) The ground-state wave function of the dimer and the electronic spin-orbitals for the donor and acceptor groups in both oxidation states were derived in a DFT scheme\(^1\), by using a B3LYP [23] exchange-correlation (xc) functional and testing various split-valence basis sets. Then, the initial (final) diabatic state was constructed as a single Slater determinant, from the spin-orbitals corresponding to the ground-states of the isolated \( D \) and \( A \) (\( D^+ \) and \( A^- \)) groups.\(^2\) Hence, the quantities \( a \) and \( b \) were computed, to be inserted in the previously presented transfer integral formula [Eq. (10) of section 2.2]

---

\(^1\) The opportunity of using DFT spin-orbitals has been discussed in the subsection 3 of section 2.2.
\(^2\) Such spin-orbitals were biorthogonalized, but, in reality, the effects of this procedure on the resultant transfer integrals were evaluated to be negligible.
The energy difference \( d \) was calculated in two different ways. (a) First we employed Eq. (3.1), that is

\[
d = (E_D + E_A) - (E_{D^+} + E_{A^-}) + U_{D-A} - U_{D^+-A^-}
\]

(5.1)

\[
= \Delta E_{IF}^{(0)} + U_{D-A} - U_{D^+-A^-}.
\]

(5.2)

The terms in \( \Delta E_{IF}^{(0)} \) were self-consistently computed within the DFT scheme. The (electrostatic) interaction energies were evaluated through an in-house program, using the RESP charges (derived from NWChem) on the donor and acceptor base pairs in the initial and final diabatic states. (b) Then, for useful comparison, we computed \( d \) from the energies (expectation values of two-electron Hamiltonian) corresponding to the (fixed) initial and final wave functions. Clearly, this non self-consistent calculation (here labeled \( nsc \) for brevity) does not resort to the decomposition in Eq. (5.2).

The calculations of \( a, b \) and \( d \) (employing Eq. (5.2) for the latter quantity) were repeated by means of the PWSCF code [20], that uses a PW91 xc-functional [24]. The energy cutoff adopted for the plane-wave basis set was \( E_{\text{cut}} = 25 \text{ Ry} \). The interaction terms were obtained from the electrostatic potential in the unit cell, exploiting the Poisson equation. The convergence of the results was controlled up to cell sizes of \( 26 \times 30 \times 21 \text{ Å}^3 \).

From the values of \( V_{IF} \) and \( d \), we derived an estimate of the energy splitting \( \Delta \) between the adiabatic MPESs, by using Eq. (1.68a), i.e.

\[
\Delta = \sqrt{d^2 + 4V_{IF}^2}.
\]

(5.3)

In fact, we found \( S_{IF} = 0.01 \) (with the more diffuse split-valence basis set) so that the inequality (2.5) and the somewhat similar condition \( S_{IF}^2 \ll 1 \) are widely fulfilled. For comparison, this excitation energy was also evaluated by means of HF calculations, using Koopmans’ theorem, and through the Tamm-Dancoff

5.2 Results and discussion

A summary of our current results is reported in Table 5.1 and Fig. 5.2.

Table 5.1*

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<th>$d$</th>
<th>$d^{(\text{inc})}$</th>
<th>$V_{\text{IF}}$</th>
<th>$V_{\text{IF}}^{(\text{inc})}$</th>
<th>$\Delta$</th>
<th>$\Delta^{(\text{inc})}$</th>
<th>$\Delta_{\text{TD}}$</th>
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</tbody>
</table>

* All the entries are in eV. $d$ indicates the energy difference between the diabatic states evaluated through Eq. (5.2). $d^{(\text{inc})}$ results from method (b) of section 5.1.2. With coherent notation, transfer integrals and adiabatic splittings were computed from Eqs. (5.1) and (5.3), respectively, by employing the different $d$ estimates. $\Delta_{\text{TD}}$ comes from the application of Tamm-Dancoff TDDFT [25], and $\Delta_{\text{Koop}}$ from Koopmans theorem.

![Fig. 5.2](image)

The estimates of $d$ in the first column of Table 5.1 employ Eq. (5.2) and are essentially determined by the interaction terms. In fact, $\Delta E_{\text{IF}}^{(0)}$ turned out to be of
the order of $10^{-3}$ eV in all cases (as expected by construction, since the only difference in $\Delta E_{\text{IF}}^{(0)}$ arises from H atoms, relaxed in the dimer structure). The relative deviations between the various determinations of $d$ are at most of 6%. Moreover, our estimates are similar to those provided in Refs. 9, 10, although the latter refer to different (and orthogonal) diabatic states. Systematically lower values were obtained through $\text{ns}^c$ calculations. This is reflected in the corresponding estimates of the transfer integral and of the adiabatic splitting, as shown by the down triangles in Fig. 5.2.

The inclusion of the self-interaction correction (SIC), with a Casida-Salahub scheme [26], induces minor changes on the estimations of $d$ that make use of Eq. (5.2), while drastically reducing the differences between the results obtained with $d$ from methods (a) and (b) of section 5.1.2 (see squares in Fig. 5.2, for what concerns $\Delta$). This fact appears to support the first method. Its possible explanation is currently under investigation.

For each basis set, the adiabatic splitting derived from formula (5.3) is much larger than that based on Koopmans’ theorem. To settle the matter, we evaluated $\Delta$ through an independent method, i.e. the Tamm-Dancoff TDDFT (circles in Fig. 5.2). In fact, $\Delta$ generally represents the excitation energy for an optical transition from the ground to the first-excited adiabatic state. The employed TDDFT approach seems to indicate a failure of Koopmans’ theorem. Such test is even more significant because TDDFT is often expected to severely underestimate excitation energies, due to the local character of the approximate xc-functionals [27]. In particular, this was clearly pointed out for valence-excited states (i.e., excited states coming from excitation processes which do not involve a net charge displacement) of molecules with spatially extended $\pi$-systems and for charge-transfer (excited) states, where the self-interaction correction works only asymptotically\(^3\) (that is, for very large distances between donor and acceptor) [27-30]. Thereby, the above test with TDDFT supports the evaluation of $\Delta$ through Eqs. (5.1-3).\(^4\)

\(^3\) In this respect, with reference to the system under study, the negligible correction to $\Delta$ by using the SIC can be reasonably expected.

\(^4\) We also computed $\Delta$ with TDHF, obtaining even higher values than with TDDFT. However, the reliability of the results is affected by a considerable spin contamination of the ground state.
As shown in the third column of Table 5.1, the plane-wave calculation, that uses a PW91 xc-functional, yields a relatively higher value of $V_{\text{IF}}$ with respect to the estimations through split-valence basis sets and the B3LYP xc-functional. This is coherent with the general finding that hybrid functionals give smaller delocalization than pure DFT. We assume the value 0.70 eV (obtained with B3LYP, the larger split-valence basis set, and the SIC) as our best estimate of $V_{\text{IF}}$.

A possible refinement may arise from further analysis on the effects of finite basis sets and different xc-functionals. Let us remark that the value $V_{\text{IF}} = 0.70\text{eV}$ is almost one order of magnitude larger than a value of 0.075 eV recently proposed in literature (making use of the Koopmans’ theorem) [9, 10]. The two values approximately differ as the respective estimates of $\Delta$.

As can be easily seen from Eqs. (5.1-3), within our method, the value of the adiabatic splitting is related to the $a$ and $b$ parameters. Even using the B3LYP hybrid xc-functional (and thus a HF exchange component), the values of such parameters (0.652 and 0.742 respectively, when using the 6-311++G** basis set) do not point to a very large difference of donor and acceptor charges in the ground state (as it is, instead, the case for the HF calculations of Refs. 9, 10). This is further illustrated by the analysis of Fig. 5.3, where we plotted the isodensity contours for the $\pi$-like $\beta$HOMO and $\beta$LUMO. They are the most relevant spin-}

![Fig. 5.3 Isodensity contours (by DFT calculations with the B3LYP xc-functional and a Casida-Salahub SIC) of the spin-orbitals mainly involved in the one-particle description of the hole-transfer (or the corresponding electron-transfer) reaction: (a) $\beta$HOMO, (b) $\beta$LUMO, (c) both spin-orbitals. Color code for atoms as in Fig. 5.1.](image)

5 Note that $\sqrt{a^2 + b^2} \approx 0.99$; hence, the two-state approximation is well-grounded.
orbitals in a one-particle picture of the hole-transfer (or the corresponding electron-transfer) reaction, describing the essential difference in the charge distribution between the initial and final adiabatic states. Moreover, according to the Görling-Levy perturbation theory [31] applied to excitation states [32], the difference between their respective eigenvalues is an approximation to the first excitation energy of the zeroth order in the electron-electron interaction. The $\beta$LUMO (see Fig. 5.3b) describes a hole density essentially localized on the guanine subsystem, as expected from previous analyses [6, 14-16] on the hole transfer between GC base pairs. The charge and hole densities depicted in Figs. 5.3a-b are delocalized on both the guanines, although not quite symmetrically (Fig. 5.3c). Moreover, we found that the $\beta$HOMO of each diabatic state has also an extended $\pi$-like character and is localized on one of the G moieties, thus leading to similar values for the $a$ and $b$ parameters. On the other hand, since the diabatic charge distributions are relatively large with respect to the average distance between the base pairs, the residual asymmetry determines a $d$ value large enough to allows a simple application of our method (i.e., without special moving away from the transition nuclear configuration).

Note that, according to our TDDFT calculations, the first excitation energy essentially corresponds (with a percentage of 98%) to an electron transition between the spin-orbitals in Fig. 5.3. Such spin-orbitals differ significantly from the charge-transfer $\beta$HOMOs, because of the proximity to the transition nuclear configuration, and the inherent transition has mostly the character of a localized (i.e., without a considerable net displacement of charge) photoexcitation. In other terms, the $\beta$LUMO in Fig. 5.3b pertains to a valence-excited state of the overall system.

As to the large discrepancy with the HF results in Refs. 9-10, a key point is that a full HF scheme usually determines an unphysical localization of the charge in the ground state, while DFT may lead to an excessive charge delocalization between the acceptor and donor groups. A minor role has been attributed to the latter problem in section 2.2, after a comparison of DFT results employing the same basis set, and either the PW91 or the B3LYP xc-functionals. A similar circumstance may be suggested by the data in the bottom row of Table 5.1, although further analysis is here undoubtedly required. At any rate, TDDFT (circles in Fig. 5.2) appears to fix a possible inferior limit for our results.
5.3 Conclusive remarks

The above discussion well fits in the long-standing debate on the relative advantages of the HF and DFT schemes in calculating electronic couplings (see also the subsection 3 of section 2.2 and references therein). A reflection of such theme is in the relative values of $V_{IF}$ obtained with the B3LYP and PW91 xc-functionals. However, the comparison is obscured by the use of different basis sets and the work in progress also aims at clarifying such point.

The analysis by means of TDDFT suggests a possible failure of Koopmans’ theorem for this specific system. On the other hand, such a statement requires further thorough investigations. It is well known that HF calculations tend to underestimate electronic couplings, because correlation effects are ignored, while the DFT approach generally tends to overestimate them, due to self-interaction errors. In reality, with reference to Fig. 5.2, our own results do not exclude that TDDFT works well for the specific system under study. In this case, the right value of the adiabatic splitting (and of the related transfer integral) would be nearly halfway between our estimate and the one in Refs. 9, 10.

References


CONCLUSIONS AND OUTLOOK

We performed a first-principles study of electron transfer in nanoscale materials, focusing on three main issues: (i) the theoretical development of a reliable \textit{ab initio} method to calculate transfer integrals (or electronic couplings) between donor and acceptor sites, and its implementation in a DFT scheme; (ii) the application of such a method to electron transfer processes in nanosystems of interest for biology and bioelectronics; (iii) the analysis of solvent effects on the ET reaction rates.

After a review of useful concepts and approximations in ET theories, we presented a new method that we developed to derive the transfer integrals between molecular redox sites by means of easily implemented DFT electronic structure computations. Such a method does not require the knowledge of the exact transition state coordinate and makes no use of empirical or semiempirical parameters. It naturally involves a complete multielectron scheme, although it allows one-electron and many-electron models. Moreover, it has been framed in a multi-state picture.

First, we tested and applied this method to find the electronic coupling between Az proteins. Our estimate of the transfer integral was suitably inserted into Marcus’ equation, to evaluate the rate constant of the inherent ET process and to confront it to available experimental data. The behavior of the electronic coupling as a function of the distance between the redox sites was also analyzed and compared to empirical evidence and/or semi-empirical analysis (average packing density model and pathways model).

Then we analyzed the effects of the water solvent on the rapidity of ET reactions, by combining different theoretical and computational tools. At first, we restricted our study to fixed water molecules, to shed light on some tangled aspects of their ET behavior. More specifically, we distinguished, quantified and rationalized different effects on ET of water molecules experimentally observed at the interface between the redox sites of azurin dimers. We have shown that the same water system can promote or oppose electron transfer as a result of the interplay between two key factors, that is, the water-protein electrostatic interaction and the quantum mediation by water of the electron tunneling between the redox sites. Thus, beyond the specific system under study, it turned out that water can be an efficient or poor electron-transfer mediator according to its relative conformation between the ET partners.
As a second step, we performed a conformational sampling on the water subsystem (including solvation water). Hence we focused our attention on the effects of different conformations of the water molecules directly involved in the ET pathways. According to our results, in the average, the ET kinetics is slightly enhanced by the presence of the interfacial water and it is dominated by quite a few strongly favorable water arrangements. Our quantum-electrostatic calculations illustrate how the ET rate can also be instantaneously decreased, whenever the water configuration does not provide an efficient quantum bridging between the protein sites and concurs to determine an ET unfavorable electron distribution on the protein matrix. Due to the rather loose contact between the water and protein subsystems, the conformational sampling provided us with a more reliable quantification of the water effects on the ET rate. Our analysis resulted consistent with the well-known multiple ET pathways picture. Furthermore, it reads the interplay between ET pathways in terms of quantum-electrostatic effects.

Finally, we examined the charge transfer between DNA stacked GC base pairs. By means of our method, we estimated the relevant transfer integral and adiabatic splitting. We also employed a method that exploits Koopmans’ theorem, and tested the relative reliability of the two methods through the application of TDDFT.

The transfer integrals play a crucial role in determining the rate constants of many ET reactions. Thus, their accurate theoretical prediction is a particularly pressing issue. We believe that our theoretical and computational approach may be a promising framework for the analysis of charge-transfer processes in biological environments. In this perspective, the application to biomolecular crystals may be a particular rewarding test, because of the drastically reduced structural ambiguity and of the availability of more accurate experimental results.

Further developments of this work include:

(i) the search for an even more convenient (and general) definition of the ET diabatic states, in order to extend the applicability of the proposed method to ET processes across covalent bridges. Along this way, our method to calculate transfer integrals may be usefully applied to systems in which the donor and acceptor sites are on the same molecule (e.g., the rigid hydrocarbon molecules extensively studied by Jordan and Paddon-
(ii) a further study of the charge transfer in DNA and the application of the method to other interesting systems, for useful predictive aim;

(iii) the exploitation of our formalism for calculating electronic couplings beyond the two-state approximation [4], so that the interaction between different ET processes can be usefully examined.

References


Appendix A

In this appendix we derive some important properties of the partial free energy, mentioned in chapter 1. First, the joint probability density of the sets \((\mathbf{r}, \mathbf{p})\) and \(\mathbf{R}\) is:

\[
f(\mathbf{r}, \mathbf{p}; \mathbf{R}) = \frac{1}{Z} \exp[-\beta E(\mathbf{r}, \mathbf{p}; \mathbf{R})],
\]

where \(\beta = 1/k_B T\) and the partition function

\[
Z = \int Z_{r,p}(\mathbf{R}) d\mathbf{R} = \int \exp[-\beta E(\mathbf{r}, \mathbf{p}; \mathbf{R})] d\mathbf{r} d\mathbf{p} d\mathbf{R}
\]

has been introduced. Then, the marginal probability density of a given \(\mathbf{R}\) is

\[
f(\mathbf{R}) = \int f(\mathbf{r}, \mathbf{p}; \mathbf{R}) d\mathbf{r} d\mathbf{p} = \frac{Z_{r,p}(\mathbf{R})}{Z},
\]

where

\[
Z_{r,p}(\mathbf{R}) = \int \exp[-\beta E(\mathbf{r}, \mathbf{p}; \mathbf{R})] d\mathbf{r} d\mathbf{p}
\]

is the partial partition function. Consequently, the conditional probability density of a set \((\mathbf{r}, \mathbf{p})\), given the occurrence of \(\mathbf{R}\), is

\[
f(\mathbf{r}, \mathbf{p} / \mathbf{R}) = \frac{f(\mathbf{r}, \mathbf{p}; \mathbf{R})}{f(\mathbf{R})} = \frac{1}{Z_{r,p}(\mathbf{R})} \exp[-\beta E(\mathbf{r}, \mathbf{p}; \mathbf{R})]
\]

Starting from the partial partition function, the partial free energy is defined as

---

6 To simply the notations, the sizes of the Boltzmann’s complexions are not introduced throughout this appendix. More correctly (from a dimensional point of view), we can say that the coordinates are suitably normalized with respect to them.

7 The dependence of the free energy on the thermodynamic variables is, as usual, not indicated. The down-scripts remind that this is the free energy of the set of modes described by the coordinates \(\mathbf{r}, \mathbf{p}\).
\[ G_{r,p}(R) = -\frac{1}{\beta} \ln[Z_{r,p}(R)]. \]  

(6A)

It is the free energy associated to the set of non-reactive modes \{r, p\}, for a fixed \( R \). Note that, using Eq. (6A), Eq. (3A) can immediately be recast as Eq. (1.9). The mean energy associated to \{r, p\}, for a given \( R \), is

\[
\langle E_{r,p} \rangle (R) = \frac{1}{Z_{r,p}(R)} \int E(r,p;R) \exp[-\beta E(r,p;R)] \, dr \, dp
\]

\[
= -\frac{1}{Z_{r,p}(R)} \frac{\partial}{\partial \beta} Z_{r,p}(R) = -\frac{\partial}{\partial \beta} \ln[Z_{r,p}(R)]
\]

(7A)

\[
= G_{r,p}(R) + \beta \frac{dT}{d\beta} \left[ \frac{\partial}{\partial T} G_{r,p}(R) \right] = G_{r,p}(R) + T \left[ -\frac{\partial G_{r,p}(R)}{\partial T} \right],
\]

so that

\[
G_{r,p}(R) = \langle E_{r,p} \rangle (R) - T S_{r,p}(R),
\]

(8A)

with

\[
S_{r,p}(R) = -\frac{\partial G_{r,p}(R)}{\partial T}.
\]

(9A)

\( S_{r,p}(R) \) is the partial entropy, that is the entropy associated to the non-reactive degrees of freedom for a given \( R \) (and, clearly, its average on \( R \) yields the conditional entropy of the non-reactive set). It measures the degree of disorder in \{r, p\}. In fact, inserting Eq. (5A) in the expression of such entropy according to the Planck-Boltzmann postulate, it is easy to see that

\[
S_{r,p}(R) = -k_B \int f(r,p|R) \ln[f(r,p|R)] \, dr \, dp = -\frac{\partial G_{r,p}(R)}{\partial T}.
\]

(10A)

By employing the above equations, we can derive Eq. (1.10), which endows the partial free energy with the significance of an effective potential energy. In fact, the component of the force along the \( k \) th reactive coordinate, averaged on
\( \{ r, p \} \), is

\[
<F_k >_{r,p} = - \frac{\partial E(r,p;R)}{\partial R_k}_{r,p} =
- \frac{1}{Z_{r,p}(R)} \int \frac{\partial E(r,p;R)}{\partial R_k} \exp[-\beta E(r,p;R)] \, dr \, dp
\]

\[
= \frac{1}{\beta Z_{r,p}(R)} \frac{\partial}{\partial R_k} \int \exp[-\beta E(r,p;R)] \, dr \, dp
\]

\[
= \frac{\partial}{\partial R_k} \frac{1}{\beta} \ln[Z_{r,p}(R)] = -\partial G_{r,p}(R)/\partial R_k .
\]

(11A)

Finally, let us consider two PESs whose energies are expressed as in Eq. (1.14), that is

\[
E_i(r,p;R) = \bar{\varepsilon}_i(R) + \overline{E}(r,p,R) \quad (i = m, n),
\]

(12A)

with

\[
\overline{E}(r,p,R) = U_N(R,r) + \sum_{j=1}^{\nu} \frac{p_j^2}{2m_j}.
\]

(13A)

Then, given

\[
Z_{r,p,i}(R) = \int \exp[-\beta E_i(r,p;R)] \, dr \, dp
\]

\[
= \exp[-\beta \varepsilon_i(R)] \int \exp[-\beta \overline{E}(r,p;R)] \, dr \, dp,
\]

\[
\equiv \exp[-\beta \varepsilon_i(R)] \overline{Z}_{r,p}(R)
\]

(14A)

it is

\[
f_i(r,p/R) = \frac{1}{Z_{r,p,i}(R)} \exp[-\beta E_i(r,p;R)]
\]

\[
= \frac{1}{Z_{r,p}(R)} \exp[-\beta \overline{E}(r,p;R)] \equiv \tilde{f}(r,p/R)
\]

(15A)

and thus

\[
S_{r,p,i}(R) = S_{r,p,n}(R) = -k_B \int \tilde{f}(r,p/R) \ln[\tilde{f}(r,p/R)] \, dr \, dp .
\]

(16A)
Consequently, from Eqs. (8A), (12A) and (16A), we find

\[
G_{r.p,n}(\mathbf{R}) - G_{r.p,m}(\mathbf{R}) = < E_{r.p,n} > (\mathbf{R}) - < E_{r.p,m} > (\mathbf{R}) = \bar{\varepsilon}_n (\mathbf{R}) - \bar{\varepsilon}_m (\mathbf{R})
\]  

(17A)

as stated in section 1.1.3.
Appendix B

In this appendix we derive some equations of section 2.4.

From the first two Eqs. (B12) in the appendix B of section 2.2 (first article) and the normalization condition for the ground-state electronic wave function, we obtain

\[
\alpha = e^{i\theta} \sqrt{\frac{A_0 + A_1 x + A_2 x^2}{1 + A_3 x + A_4 x^2 + A_5 x^3 + A_6 x^4}}
\]

(1B)

and

\[
\beta = -se^{i\theta} \sqrt{\frac{B_0 + B_1 x + B_2 x^2 + B_3 x^3 + B_4 x^4}{1 + B_5 x + B_6 x^2 + B_7 x^3 + B_8 x^4 + B_9 x^5 + B_{10} x^6}}
\]

(2B)

with

\[
A_0 = \frac{1}{2} \left( 1 - \frac{d}{\Delta_0} \right), \quad A_1 = \frac{1}{2} \frac{d - w}{w\Delta_0}, \quad A_2 = \frac{1}{4w\Delta_0}, \quad A_3 = -\frac{1}{\Delta_0},
\]

\[
A = \frac{\Delta_0^2 + 2H_{\Pi}^2}{4H_{\Pi}^2 \Delta_0 (\Delta_0 + 2|H_{\Pi}|)}, \quad A_4 = -\frac{1}{4H_{\Pi}^2 w}, \quad A_5 = \frac{1}{16H_{\Pi}^2 w\Delta_0}, \quad B_0 = \frac{\Delta_0 + d}{\Delta_0 - d},
\]

\[
B_1 = A_1 B_0 + A_2 C_1, \quad B_2 = A_2 B_0 + A_3 C_1 + A_4 C_3, \quad B_3 = A_2 C_1 + A_3 C_3, \quad B_4 = A_2 C_3,
\]

\[
B_5 = A_3 + C_2, \quad B_6 = A + A_3 C_2 + C_3, \quad B_7 = A_3 + AC_2 + A_3 C_3,
\]

\[
B_8 = A_5 + A_4 C_2 + AC_3, \quad B_9 = A_5 C_2 + A_4 C_3, \quad B_{10} = A_5 C_3, \quad C_1 = -\frac{d + w}{w(\Delta_0 - d)},
\]

\[
C_2 = \frac{d - w}{w(\Delta_0 - d)}, \quad C_3 = \frac{1}{2w(\Delta_0 - d)}, \quad w = \Delta_0 + 2|H_{\Pi}|. \text{ If } rH_{\Pi} \text{ is small enough, then}
\]

\[
\Delta_0 = \sqrt{4(H_{\Pi}^{(0)} + s r H_{\Pi}^2) + d^2} \equiv \frac{\alpha^2 + \beta^2}{\alpha^2 - \beta^2} d = \frac{-4\alpha\beta}{\alpha^2 + \beta^2} s r H_{\Pi}.
\]

(3B)

In the same hypothesis, it is

\[
s = \text{sgn} \left( \frac{\alpha\beta d}{\alpha^2 - \beta^2} \right) = s_a (-s)s_a \text{ sgn} \left( \frac{d}{\alpha^2 - \beta^2} \right) = -s \text{ sgn} \left( \frac{d}{\alpha^2 - \beta^2} \right)
\]

\[
\Rightarrow \text{sgn}(d) = -\text{sgn}(\alpha^2 - \beta^2) \Rightarrow \left| \frac{\alpha^2 + \beta^2}{\alpha^2 - \beta^2} d \right| = -\frac{\alpha^2 + \beta^2}{\alpha^2 - \beta^2} d
\]

(4B)
By exploiting again the Eqs. (B12), the expression of \( r \) [rightmost Eq. (14) in section 2.2] and the fact that \( \alpha - s \beta = s_\alpha |\alpha| - s(-s \cdot s_\alpha \beta) = s_\alpha (|\alpha| + |\beta|) \), where \( s_\alpha \equiv \text{sgn}(\alpha) \), we find

\[
x = \Delta_0 + 2|H_{IF}| + \frac{|\alpha| + |\beta|}{|\alpha| - |\beta|} d \equiv 2 s_\alpha \gamma \frac{|\alpha| + |\beta|}{\alpha^2 + \beta^2} H_{IT},
\]

and thus

\[
\lim_{x \to 0} A \frac{Ax^2}{x} = \lim_{H_{IT} \to 0} \frac{\left(\Delta_0^2 + 2H_{IT}^2\right)\frac{x^2}{\Delta_0 + 2|H_{IF}|}}{4H_{IT}^2 \Delta_0 (\Delta_0 + 2|H_{IF}|)}
\]

\[
= \lim_{H_{IT} \to 0} \left[ \frac{\Delta_0}{4(\Delta_0 + 2|H_{IF}|)} \left( \frac{x}{H_{IT}} \right)^2 \right] = \frac{\gamma^2}{\alpha^2 + \beta^2},
\]

that is the Eq. (2.13) of section 2.4. Moreover, from Eqs. (1B)-(5B) and from the expressions of the coefficients \( A_i \ (i = 1, \ldots, 5) \) and \( B_j \ (j = 1, \ldots, 10) \), it can be seen that \( Ax^2 \) is the main term due to the presence of \( H_{IT} \). Hence, Eqs. (2.11) immediately descend as approximations to Eqs. (1B)-(2B).
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