# **Electron Transfer Between Biological Molecules by Thermally Activated Tunneling**

(photosynthesis/oxidative phosphorylation/cytochromes)

#### J. J. HOPFIELD

Department of Physics, Princeton University, Princeton, New Jersey 08540; and Bell Laboratories, Murray Hill, New Jersey 07974

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ABSTRACT A theory of electron transfer between two fixed sites by tunneling is developed. Vibronic coupling in the individual molecules produces an activation energy to transfer at high temperatures, and temperature-independent tunneling (when energetically allowed) at low temperature. The model is compared with known results on electron transfer in *Chromatium* and in *Rhodopseudomonas spheroides*. It quantitatively interprets these results, with parameters whose scale is verified by comparison with optical absorption spectra. According to this description, the separation between linking sites for electron transfer is 8-10 Å in *Chromatium*, far smaller than earlier estimates.

The transfer of an electron from one molecule to another is an essential part of oxidative phosphorylation and photosynthesis. The reversible oxidation of the heme of cytochrome *c* by cytochrome oxidase is a specific example of such a process, one of several electron transfers in the sequence of reactions resulting in oxidative phosphorylation. The overall effectiveness of such processes as photosynthesis or oxidative phosphorylation depends both on there being a large electron transfer rate for desired transfers and a small rate for inappropriate transfers. A particular cytochrome (or iron-sulfur protein) seems to have, as its sole chemical function, the ability to exchange electrons with two other molecules A and B, which (apparently) cannot directly exchange electrons. The absence of direct exchange may be due either to spatial localization or stereochemical constraints.

Since electron-transfer proteins play a specific chemical role, one should be able to explain in quantitative physical terms how the observed functional properties are related to aspects of molecular structure. There are two major obstacles to attempting such an explanation at present. First, very little is known about the relative geometry of the donor and acceptor during the electron transfer process. Second, even when a geometry is known or surmised, the mechanism of electron transfer is unsure. A wide variety of transfer descriptions have been utilized for particular systems. Hodges, Holwerda, and Gray (1) have described the electron transfer between cvtochrome c and Fe(EDTA) in terms of the "outer sphere electron transfer" of solution electrochemistry (2, 3). In the Winfield mechanism (4) of electron transfer in cytochrome  $c_{i}$ the electron is visualized as being passed along a chain of binding sites with a thermally activated transfer between these sites. Thermal activation of an electron to a "conduction band" and, thence, free motion to a second site has been suggested (5). Quantum mechanical tunneling of the electron between two sites has also been invoked (5, 6).

In this paper, we bypass the first problem by assuming the electron to be transferred between two sites in fixed geometry.

We bypass possible Winfield-like complications, and assume that there are no other electron states available at low enough energies to be thermally accessible. Section I shows that transfer between two fixed sites, in suitable approximation, is mathematically isomorphic with the conceptually simpler problem of excitation transfer by the Förster (7, 8) (dipolar) mechanism. In Section II, the simplest possible model of the coupling of electronic states to molecular thermal motions is developed and used to calculate the temperature-dependent electron transfer rate. The model is compared with experimental results in Section III.

#### I. The two-site tunneling description of electron transfer

We consider the problem of the transfer of an electron between two sites a and b, with the electron initially in a wave function  $\varphi_a$  localized around site a. The final state will have the electron in  $\varphi_b$ , localized around b.  $\varphi_a$  and  $\varphi_b$  weakly overlap, as sketched in Fig. 1. Because of the overlap between these wave functions, there is a matrix element  $T_{ab}$  of the Hamiltonian between these two one-particle states. The meaning of  $T_{ab}$  can be seen from the special case of sites aand b being equivalent, in which case the overlap generates a splitting  $2T_{ab}$  between the bonding and anti-bonding states  $(\varphi_a \pm \varphi_b)/\sqrt{2}$ . The smallness of  $T_{ab}$  results from the exponential decrease of wave functions in the barrier penetration region between the sites. The transfer process thus involves tunneling, and  $T_{ab}$  will be called the *tunneling matrix element*.

To develop a simple analog with excitation transfer, consider two atoms a and b. Let the product  $\psi_a'\psi_b$  be the wave function for the electrons on a and b when atom a is excited and b is in its ground state, and  $\psi_a\psi_b'$  be the wave function for all electrons when atom b is excited and a is in its ground state. Define for convenience  $\Psi_a = \psi_a'\psi_b$  and  $\Psi_b = \psi_a\psi_b'$ . There is an excitation transfer matrix element  $U_{ab}$  between states  $\Psi_a$  and  $\Psi_b$ . In the Förster (7, 8) description, excitation transfer arises from the coupling of the transition dipoles on atoms a and b, and is proportional to each transition dipole and to the inverse cube of their separation. If atoms a and bare identical, the symmetric and anti-symmetric excitation states are split by  $2U_{ab}$ . Thus, while the mechanisms of generating  $U_{ab}$  and  $T_{ab}$  are totally different, the identifications

$$U_{ab} \rightarrow T_{ab}, \quad \Psi_a \rightarrow \varphi_a, \quad \Psi_b \rightarrow \varphi_b$$

makes the mathematical descriptions of transfer identical.

In the calculation of the rate of excitation transfer interand intramolecular vibrations of the atoms play an essential role by giving an energy width to states that would otherwise



FIG. 1. The wave functions  $\varphi_a$  and  $\varphi_b$ , well separated by a distance R, with exponentially decaying tails overlapping weakly. Irrelevant detail near the wave function centers is omitted.

be infinitely sharp. The single atom state characterizing an excitation on atom *a* is given a spectral shape  $S_a(E)$  characterized by a weighted optical emission spectrum at energy *E* of the transition  $\psi_a' \rightarrow \psi_a$ , with an appropriate normalization. This emission spectrum includes all effects of the interaction of the electronic excitation on atom *a* with its environment. Similarly, the excitation of *b* is characterized by its absorption spectrum  $S_b'(E)$ , including all effects of the motions of atoms in the transition  $\psi_b \rightarrow \psi_b'$ . The rate of excitation transfer from *a* to *b* by the Förster mechanism can then be written (7, 8)

$$W_{ab} = (2\pi/\hbar) |U_{ab}|^2 \int_{-\infty}^{\infty} S_a(E) S_b'(E) dE.$$
 [1]

While  $U_{ab}$  is essentially temperature-independent,  $W_{ab}$  and  $W_{ba}$  are both temperature-dependent due to the temperature dependences of the spectra involved in the overlap integral.

A precise parallel exists for the transfer of an electron from site a to b, including the effects of vibronic coupling. The analog to the emission spectrum  $S_a(E)$  of  $\psi_a' \rightarrow \psi_a$  is the electron removal spectral distribution  $D_a(E)$ . In the presence of the coupling between the electronic state  $\varphi_a$  and the nuclear motions, the removal of an electron (which can be thought of as being destroyed or transferred to a fictional state of zero energy) is characterized by a distribution of energies  $D_a(E)$ .  $D_a(E)$  is broad for exactly the same reasons of atomic position readjustment that make  $S_a(E)$  broad. Similarly, there is an electron insertion spectrum  $D_b'(E)$ that describes the distribution of energy changes that result from the insertion of an electron (from the fictional state at zero energy) into electronic state  $\varphi_b$ . The rate of electron transfer can then be written in exact analogy to Eq. 1 as

$$W_{ab} = (2\pi/\hbar) |T_{ab}|^2 \int_{-\infty}^{\infty} D_a(E) D_b'(E) dE. \qquad [2]$$

This equation can also be directly calculated from the usual quantum mechanical expression for first-order transition rates.  $W_{ab}$  is in this problem always due to tunneling, although the usual temperature dependence of  $D_a(E)$  and  $D_b'(E)$  will make this tunneling rate temperature-dependent.

Eq. 2, with D(E) approximated by a high temperature form of Eq. 4, represents a special case of the general theory (9) of electron transfer in solution electrochemistry. The suppositions (a) of fixed, well-separated sites, (b) of independent atomic motions interacting with the electron at each site, and (c) no important effect of atomic motions on  $|T_{ab}|$  are particularly appropriate to transfer between distant sites embedded in a more or less rigid matrix. These approximations are relevant to many cases of transfer in biological



FIG. 2. The description of an electron removal process by a configuration-coordinate diagram. The two curves represent the total energy of the system as a function of the coordinate for the two states with and without the electron.  $D_a(E)$  is the thermal probability distribution of the vertical separation between these states.

systems, and lack some of the complexity of the electrochemical problem. At the same time, Eq. 2 will permit extensions beyond Gaussian and high-temperature spectral functions. The treatment of our simpler problem is modeled on the usual description of tunneling through an insulating barrier between two metals (10).

## II. Results from a symmetric model of D(E)

We next describe the simplest available model of D(E), which can be based on the analog to a symmetric configuration-coordinate description (11) of optical emission spectra. Fig. 2 gives the essence of the physical description of this configuration-coordinate description. The upper curve describes the energy as a function of a vibrational coordinate xwith the electron in state  $\varphi_a$ , and the lower curve the energy as a function of the same coordinate in the absence of an electron in  $\varphi_a$ . In the symmetric model, the curvature  $k_a$  of the ground and excited states are the same, and there is no entropy of electron transfer. At temperature T, the classical probability distribution of being at x if the electron is present is

$$P(x) = \left(\frac{k_a}{2\pi\kappa T}\right)^{1/2} \exp(-k_a(x-x_a)^2/2\kappa T).$$
 [3]

The electronic removal is a vertical transition between the two energy curves. Given P(x), the energy distribution  $D_a(E)$  is

$$D_{a}(\vec{E}) = \left(\frac{1}{2\pi\kappa T k_{a} x_{a}^{2}}\right)^{1/2} \exp\left(-\frac{(E - E_{a} + \frac{1}{2} k_{a} x_{a}^{2})^{2}}{2\kappa T \cdot k_{a} x_{a}^{2}}\right).$$
 [4]

Eq. 4 is based on a classical probability distribution, valid when  $\kappa T$  is greater than the vibrational energies  $\hbar \omega = \kappa T_a$ of the relevant vibrational coordinates. The single most important effect of quantum mechanical corrections is to product a zero-point width (11) to the distribution Eq. 3. The modification of Eq. 4 valid (with restrictions—see next paragraph) to lower temperatures is

$$D_a(E) = (1/2\pi\sigma_a^2)^{1/2} \exp -((E - E_a + 1/2k_a x_a^2)^2/2\sigma_a^2)$$
[5]  
$$\sigma_a^2 = k_a x_a^2 (\kappa T_a/2) \operatorname{coth} T_a/2T$$

which reduces to Eq. 4 at high temperature.



FIG. 3. The rate of photolysis-initiated transfer of an electron from cytochrome in *Chromatium* as a function of temperature. The experimental points are from deVault and Chance (5). The solid line is a plot of Eq. 8 with  $T_a = T_b = 350^{\circ}$ K,  $E_a - E_b = 0.05 \text{ eV}$ ,  $\frac{1}{2k_a x_a^2} = \frac{1}{2k_b x_b^2} = 0.5 \text{ eV}$ , and  $|T_{ab}| = 4 \times 10^{-4} \text{ eV}$ .

The form of  $D_b'(E)$  follows from an exactly parallel model, except that P(x) is replaced by

$$(k_b/2\pi\kappa T)^{1/2}\exp(-k_bx^2/2\kappa T)$$
 [6]

and the transition is in the opposite direction, whence

$$D_{b}'(E) = (1/2\pi\sigma_{b}^{2})^{1/2} \exp(-(E + E_{b} - 1/2k_{b}x_{b}^{2})^{2}/2\sigma_{b}^{2})$$
[7]
$$\sigma_{b}^{2} = k_{b}x_{b}^{2}(\kappa T_{b}/2) \operatorname{coth} T_{b}/2T.$$

From Eqs. 2, 5, and 7

 $W_{ab} =$ 

$$2\pi/\hbar |T_{ab}|^2 (1/2\pi\sigma^2)^{1/2} \exp(-(E_a - E_b - \Delta)^2/2\sigma^2)$$
 [8]

where

and

 $\sigma^2 = (k_a x_a^2/2) \kappa T_a \operatorname{coth} T_a/2T + (k_b x_b^2/2) \kappa T_b \operatorname{coth} T_b/2T$ 

$$\Delta = \frac{1}{2}k_a x_a^2 + \frac{1}{2}k_b x_b^2 \qquad W_{ba} = W_{ab} \exp(-(E_a - E_b)/\kappa T).$$

At high temperatures, quantum effects are unimportant, and the approximations involved in calculating Eq. 8 are valid. The process appears thermally activated, for at high temperatures,  $\sigma^2 \propto T$ . At low temperatures, the use of this expression is limited at best to the case  $E_a > E_b + \kappa T_{a \text{ or } b}$ , with further possible restrictions depending on the size of  $\sigma$ . Eq. 8 is a strong coupling result, also requiring  $1/2k_a x_a^2/\kappa T_a \gg 1$ .

### III. The scale of parameters

The general scale of parameters for electron transfer can be established by making a fit to an appropriate experiment. The transfer of an electron from a cytochrome to fill a hole made available by a flash of light (the earliest stages of photosynthesis) has been studied in *Chromatium* by deVault and Chance (5). This transfer seems likely to come close to the idealized problem the theory describes. It has simple kinetics, has been studied over a wide range of temperatures, persists to very low temperatures, and does not appear closely coupled to water and its phases. Figure 3 shows the experimental electron transfer rate and an approximate fit to the experimental data by use of Eq. 8. In our ignorance of the two sites of transfer, it is pointless to differentiate between the two sites, a and b, as far as vibronic parameters are concerned. We pick  $k_a x_a^2 = k_b x_b^2$  and  $T_a = T_b$ . Eq. 8, thus reduced, contains four effective parameters, namely  $T_a$ ,  $k_a x_a^2$ ,  $|T_{ab}|$ , and  $(E_a - E_b)$ .

The characteristic temperature  $T_a$  is  $350^\circ \pm 70^\circ$ . (About 150° marks the turning point of the data between two regions of temperature behavior, and the characteristic turning point involves  $T_a/2$  in Eq. 5.) The other three parameters are not uniquely determined. Fortunately,  $E_a - E_b$  is well limited by usual constraints on electron transfer.  $E_a$  is greater than  $E_{b}$ , for the electron transfer takes place even at zero temperatures. But successive steps in electron transfer chains normally have their standard redox potentials within about 0.05 V (unless energy is being usefully extracted in the step).  $(E_a - E_b)$  occurs only in the exponential of Eq. 8. If it is given a "typical" value of 0.05 V (1.18 kcal), then  $\Delta$  is so large in order to fit the data that the values of both  $\Delta$  and  $T_{ab}$  are insensitive to whether  $(E_a - E_b)$  is in error by a factor of five. We thus obtain  $1/2k_ax_a^2 = 0.5 \pm 0.1$  eV (11.5 kcal) and  $|T_{ab}| = 4 \times 10^{-4 \pm 0.6} \text{ eV}$  (9.6 cal). The value of  $1/2k_a x_a^2$  is sharply constrained by the high temperature activation energy.  $|T_{ab}|$  is much less definitely determined because it occurs only as a prefactor.

The magnitude of  $T_a$  and  $1/{_2k_ax_a^2}$  can be directly checked on a semiquantitative basis by comparing the parameters just determined, appropriate to *adding* (or *removing*) an electron to a cytochrome, to the parameters relevant to optically *exciting* a similar heme electron without removing it. The general considerations that were used to generate the shape of  $D_a(E)$  in Section II are identical with those of the configuration-coordinate description of the broadening of optical spectral lines. The only important difference between optical excitation of electrons and the removal of electrons is that the removal of an electron is a somewhat larger perturbation, so the *effective*  $1/{_2k_ax_a^2}$  for an optical transition of the heme is expected to be comparable to, but smaller than, that for electron removal. Similar vibrations will be involved, so  $T_a$  should be essentially the same for the two cases. The full width at half maximum for an optical transition with a distortion parameter  $(1/2k_ax_a^2)_{optical}$  is

width  $(T) = 2.34[(\kappa T_a)(1/2k_a x_a^2)_{optical} \operatorname{coth} (T_a/2T)]^{1/2}$ .

If we use the value of  $1/2k_a x_a^2$  deduced from tunneling, the predicted linewidth as a function of temperature is 0.290 eV at 100°K and below, 0.337 eV at 200°K, and 0.388 eV at 300°K. For a typical Soret transition at 430 nm, the corresponding full widths at half maximum are 43, 50, and 58 nm, respectively. For comparison, the full width at half maximum of the Soret band of typical six-coordinated iron in oxyhemoglobin at room temperature (12) is about 32 nm, and it sharpens (13) about 10% on going to 210°K. As anticipated, the scale of the temperature variation is similar to that interpreted from the electron transfer data. The optical linewidth is similar in scale but somewhat smaller than the electron transfer linewidth, also as expected. The optical transition has been calculated for a typical Soret  $\pi - \pi^*$  transition, while the electron to be added is placed in an "iron" orbital. However, the nuclear magnetic resonance spectra (14) show that the highest energy orbital on ferric iron, the orbital from which the electron is being transferred, is widely delocalized on the heme, and the  $\pi - \pi^*$  optical transition is strongly mixed with iron *d*-states. Since the orbitals involved in electron transfer and in the optical excitation are similar mixtures, there is no need to distinguish between them in their general properties.

The magnitude of the tunneling matrix element can be used to construct an approximate distance between the donor and acceptor.  $T_{ab}$  will fall approximately exponentially with separation R, with a characteristic length determined by the barrier height. An upper limits to the barrier height is about half the  $\sigma \rightarrow \sigma^*$  band-gap of the surrounding material, yielding a height of about 3 eV. That hemes in hemoglobin are not readily photooxidized in the Soret band suggests that the barrier is not unusually small. A 2-eV barrier height is taken as a reasonable estimate. For two carbon atoms in a  $\pi$ bonding configuration, then

$$T_{ab} \approx 2.7 \exp(-0.72 R)$$

where  $T_{ab}$  is in electron volts and R in Ångstroms. The prefactor is evaluated by getting the correct  $\pi$  resonance integral (15) at a normal bond length.\* If two large aromatic groups of  $N_a$  and  $N_b$  atoms are in contact through one "edge" atom on each,  $T_{ab}$  will be multiplied by a normalization factor  $(N_a N_b)^{-1/2}$ , and R then measures the separation between the edge atoms. Based on such an edge-to-edge contact between two such  $\pi$ -systems with  $N_a \approx N_b \approx 20$ , the  $T_{ab}$  of  $4 \times 10^{-4}$ eV corresponds to a separation of 8.0 Å between the two atoms through which the transfer takes place.

The scale of parameters shows that within a fixed geometry, the rate of electron transfer will be greatly enhanced in transfer from an excited state. In the example just examined, the rate of electron transfer  $W_{ab}$  at low temperatures is 260 sec<sup>-1</sup>. In an excited state higher by 1.0 eV instead of by 0.05 eV but with no other factor changed, the argument of the exponential in Eq. 8 would vanish. For the excited state, the rate of transfer would be almost temperature independent, and enhanced from the low-temperature ground state result (above) by a factor of  $1.7 \times 10^7$ . In addition, the excited state is less well bound, and the tunneling barrier appears less high. With the parameters previously used, the tunneling barrier would now be only 1 eV high, and the matrix element  $T_{ab}$  would be raised a factor of 6 from its ground-state value. The total increase in the rate of transfer from the excited state compared to the ground state is a factor of  $6 \times 10^8$ , with the dominant factor arising from the change in the exponential of Eq. 8, which eliminates the usual Stokes shift suppression of the transfer rate. This general effect in Marcus theory has recently been noted (16).

Experiments perhaps related to his calculation have been carried out on the bacterium *Rhodopseudomonas spheroides* and on photosynthetic reaction centers taken from them. The rate of electron transfer from an *excited* state of molecule a to molecule b is  $\geq 1.4 \times 10^{11} \sec^{-1} (17)$ . The rate of electron transfer from b back to the *ground* state of a below 80°K is 30 sec<sup>-1</sup> (6). This enormous difference in rates may be an indication of the strong effect of the energy difference on the transfer rate. [The failure of the reaction  $b \rightarrow a$  to be thermally activated (18) can be accommodated within the general tunneling framework, but involves details too complicated to treat here.]

## **IV. Discussion**

Our conclusions on the nature and range of the electron transfer process are totally different from the interpretations that have previously been used in analyzing the same experiments. We believe that previous errors of principle and of emphasis are responsible for the divergent conclusions. These models and their problems are summarized for comparison.

(a) "Low Temperature" Tunneling Description. These calculations (Eq. 1 of ref. 5 or Eq. 4 of ref. 6) are based on the penetration of a square barrier by a particle that is otherwise free. In order to make a comparison with a problem of transfer between two localized sites, an effective collision frequency was introduced in an ad hoc fashion. It was guessed that this frequency factor should be constant and about  $10^{15}$  sec<sup>-1</sup>. No discussion of the physics of how that frequency factor came about was given (5, 6). The approach omits the Franck-Condon factors that must always be present. The present paper is equivalent to constructing a detailed quantum mechanical description of this frequency factor. Because of vibronic coupling and Stokes shifts, this frequency factor is many orders of magnitude smaller than previously assumed, and is temperature dependent. The estimates of 30 Å for the transfer distance (5, 6), therefore, lack a legitimate theoretical basis.

(b) "Barrier Fluctuation" Description of Temperature-Dependent Tunneling. Two descriptions of temperaturedependent transfer rates have been given (5). In these descriptions, the effective distance an electron must tunnel is modulated by thermal fluctuations, and tunneling is easier at high temperatures. One of these descriptions was rejected by its authors on the basis of unreasonable parameters required, while the other seemed to its authors reasonable. Both descriptions make the same error as in (a) of completely failing to come to terms with the frequency factor.

Extensive studies have been made of tunneling through an insulating barrier between two metals. In this case, the tun-

<sup>\*</sup> We have used a resonance integral of 1.0 eV as a compromise between various views.

neling current is closely related to Eq. 2, with the functions  $D_a(E)$  and  $D_b'(E)$  replaced by their appropriate counterparts in metals. The tunneling matrix element is generally not appreciably temperature dependent. Though the analog is not exact, it suggests that the temperature dependence of the barrier is not the most likely source of temperature dependence.

(c) Transfer by Thermal Excitation to a Free Electron State. The idea of this transfer description (5) is that the 3.3 kcal (0.14 eV) activation energy observed for electron transfer from cytochrome c represents the binding energy of an electron in cytochrome c with respect to the conduction band of the surrounding material, and that thermally freed electrons react rapidly with the hole generated by the photon initiating the transient process. The cytochrome then acts like a donor in silicon. This description is unfortunately not internally consistent. Donors of a depth of only 0.14 eV will be largely ionized (18) at room temperature, with their electrons in the conduction band (unless the cytochrome c concentration is greater than 1 mM). This model has also been used to suggest that the barrier height for tunneling is only 0.14 eV (with concomitant huge distances possible in electron transfer), an interpretation we believe to be erroneous.

The experiments in *Chromatium* on which these various interpretations of electron transfer have been based are all consistent with a single model containing four parameters, of which one is insensitively involved, and of which two others can be semiquantitatively verified in optical absorption studies. Enough information is available to evaluate the tunneling parameter  $T_{ab}$  of the theory and to estimate the separation between the linking sites on the donor and acceptor as 8 Å. (A barrier height of 1 eV would have increased this estimate by 2.5 Å.) This distance is so much smaller than previous estimates (5, 6) (30–80 Å) for such transfers that, if correct, it must profoundly affect the view of the structural requirements for electron transfer.

A relatively short range of electron transfer is probably imperative to the operation of electron transport molecules. They seem to be used to exchange electrons with another molecule of similar standard redox potential. If they could also exchange electrons with molecules with a very different redox potential, this would short-circuit the useful paths of the oxidative phosphorylation or photosynthetic electron transport chains. The transfer mechanism described here has a propensity toward such short-circuits. It was shown in Section III that, other things being equal, electron transfer between levels differing by one volt in redox is about 10<sup>9</sup> times faster at room temperature than electron transfer between equivalent levels. These short-circuiting transfers must be prevented (i.e., other things kept from being equal, as by preventing approach) by structural and stereochemical considerations. When the range of electron transfer is too great, it would be impossible to prevent these short-circuiting transfers. (This rapid transfer between levels of considerably different redox potentials may, however, be functionally useful in photosynthesis for separating electrons and holes in spite of its free energy cost.)

This description of electron transfer by tunneling can provide a framework for interpreting the function of structural features of electron transport molecules. To apply the model more generally and quantitatively it will be necessary to extend descriptions of D(E) to include the case in which there is an entropy change on electron transfer, a feature not included in the present description.

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