Journal of Molecular Structure: THEOCHEM 943 (2010) 115–120

Contents lists available at ScienceDirect

Journal of Molecular Structure: THEOCHEM

journal homepage: www.elsevier.com/locate/theochem

Derivation of interpretative models for long range electron transfer from constrained density functional theory

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ARTICLE INFO

Article history:
Received 15 September 2009
Received in revised form 6 November 2009
Accepted 9 November 2009
Available online 13 November 2009

Keywords:
Constrained density functional theory
Electron transfer
Marcus theory
Pathway model

ABSTRACT

The constrained DFT approach of Wu and Van Voorhis is a promising tool for the study of long range biological electron transfers within Marcus theory. This approach allows one to define chemically relevant non-adiabatic states and to compute the three key parameters entering the rate constant expression; the driving force (ΔG°), the reorganization energy (λ) and the electronic coupling H_{DA}. Here we present the implementation of the method in deMon2k and we then successively use it to derive new parameters for the Pathway model which is one of the most common interpretative models used in biochemistry to relate the H_{DA} amplitude to the composition of proteins. This original application of CDFT also opens the door towards more elaborate models.

1. Introduction and background

Long range electron transfer (LRET) plays a major role in numerous biochemical processes [1]. Prominent examples are given by the cell's respiratory chain or the photosynthetic system, where electrons are shuttled by means of a succession of electron jumps from the energy source (light or nutrient) toward the ATP synthases [2]. Various enzymes also provide examples of such processes: it is common that electrons have to be supplied to enzymes to enable them to fulfil their catalytic role. In the above cases the electrons are transferred between redox cofactors that belong, or not, to distinct proteins and because of the relative rigidity of the proteins the cofactors are maintained at considerable distances from each other (ca. 10 Å or more) [3].

It is of fundamental importance to develop appropriate theoretical frameworks to investigate such chemical reactions. The Marcus Hush Levich theory provides a useful physical–chemical reference framework (Fig. 1) [4,5]. The model assumes that one can define two "diabatic" states {D,A} and {D^+,A^-} that correspond to two electronic states with the electron respectively localized either on the donor D or the acceptor A. To enable ET thermal fluctuations have to bring the system into degeneracy where, according to Landau–Zener theory [6], the probability for hopping from one electronic state to the other reaches a maximum. In the high temperature regime and for weak-electronic couplings, both of which conditions are generally fulfilled for biological LRET, the reaction rate may be written as follows [4,7].

$$k_{ET} = \frac{2\pi}{h}\frac{1}{\sqrt{4\pi\lambda k_B T}}|H_{DA}|^2 \exp\left(\frac{-(\Delta G^\circ + \lambda)^2}{4\lambda k_B T}\right) \quad (1)$$

In this equation ΔG° is the driving force, *i.e.* the Gibbs free energy change accompanying the electron transfer, λ is the reorganization energy and H_{DA} is the coupling between the two non-adiabatic electronic states at the degeneracy point. In the adiabatic basis, this quantity represents half of the energy gap between the two electronic states at the crossing point.

Density functional theory (DFT) provides a method of choice to investigate biochemical processes especially when it is merged into hybrid DFT/MM (Molecular Mechanics) schemes. DFT capabilities are however seriously challenged in the case of LRET [8]. This difficulty is mainly related to the large distance separating D and A (>10 Å). Indeed it is well known that current DFT functionals fail to model charge transfer reactions when large distances are involved due to the self-interaction problem [9,10]. In addition, one faces the problem of the level of accuracy that is required for such biological processes. For large distances H_{DA} (>10 Å) generally amounts to a few tens of cm^{-1} or less (ca. 5.10^{-5} Ha) [11–13], a value far below the intrinsic accuracy of LCAO-KS (Linear Combination of Atomic Orbitals-Kohn Sham) DFT approaches (ca. 2×10^{-3} Ha). In these conditions it is nearly hopeless to evaluate accurately the energy gap between the two adiabatic states and the

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doi:10.1016/j.theochem.2009.11.012

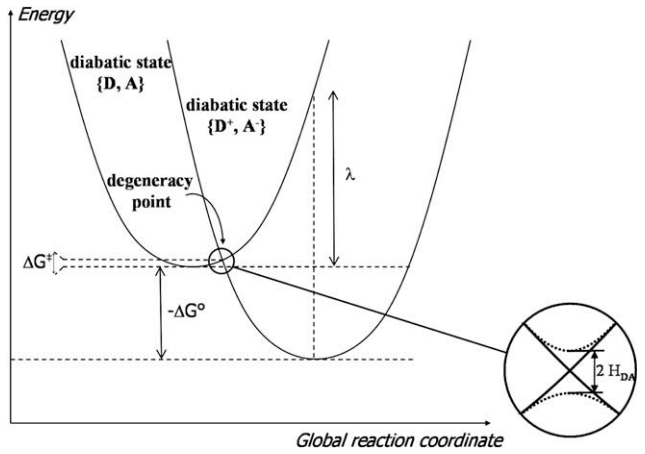

Fig. 1. Simplified one dimensional diagram of Marcus theory. The diabatic potential energy surfaces are represented with full lines while the adiabatic states (inset) are represented with dashed lines.

electronic coupling term entering the rate expression. An alternative would be to consider the diabatic states as in the usual Marcus picture. This would have the advantage of providing a chemically sound approach: the electron is localized either on the donor or on the acceptor. The electronic coupling between these diabatic states can then be computed according to the following formula, and, indeed, several techniques have been proposed to evaluate such coupling matrix elements for semi-empirical Hartree–Fock-based formalisms [14,15].

$$H_{DA} = \langle \Psi_{DA} | H | \Psi_{D^+A^-} \rangle \tag{2}$$

The constrained DFT (CDFT) approach recently proposed by Wu and Van Voorhis constitutes an appealing strategy to define such diabatic states at the DFT level [16]. It relies on the addition of an external potential to the usual KS potential whose role is to lead, after SCF convergence (Self Consistent Field), to a constrained electronic ground state that can be identified with the diabatic states. In other words, CDFT allows one to bridge the gap between the rigorous DFT framework and the Marcus phenomenological picture. The method has already been used to evaluate the different quantities needed in Marcus theory [17,18]. Very recently, a pioneering study has investigated the use of CDFT for the evaluation of ΔG° and λ including thermal and entropic effects [19].

We are interested in developing fast and accurate CDFT approaches to model biological ET. Such systems are in general large and typically involve at least 150–200 atoms that need to be treated at the quantum level. These are the two redox cofactors as well as the intervening medium. Despite its promise, one of the main drawbacks of constrained DFT is its cost. As detailed below, the method requires many more KS matrix diagonalizations than in usual DFT computations and this operation may become the CPU-time bottleneck in this case. We have thus decided to implement the method in the DFT code deMon2k [20] that has greatly benefited from the development of density fitting and parallelization techniques making this program a good starting point for the future [21,22].

2. Empirical approaches for H_{DA}

In the present paper we focus on the electronic coupling H_{DA} and explore the possibility of deriving interpretative models from CDFT computations. The electronic coupling is one of the key parameters of long range electron transfer rates. Whereas ΔG° and λ are mainly related to the structural characteristics of the cofactors, H_{DA} is essentially related to the chemical composition of the intervening medium (the "bridge"). A great deal of effort has been spent in the past years to discover the connections between the H_{DA} amplitudes and the detailed chemical structure of the bridge [23–26]. It is now recognized that thermal fluctuations have a determining influence on $\langle H_{DA} \rangle$ and a complete description requires evaluating this quantity in conjunction with atomistic simulations [27]. To circumvent the prohibitive cost of such protocols, empirical models have been derived and they allow the estimation of this quantity from geometrical considerations only. For instance, the packing density (PD) [28] and the pathway models (PM) [29], both developed in the 90s, attempt to write the total electronic coupling as a product of a contact value ($H_{DA}^{contact}$) times an attenuation factor ε_{total} which can be easily computed (Eq. (3)). The first term represents the electronic coupling that would appear if the donor and acceptor could be placed in Van der Waals contact. The two models differ in the form used for the total decay factor. The PD model considers the fraction of space that is beyond or within the atoms' Van der Waals radius along the D–A axis (respectively f_{space} and $(1-f_{space})$). A decay factor parameter β_{space} and β_{filled} is associated with each situation (Eq. (4)) and these enter into the exponential law. On the other hand, the PM provides a more detailed picture since the total decay factor explicitly considers the chemical composition of the pathway: ε_{total} is a product of individual covalently-bonded, hydrogen-bonded, and through vacuum decay factors (resp. ε_c, ε_{hb}, ε_v, Eqs. (5)–(8) and Fig. 2) for each pair of adjacent atoms along any particular pathway between donor and acceptor. A search algorithm like that of Dijkstra [30] is then employed to search for the single best pathway linking the donor to the acceptor, *i.e.* the one associated with the highest ε_{total}.

$$H_{DA} = H_{DA}^{contact} \cdot \varepsilon_{total} \tag{3}$$

$$\varepsilon_{total}^{packing\ den.} = e^{[f_{space}\beta_{space}R_{DA}]} \cdot e^{[(1-f_{space})\beta_{filled}R_{DA}]} \quad \text{(packing density)} \tag{4}$$

$$\varepsilon_{total}^{pathway} = \prod_{i=1}^{Nc}(\varepsilon_c)_i \prod_{j=1}^{Nhb}(\varepsilon_{hb})_j \prod_{k=1}^{Nv}(\varepsilon_v)_k \quad \text{(pathway model)} \tag{5}$$

$$\varepsilon_c = 0.6 \tag{6}$$

$$\varepsilon_{hb} = 0.36 \cdot e^{[-1.7(R-2.8)]} \tag{7}$$

$$\varepsilon_v = 0.6 \cdot e^{[-1.7(R-1.4)]} \tag{8}$$

Obviously, the development of quantum chemistry tools like CDFT and the availability of more powerful computational resources should allow the quantum evaluation of H_{DA} so that one might expect the previous models to be rapidly replaced. However, far from providing only simple formulas for a cheap estimation of H_{DA}, these models also provide guiding rules to interpret the computed values in terms of chemically understandable concepts. For example, if one wishes to relate the enhancement of the electronic coupling to the presence of a particular amino acid residue within the intervening medium, the above models are very useful, if not mandatory. This approach has found compelling applications for instance for intramolecular ET within some Ruthenium-modified proteins in which an axial methionine ligand has been shown to limit the ET rates by providing a narrow ET pathway, Another example is provided by cytochrome bo_3 for which electron pathways could be identified between heme groups [31,32]. In the case of the dicopper enzyme peptidylglycine α-hydroxylating monooxygenase, de la Lande et al. showed the specific role of the residue Glutamine 170 in the stabilization over time of a water mediated pathway connecting the two copper active sites, thus enabling efficient ET between them.