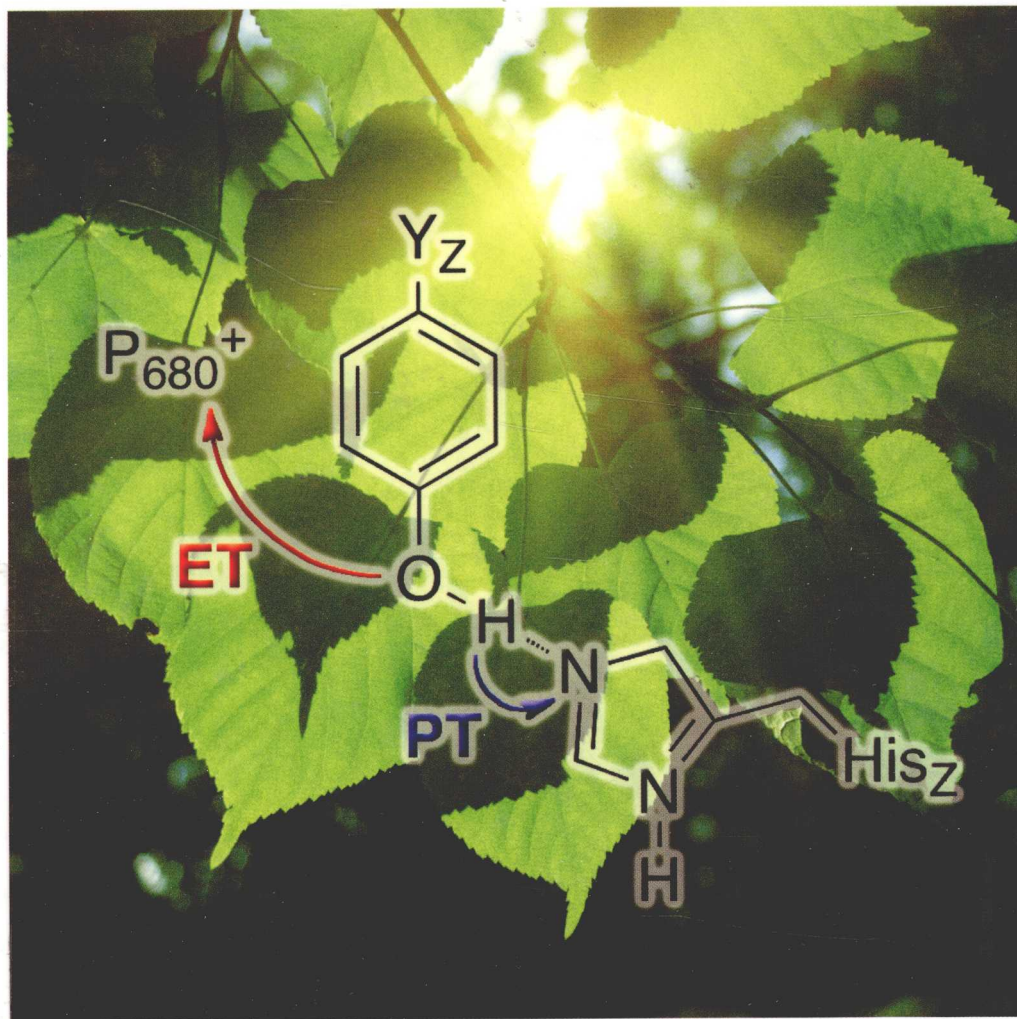Edited by Sebastião Formosinho and Mónica Barroso

Proton-Coupled Electron Transfer

A Carrefour of Chemical Reactivity Traditions

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Preface

The topic of "proton-coupled electron transfer" (PCET) has received increasing attention in the last decades, partly due to the realization of its role in the context of important biological and chemical (catalytic) processes. The mechanisms of vital functions like respiration and photosynthesis, and in general most of the biological enzyme processes, are now known to benefit from combining proton and electron movements in many of the charge transfer steps. The level of understanding of such systems and processes has increased rapidly in recent times, as a consequence of advances in characterisation techniques, particularly X-ray crystallography, time-resolved spectroscopies and electrochemistry, together with advances in theory and computational methods. Interestingly, the concept of PCET itself has been the subject of some dispute, with several groups disagreeing on the significance of that designation. A reasonably consensual definition of PCET is the combined transfer of protons and electrons from different sites and/or to different sites of the system, resulting in the overall transfer of an hydrogen atom, in opposition to the conventional hydrogen atom transfer (HAT). Further mechanistic considerations can then be added, to distinguish between concerted and stepwise processes and, in the latter case, the ones which start with the transfer of the proton and those where proton transfer follows the electron transfer. A better knowledge of the thermodynamic and kinetic aspects of these reactions can help clarify the mechanistic differences and contribute to further develop relevant theories and models, ultimately guiding the design of artificial systems, particularly relevant in the contexts of enzyme catalysis and energy conversion.

Chemical reactivity is currently explained in terms of several scientific traditions. One of them is the bond-breaking–bond-forming process and conceptually based on Potential Energy Surfaces. A second one is based on the role of Franck–Condon factors due to the overlap of vibrational wavefunctions.

Quantum mechanical tunnelling of vibrational modes is an equivalent way to account for such factors. A third tradition has emerged from a proposal of Prof. Rudolph Marcus on the role of the solvent configuration around a charged species, the so-called solvent reorganization. PCET is a "Carrefour" of such traditions, together with quantum mechanical tunnelling of the electron particle. Therefore, a purpose of the book is, through personal accounts, to bring together such traditions, which in science have always an intention of universality due to the contact of the scientist with reality through the experimental observations. Are all the abovementioned traditions compatible with each other and with the present level of experimental observation in the field? Chapters 1 and 2 of this book aim to give some insight on this problem, discussing the problem of PCET and HAT in the frameworks of Marcus theory and the Intersecting/Interacting State Model, respectively.

From the experimental point of view, the role of PCET in biological or biologically inspired systems will be explored. Chapter 3 presents an overview of theoretical and experimental techniques used to analyse PCET and their application in practical examples of enzyme reactions. The last chapters focus on two other important biological functions where PCET plays a central role, respiration (Chapter 4) and photosynthesis (Chapter 5), and how the design principles used by nature to optimise and regulate these processes can be a useful guide to the design of artificial systems, particularly in the context of fuel cells and artificial photosynthesis/solar fuel production. We hope that these accounts will bring together what have been some of the most recent developments in the topical subject of PCET, and provide the reader with an insight in the current understanding and applications of this important type of reactions.

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Sebastião Formosinho
Mónica Barroso

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Contents

CHAPTER 1

Application of the Marcus Cross Relation to Hydrogen Atom Transfer/Proton-Coupled Electron Transfer Reactions

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1.1 Introduction

Many important chemical and biological reactions involve transfer of both electrons and protons.[1] This is illustrated, for instance, by Pourbaix's extensive 1963 Atlas of Electrochemical Equilibria.[2] These have come to be called 'proton-coupled electron transfer' (PCET) reactions.[3–5] Due to the widespread interest in this topic, the term PCET is being used by many authors in a variety of different contexts and with different connotations. As a result, a very broad definition of PCET has taken hold, encompassing any redox process whose rate or energetics are affected by one or more protons. This includes processes in which protons and electrons transfer among one or more reactants, regardless of mechanism, and processes in which protons modulate ET processes even if they do not transfer.[6]

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Mechanistic issues are central to PCET. In contrast to electron transfer (ET) and proton transfer (PT), which are two of the most fundamental and well-understood reactions in chemistry, our understanding of how protons and electrons are transferred *together* is still emerging. The importance of mechanism was emphasized by Njus in a biochemical context almost two decades ago: "Many [biological redox] reactions involve the transfer of hydrogen atoms (or the concerted transfer of H^+ and e^-) rather than electron transfer alone. This distinction is generally disregarded because $H^{\bullet}$ and e^- are considered interchangeable in the aqueous milieu of the cell, but the focus on electrons obscures some of the general principles underlying the functioning of redox chains".[7]

This chapter focuses on hydrogen atom transfer (HAT) reactions, which involve concerted transfer of a proton and an electron from a single donor to a single acceptor in one kinetic step (eqn (1.1)). These are one subset of PCET processes and are one type of 'concerted proton-electron transfer' (CPET).[8]

$$X–H + Y \xrightarrow{k_{XH/Y}} X + Y–H \qquad (1.1)$$

"Concerted" implies a single kinetic step for transfer of the two particles, but does not imply synchronous transfer. HAT is a fundamental reaction studied by physical and organic chemists for over a century, critical to combustion and free-radical halogenations, for example.[9] More recently, it has been recognized that transition metal coordination complexes and metalloenzymes can undergo HAT reactions, and the recognition of overlap between traditional HAT reactions and PCET has stimulated much new thinking.[10–13] Our focus has been to understand the key factors that dictate HAT and PCET reactivity and to build a simple and predictive model that can be used in chemistry and in biology.[5]

In this chapter, we show that the Marcus cross relation holds remarkably well for HAT reactions in most cases. This provides important insights into HAT and allows the prediction of rate constants. We begin with an introduction to Marcus theory and the cross relation. This is followed by applications the cross relation to purely organic reactions (Sections 1.3),[14] and then to HAT reactions involving transition metal complexes (Sections 1.4).[15] Finally, Section 1.5 describes the intuitive picture of HAT derived from the success of the cross relation, and also emphasizes some of the weaknesses of this treatment and the questions that remain.

1.2 An Introduction to Marcus Theory

The Marcus theory of electron transfer has proven invaluable for understanding a variety charge transfer reactions, from simple solution reactions to long-range biological charge transfer.[16–19] The primary equation of Marcus theory, equation (1.2), is derived from a model of intersecting parabolic free energy surfaces.[19] When the coupling between these diabatic surfaces H_{AB} is small, the reaction is non-adiabatic and the reaction does not always occur

$$k_{et} = \frac{2\pi}{\hbar} H^2_{AB} \frac{1}{\sqrt{4\pi\lambda RT}} \exp\left(-\frac{(\Delta G^\circ + \lambda)^2}{4\lambda RT}\right) \qquad (1.2)$$

$$k_{et} = A e^{-(\Delta G^\circ + \lambda)^2 / 4\lambda RT} \qquad (1.3)$$

when the system reaches the intersection (the transition state). When the coupling is sufficiently large the reaction is adiabatic and equation (1.2) reduces to equation (1.3). The pre-exponential factor A in equation (1.3), for a bimolecular reaction, is typically taken as an adjusted collision frequency. The intrinsic barrier λ is the energy required to distort the reactants and their surrounding solvent to the geometry of the products. Because electron transfer occurs over relatively long distances, with little interaction between the reagents, it is typically assumed that λ can be taken as a property of the individual reagents. λ for a reaction is then commonly taken as the average of the individual reagent λ's (the 'additivity postulate,' eqn (1.4)). In the adiabatic limit, λ for an individual reagent can be determined from the rate of the self-exchange reaction (eqn (1.5)). Combining equations (1.3) and (1.4) gives the cross relation (eqn (1.6) and (1.7)), which relates the rate constant of a cross reaction, $X + Y^-$, to the self exchange rate constants for reagents X and Y (eqn (1.5)) and the equilibrium constant K_{XY}. The constant f is defined by equation (1.7) and is typically close to unity, unless $|\Delta G^\circ| \geq \lambda/4$.[17]

$$\lambda_{XY} = \frac{1}{2}(\lambda_{XX} + \lambda_{YY}) \qquad (1.4)$$

$$X + X^- \xrightarrow{k_{XX}} X^- + X \qquad (1.5)$$
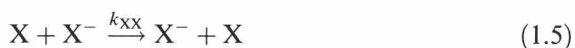
$$k_{XY} = \sqrt{k_{XX}k_{YY}K_{XY}f} \qquad (1.6)$$

$$\ln f = \frac{(\ln K_{XY})^2}{4\ln(k_{XX}k_{YY}Z^{-2})} \qquad (1.7)$$

Theoretical treatments of PCET reactions typically have equation (1.2) as a conceptual starting point. In Hammes–Schiffer's multistate continuum theory for PCET,[13] the pre-exponential factor includes both electronic coupling and vibrational overlaps, and the rate is a sum over initial and final vibrational states integrated over a range of proton-donor acceptor distances. This theory has been elegantly applied to understand the intimate details of a variety of PCET reactions, but many of its parameters are essentially unattainable experimentally.

The cross relation can be written for an HAT reaction (eqn (1.1) and (1.8)). It is a very simplistic model, but it has the advantage that all of the parameters are experimentally accessible (in many cases).

$$k_{XH/Y} = \sqrt{k_{XH/X}\, k_{YH/Y}\, K_{XH/Y} f} \tag{1.8}$$

It should be emphasized that the cross relation is not a corollary of current PCET theory and that there is little theoretical justification for applying it (although Marcus has briefly discussed this).[20] Still, the cross relation has been successfully applied to group transfer reactions including proton[21] and hydride transfers,[22] and S_N2 reactions.[23] While these successes are notable, in each instance the cross relation holds only over a narrow set of reactants and reactions. In contrast, the treatment described here has shown to be a powerful predictor for a wide array of HAT reactions.

Our interest in applying the Marcus cross relation grew out of our finding that the traditional Bell–Evans–Polanyi (BEP) relationship, $E_a = \alpha(\Delta H) + \beta$,[9,24] holds well for transition metal complexes abstracting hydrogen atoms from C–H bonds.[25] The BEP equation relates HAT activation energies to the enthalpic driving force (ΔH) (although, as discussed in Section 1.4 below, free energies should be used, as in Marcus theory). The ΔH is typically taken as the difference in bond dissociation enthalpies (BDEs) of X–H and Y–H.[26] The BEP equation has been a cornerstone of organic radical chemistry for many decades, typically holding well for reactions of one type of oxidant $X^{\bullet}$ with a series of substrates Y–H. The success of this treatment is one reason why organic textbooks list BDEs.[27] We initially found that the rate constants for HAT from C–H bonds to CrO_2Cl_2 or MnO_4^- show good BEP correlations with the BDE of the C–H bond.[28] Later, we found an excellent BEP correlation for C–H bond oxidations by $[Ru(O)(bpy)_2(py)]^{2+}$ (Figure 1.1).[29] Such a correlation, with a Brønsted slope $\Delta\Delta G^{\ddagger}/\Delta\Delta H^{\circ}$ close to $\frac{1}{2}$, is a strong indicator of an HAT mechanism. Many other groups have also used these correlations to understand the relationship between rate and driving force for HAT reactions of transition metal containing systems.[30] Marcus theory and the cross relation also predict a Brønsted slope ($\Delta\Delta G^{\ddagger}/\Delta\Delta G^{\circ}$) close to $\frac{1}{2}$, for reactions at low driving force (specifically when $\Delta G^{\circ} \ll \lambda/2$).

The BEP correlation between rates and driving force for HAT is very valuable, but it applies only to a specific set of similar reactions, for instance MnO_4^- abstracting $H^{\bullet}$ from hydrocarbons.[31] In addition, the α and β parameters are defined only with the context of the correlation and have no independent meaning. In contrast, cross relation uses three independently measurable parameters: the equilibrium constant $K_{XH/Y}$ (which is equal to $e^{-\Delta G^{\circ}_{XH/Y}/RT}$) and the rate constants for the hydrogen atom self-exchange reactions $k_{XH/X}$ and $k_{YH/Y}$ (eqn 1.9).
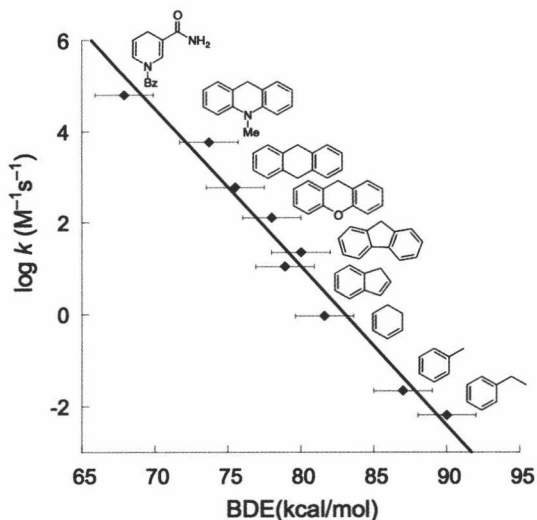
$$XH + X \rightarrow X + XH \tag{1.9}$$

Figure 1.1 Plot of statistically corrected rate constants *versus* BDE for H-abstraction from C–H bonds by $[Ru(O)(bpy)_2py]^{2+}$.[29]

1.3 Predicting Organic Hydrogen Atom Transfer Rate Constants

Hydrogen atom transfer (HAT) reactions of organic compounds are fundamental to combustion, industrial oxidation processes, and biological free radical chemistry, among other areas of chemistry and biology. One important example is the series of H-transfers that is thought to be involved in lipid oxidation. Peroxyl radicals (ROO•) abstract H• from a lipid to give a lipid radical that adds O_2 to form a new peroxyl radical and propagate the radical chain.[32] ROO• can also abstract H• from α-tocopherol (a component of vitamin E) and the resulting α-tocopheroxyl radical is thought to be regenerated *via* HAT from ascorbate (vitamin C).[32] Understanding such a web of free radical reactions requires knowledge of the rate constants for each of the steps. To this end, we have developed a predictive model for organic HAT reactions[14] based upon the Marcus cross relation and the kinetic solvent effect model of Ingold *et al.*[33]

We begin this section discussing the application of the cross relation to real systems, how the needed rate and equilibrium constants can be obtained. These same principles also apply to the metal-mediated HAT reactions discussed in Section 1.4. A set of reactions are used to test the Marcus model, using inputs all obtained in the same solvent. Then we address how to extrapolate rate and equilibrium constants from one solvent to another, using the H-bonding descriptors developed by Abraham and co-workers.[34–36] Finally, we show that this allows remarkably accurate prediction of a very wide range of HAT cross rate constants.[14]

1.3.1 Obtaining Self-Exchange Rate Constants and Equilibrium Constants

Ideally, all three of the parameters needed for the cross relation, $K_{XH/Y}$, $k_{XH/X}$ and $k_{YH/Y}$, are measured in the same medium under the same conditions. When the values are only available in different solvents, solvent corrections must be included, as described in Section 1.3.3 below. The f term can be calculated from the three parameters, with the collision frequency Z typically taken as 10^{11} M^{-1} s^{-1}.[37,38]

The driving force for a HAT reaction, $\Delta G°_{XH/Y} = -RT \ln K_{XH/Y}$, is best determined by direct equilibrium measurements in the solvent of interest. However, this is typically limited to reactions where $|\Delta G°_{XH/Y}|$ is small, less than about 5 kcal mol^{-1}. Also, this is only possible for reactions in which all of the species are fairly stable, which is unusual for organic radical reactions. The $\Delta G°$ for a HAT reaction is typically more easily derived as the difference in bond dissociation free energies (BDFEs) of X–H and Y–H in the solvent of interest. We have recently reviewed BDFEs of common organic and biochemical species and how they are obtained,[39] so only an overview is given here.

One powerful method to determine BDFEs uses a solution thermochemical cycle with the reduction potential of XH and the pK_a of XH$^+$, or with $E°(X^-)$ and $pK_a(XH)$. The BDFE in kcal mol^{-1} is given by $23.1E° + 1.37pK_a + C_G$.[39–42] Bordwell and others have used this approach to measure many bond *dissociation enthalpies* (BDEs)[40] but it is more appropriate to use BD*FE*s because the $E°$ and pK_a values are free energies.[39,41,42] Determining X–H BDEs from $E°$ and pK_a measurements is valid when XH and X have similar absolute entropies, as is typically the case for organic molecules but not for transition metal complexes (see Section 1.4.1 below).[39,41,42] Due to the uncertainties in the C_G value in thermochemical cycle, and typical uncertainties in the $E°$ and pK_a values, this procedure yields BDFEs accurate to no better than ± 1 kcal mol^{-1}. This leads to estimated uncertainties in rate constants calculated from the cross relation of an order of magnitude.

Solution-phase BDFEs can also be obtained from gas-phase BDEs, which are available for many small organic molecules. An extensive tabulation of such BDEs can be found in the recent book by Luo, portions of which are available online.[43] As described in detail elsewhere,[14,39] a gas-phase BDE can be converted into the corresponding solution-phase BDFE using data from standard tables [$S°(H^•)_{gas}$, $\Delta G°_{solvation}(H^•)$] and an estimate of the difference in the free energies of solvation of XH and X (see below).

Self-exchange rate constants, $k_{XH/X}$ and $k_{YH/Y}$, are best measured directly when this is possible. NMR line broadening is a powerful technique for degenerate exchange reactions of stable species if the rate constant is *ca.* 10^3–10^6 M^{-1} s^{-1};[44] faster reactions can be monitored by EPR methods.[45] In the ^{1}H NMR experiments, typically one reactant is diamagnetic and has a sharp spectrum while the other is paramagnetic. In the slow-exchange limit, addition of the paramagnetic species to the diamagnetic causes broadening of the

spectrum but not shifting, and the amount of broadening is directly related to the rate constant. We have used this method to measure a number of $k_{XH/X}$ values for transition metal reagents.[29b,46–49]

Self-exchange rate constants can also be determined through the use of 'pseudo-self-exchange' reactions, that is H$^•$ exchange reactions using two very similar reagents X(H) and *X(H) (eqn (1.10)). The reagents can differ in just an isotopic label (*e.g.* toluene/3-deuterotoluene)[50] or just be chemically similar. For instance, we have examined the pseudo-self-exchange reaction of oxovanadium complexes that differ only in their 4,4'-dimethylbipyridine *vs.* 4,4'-di-(*t*-butyl)bipyridine supporting ligands.[51] This reaction has $K_{XH/*X} = 1$ within experimental error, so it is very close to a true self-exchange reaction. Reaction of the hydroxylamine TEMPO-H (2,2,6,6-tetramethyl-*N*-hydroxypiperidine) with the aminoxyl radical 4-oxo-TEMPO (eqn (1.11)) has $K_{XH/*X} = 4.5 \pm 1.8$.[52] In such cases the self-exchange rate constant $k_{XH/X}$ is taken to be the geometric mean of the forward ($k_{XH/*X}$) and reverse ($k_{*XH/X}$) rate constants (eqn (1.12)).[53]

$$XH + {}^*X^• \rightarrow X^• + {}^*XH \qquad (1.10)$$

TEMPOH   4-oxo-TEMPO   TEMPO   4-oxo-TEMPOH

$$(1.11)$$
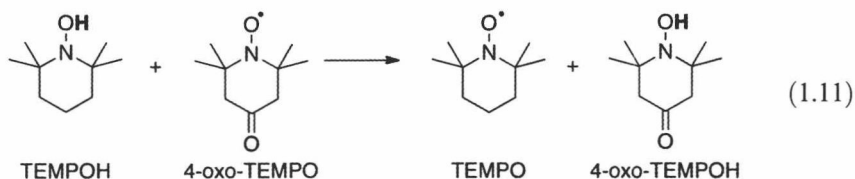
$$k_{XH/X} = \sqrt{k_{XH/*X}k_{*XH/X}} = k_{XH/*X}\left(K_{XH/*X}\right)^{-1/2} \qquad (1.12)$$

Using these various approaches, homolytic bond strengths and self-exchange rate constants have been derived for a number of reagents. A selection of those used in this chapter are summarized in Table 1.1;[54,55] a more complete list of BDEs and BDFEs is given in references 14 and 39.

1.3.2 Tests of the Cross Relation for Organic HAT Reactions

To test the applicability of the cross relation to HAT, a set of 17 organic reactions have been compiled in which cross and self-exchange rate constants have all been measured under similar conditions (the self-exchange rate for 9,10-dihydroanthracene (DHA) has been estimated by applying the cross relation).[51] These reactions, indicated with a * in Table 1.2,[56–68] involve oxyl radicals abstracting H$^•$ from O–H and C–H bonds. The equilibrium constants are either available under the same conditions or have been adjusted using the solvent corrections described below.