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Review

Thermodynamics and kinetics of proton-coupled electron transfer: stepwise vs. concerted pathways

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Abstract

Reactions that involve transfer of an electron and a proton can proceed by stepwise pathways involving initial electron transfer (ET) or initial proton transfer (PT), or by a concerted pathway without an intermediate. The concerted mechanism is termed proton-coupled electron transfer (PCET). Understanding such reactions requires knowledge of the thermodynamics of the possible ET, PT, and PCET steps. Many reactions have a large thermochemical bias favoring the PCET pathway. This bias is often sufficient to rule out stepwise mechanisms. The ΔG° for ET, PT, or PCET has a strong influence on the rate of that step. Using the terminology of Marcus theory, PT and PCET reactions at C–H bonds have higher intrinsic barriers than such reactions at O–H or N–H bonds. The intrinsic barriers to ET and PCET are often similar when there is a small intrinsic barrier to PT. Reactions with a thermochemical bias toward PCET and with similar intrinsic barriers for all the pathways are most likely to occur by concerted PCET.

Keywords: Proton-coupled electron transfer; Hydrogen atom transfer; Electron transfer; Proton transfer; Marcus theory; Iron

1. Definitions and overview

There are almost as many definitions of "proton-coupled electron transfer" (PCET) as there are groups working in this area. In our view, PCET refers to a single chemical reaction step involving concerted transfer of both a proton and an electron. Concerted in this context means that the reaction occurs without an intermediate. This definition is illustrated by the square schemes in Scheme 1, where horizontal lines refer to proton transfer (PT) and vertical lines to electron transfer (ET). PCET is the diagonal process. It is to be contrasted with stepwise pathways that involve mechanistically distinct ET and PT steps and involve an intermediate. In the square schemes, the stepwise mechanisms correspond to moving around the edges of the square. Stepwise reactions where ET and PT occur at comparable rates and/or cannot be separated kinetically have at times been called PCET processes (cf., Ref. [1]) and are quite important, but such coupling can be treated by standard kinetic treatments.

The definition of PCET used here encompasses both hydrogen atom transfer (HAT) and other kinds of concerted electron/proton transfers. HAT is an important area of chemistry that has been widely studied—tens of thousands of rate constants are known—in the contexts of combustion, halogenation, antioxidant oxidation, and other processes [2]. HAT is typically defined as a process in which a hydrogen atom moves between two groups X and Y, as in the diagonal of Scheme 1A. There are also PCET reactions in which the proton and electron are somehow separated in the reactants, products, or at the transition state. One example of such a non-HAT process occurs when electron transfer from a hydrogen bonded YH–Z unit is coupled to proton transfer across the hydrogen bond, as illustrated in Scheme 1B. It is more common practice to define PCET as concerted proton/electron transfer that is *not* HAT, but we have found that this distinction can be difficult to make in practice, especially when metals are involved.

The Tommos and Babcock [3] proposal for S-state transitions in Photosystem II (PS II) includes an example of Scheme 1A: HAT from a water or hydroxide on the manganese cluster to the tyrosyl radical $Y_Z^{\cdot}$. An example of Scheme 1B from PS II is the oxidation of the tyrosine Z-histidine unit (Y_Z-D1-His190) by long-range electron transfer from $P680^{+\cdot}$ [4]. Whether the oxidation of Y_Z occurs by a pathway that is concerted (PCET) or stepwise (ET/PT or PT/ET) is a matter of continuing discussion [5]. It should be

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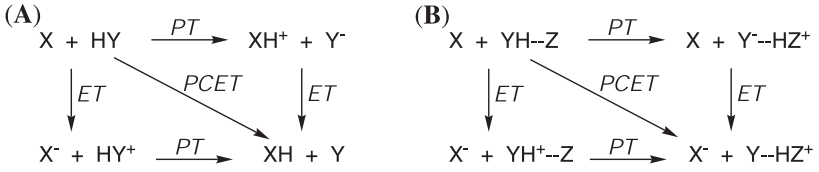


Scheme 1. Square schemes for PCET.

noted that the coupling of electron and proton motions is critical in a wide range of biochemical processes, not only in PS II. This was perhaps first discussed many years ago by Stiefel [6] in the context of molybdenum enzyme reactions.

To understand whether a reaction proceeds by a concerted or a stepwise pathway, it is very valuable to know the thermochemistry of each step. Hence, this short review begins with a discussion of energetics, emphasizing that there is often a thermodynamic bias toward PCET. Then the relationship between the thermochemistry and the kinetics of ET, PT, and PCET is discussed, using the concepts of Marcus theory [7].

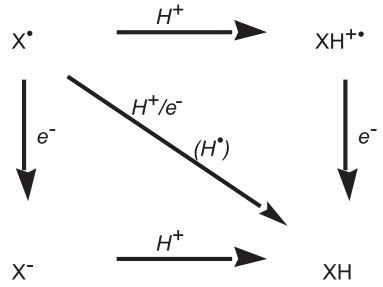
2. Thermochemistry of ET, PT, and PCET processes

The thermodynamics of electron transfer and proton transfer reactions are characterized by redox potentials (E) and pK_a values, respectively. Both are free energy (ΔG°) measurements. Discussions of HAT processes typically use bond dissociation energies (BDEs, bond strengths), which are enthalpies (ΔH°). BDEs have the advantage that they are not very dependent on solvent or on temperature, but they are less directly connected to rate constants (which are related to free energies of activation via transition state theory). The ΔG° and ΔH° for a HAT reaction XH + Y → X + HY are typically quite close since $\Delta S^\circ \cong 0$ (for reactions accompanied by minor changes in solvation) [8a]. Bond strengths for small, simple gas phase species are available in standard tables (the most recent should be used whenever possible as current, more accurate values are often higher than previous ones [8]). About 15 years ago, Bordwell et al. [9] showed that bond strengths could be accurately determined from solution measurements of E and pK_a. Using a square scheme for a single reagent (Scheme 2), the energy of the diagonal is simply the sum of the energies of the two steps around the square to get to the same point. There are two such two-step paths, and the energies of these two paths must be equal: $2.3RTpK_a(XH) + nFE(X^{\cdot}/X^{-}) = nFE(HX^{\cdot+}/HX) + 2.3\ RTpK_a(XH^{\cdot+})$.

We have adapted the Bordwell cycle to calculate the affinity of inorganic complexes for a hydrogen atom, first determining that $\Delta H^\circ = -80 \pm 3$ kcal mol^{-1} for the addition of H$^{\cdot}$ to permanganate in aqueous solution [10]. This was the result that brought one of us (JMM) into contact with Jerry Babcock. Jerry's proposal of HAT from a manganese-bound water to the tyrosyl radical $Y_Z^{\cdot}$ in PS II was criticized because HAT from water to a phenoxyl radical is about 31 kcal mol^{-1} uphill (this ΔH° is simply the difference between BDE(HO–H) = 119 kcal mol^{-1} and BDE(PhO–H) = 88 kcal mol^{-1} [8,11]). Our work showed—and this was subsequently confirmed for PS II model complexes by Pecoraro et al. [12] and by Wang and Mayer [13] in our laboratory—that O–H bonds in ligands bound to manganese are significantly weaker than the O–H bond in water. In fact, O–H bond strengths in manganese complexes typically are in the range required for the Babcock proposal.

A year or two later, in 1997, I had the pleasure of giving a seminar at Michigan State University. By a quirk of scheduling, the visit was on the day of commencement. As department chair, Jerry was running in and out of the department in his full academic robes, much to everyone's amusement. The benefit for me was that all the hotels were booked. So the night before my visit Jerry put me up at his house, and we spent hours at his kitchen table, drinking beer and talking science. Jerry raised all sorts of questions, trying to connect the inorganic chemistry I knew with the enzymatic mechanisms he was probing. While I could only begin to answer most of the questions, that and subsequent discussions, and many, many e-mails, have strongly influenced the directions of my work. We now have a few more answers for Jerry. Would that he were here to get excited and to challenge us to bigger and better things.

Applications of the Scheme 2 thermochemical cycle to enzymes are interesting to contemplate. Bond strengths—the enthalpy of the diagonal—typically vary little with solvent or phase. For instance, gas phase and solution bond strengths are typically taken to be identical. In contrast, differing solvent dielectrics and protein electrostatics often strongly affect E and pK_a values. If the bond strength for a group XH



Scheme 2. Square scheme for net H$^{\cdot}$ transfer.

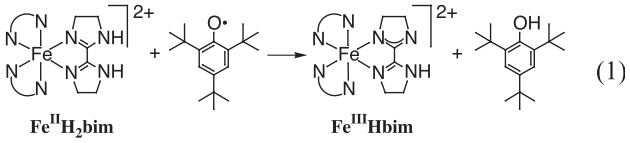
is constant, then any shift in E that results from a solvent change or placement in a protein matrix must have an *exactly compensating opposite shift* in the pK_a. For instance, placement of a positive charge near XH will make it more difficult to remove an electron, but easier to dissociate a proton. Similarly, a less polar protein environment makes it more difficult to deprotonate XH but easier to oxidize the X^- formed to $X^{\cdot}$. A change in E of 59 mV must be balanced by a one unit change in pK_a to keep the bond strength the same. The $E - pK_a$ compensation may not hold as well when the proton being removed is distant from the redox center (as can be the case in Scheme 1B) or when the proton is part of an extended hydrogen bond network in a protein. This may be indicated by an unusual dependence of E on pH. For small molecule redox couples in aqueous solution, E vs. pH plots (Pourbaix diagrams) have slopes of $n \times 59$ mV/pH unit, where n is the ratio of the number of protons transferred to the number of electrons transferred in the redox couple [14].

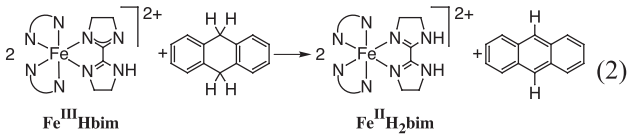
3. Case studies: the thermochemical bias toward PCET

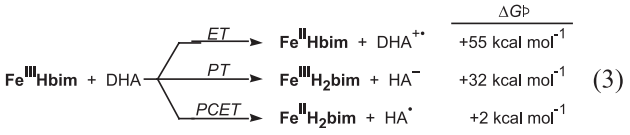
The thermochemistry and reactivity of iron–biimidazoline complexes have been extensively studied in our labs. Scheme 3 gives the pK_a values, redox potentials (vs. $Cp_2Fe^{+/0}$ which is $\sim +0.6$ V vs. NHE), and the N—H bond strength (all in MeCN [15–17]). The NH protons are significantly more acidic in the iron(III) complex (abbreviated $Fe^{III}H_2bim$), and the fully protonated $Fe^{III}H_2bim$ is significantly more oxidizing than the deprotonated Fe(III) complex $Fe^{III}Hbim$. This is always the pattern: within a system, the higher oxidation state species are more acidic and the more protonated species are more oxidizing [18]. Because they are part of the same square, the difference between the pK_a values is always equal to the difference in redox potentials divided by 0.059 V (to convert ΔE to a $\log_{10}$ equilibrium constant). In Scheme 3, the ΔpK_a of 8.5 is equal to the ΔE of 0.5 V/0.059 V.

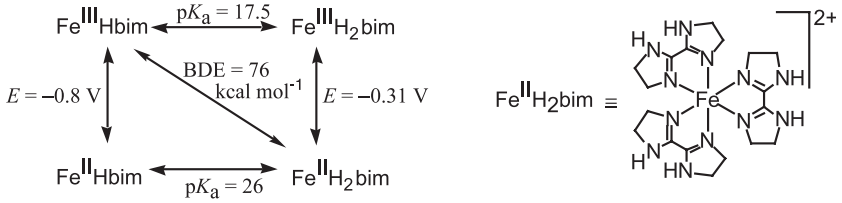
The shift in redox potential of ca. 0.5 V upon protonation and the change of ca. 10 pK_a units upon redox change are not unusual for metal complexes, although a range of values can be found. The ΔE or ΔpK_a value is the thermodynamic coupling between the proton and the electron, describing how sensitive the proton properties are to the presence or absence of the electron and vice versa. It is a key parameter in any PCET process.

The $\Delta H°$ for removal of a hydrogen atom from $Fe^{II}H_2$-bim, the N—H bond strength, is 76 kcal mol^{-1} (Scheme 3). Consistent with this value, a hydrogen atom is removed from $Fe^{II}H_2bim$ by 2,4,6-tri-*t*-butylphenoxyl radical since the radical forms an 81 kcal mol^{-1} O—H bond ([19], Eq. (1); N—N is an H_2bim ligand). This is a rare example of an oxygen radical abstracting a ligand-based hydrogen atom [20]. In the reverse direction, $Fe^{III}Hbim$ can oxidize substrates with weak O—H and C—H bonds, including dihydroanthracene (DHA, Eq. (2) [15]) and hydroxylamines [17].

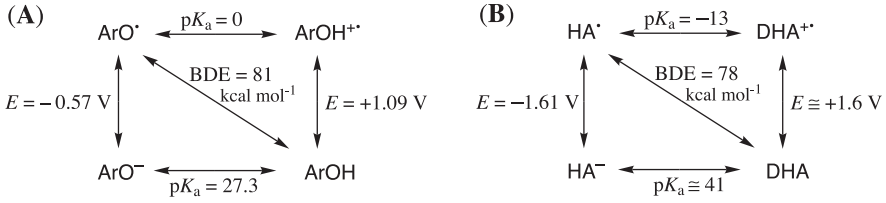








Scheme 3. Thermochemistry of iron–biimidazoline complexes in MeCN (E vs. $Cp_2Fe^{+/0}$).

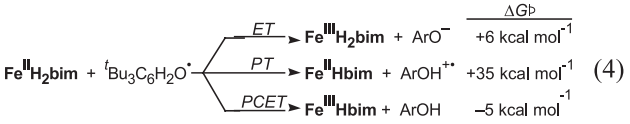


Scheme 4. Thermochemistry of 2,4,6-^{t}Bu$_3$C$_6$H$_2$OH (ArOH) and dihydroanthracene (DHA) in MeCN (E vs. $Cp_2Fe^{+/0}$) [21]; HA$^{\cdot}$ and HA$^-$ refer to the hydroanthracenyl radical and hydroanthracenyl anion, respectively.

The thermochemical properties of DHA and the phenol in Scheme 4 [21] can be used to analyze the possible rate-limiting steps in reactions (1) and (2), as summarized in Eqs. (3) and (4).

Electron transfer from DHA ($E \cong 1.6$ V) to $Fe^{III}Hbim$ ($E \cong -0.8$ V) is uphill by ~ 2.4 V ($\Delta G^\circ = \sim 55$ kcal mol^{-1}). Similarly, initial proton transfer is uphill by 32 kcal mol^{-1}. These values directly rule out mechanisms involving initial ET or PT, since the ΔG° values for these processes are much higher than the observed barrier $\Delta G^\ddagger = 22$ kcal mol^{-1} [15]. The mechanism must therefore be concerted transfer of the two particles, PCET. The mechanistic conclusion can be made even without knowledge of how the reaction rates depend on their driving force, because the stepwise paths are so unfavorable. ΔG° for PCET is approximately equal to the difference in bond strengths, $\Delta H^\circ = +2$ kcal mol^{-1}. In sum, the oxidation of DHA by $Fe^{III}Hbim$ has a very large thermochemical bias, favoring PCET over initial ET and PT by 53 and 30 kcal mol^{-1}, respectively.

In the reaction of 2,4,6-$^t Bu_3C_6H_2O^\cdot$ with $Fe^{II}H_2bim$, PCET is again strongly favored (Eq. (4)). In this case, PT is the most unfavorable and is directly ruled out.



(4)

However, ET is only 6 kcal mol^{-1} uphill and is therefore a possible mechanism given the observed $\Delta G^\ddagger$ of 8.5 kcal mol^{-1} [17]. PCET, *down*hill by 5 kcal mol^{-1}, is also a reasonable mechanism. In this case, the thermochemical arguments are not sufficient to determine the pathway.

In both of these case studies, PCET is significantly more favorable thermodynamically than the stepwise paths, because of the inherent properties of the reactants (Schemes 2 and 3). Many organic compounds have similar biases. Oxidation of neutral compounds typically generates acidic radical cations, and reduction of neutrals typically generates quite basic radical anions. Thus, in most reactions involving organic compounds, PCET processes will be significantly favored over stepwise ET/PT or PT/ET. The bias toward PCET is reduced with larger and more delocalized radical ions, such as diaminobenzenes or quinones (semiquinone radical anions are only mildly basic [22]). It should also be noted that some redox agents lack a dissociable proton and therefore engage only in ET, not PCET. Examples include metallated porphyrins (e.g., cytochrome *c*), most iron–sulfur clusters [1b], and ferrocene.

4. Thermodynamic influences on the kinetics of ET, PCET, and PT

The arguments in the previous section use the constraint that the free energy barrier $\Delta G^\ddagger$ must be larger than the free energy change ΔG°. For electron transfer reactions, there is a more detailed relationship between $\Delta G^\ddagger$ and ΔG°, Marcus theory (Eq. (5)) [7]. For simplicity, the discussion here will ignore work terms, non-adiabatic effects, and many other extensions of the Marcus-Hush approach [7]. A key concept in Marcus theory is the intrinsic barrier λ, which is four times the activation free energy at $\Delta G^\circ = 0$. By the additivity postulate, λ_{XY} for electron transfer from X to Y^+ is equal to the average of the λ's for the degenerate electron self-exchange reactions, λ_{XX} (for $X + X^+$) and λ_{YY} ($Y + Y^+$) (Eq. (6)). Self-exchange reactions are thus a way to determine intrinsic barriers and are a key component of the Marcus cross-relation, which relates the rate constant for a cross-reaction to its equilibrium constant (Eq. (7); f_{XY} is usually ~ 1[7]).

$$\Delta G^\ddagger = \frac{\lambda}{4}\left(1 + \frac{\Delta G^\circ}{\lambda}\right)^2 \tag{5}$$

$$\lambda_{XY} = \frac{1}{2}(\lambda_{XX} + \lambda_{YY}) \tag{6}$$

$$k_{XY} = \sqrt{k_{XX} k_{YY} K_{XY} f_{XY}} \tag{7}$$

We have recently shown that the cross-relation also holds fairly well for a range of PCET reactions [17]. This is particularly valuable because it provides a new perspective on the reactions. In the Marcus approach, the kinetic insight about a reaction is in the intrinsic barriers (λ) and self-exchange rates. This contrasts with the typical approaches to organic and inorganic reactions using the concepts of frontier orbital control or charge control. Within these paradigms, a frontier orbital or charge-controlled reaction X + Y has very little in common with the self-reactions.

Rate constants have been determined for a number of self-exchange or close to self-exchange PCET reactions [16]. For instance, the rate constant for degenerate exchange (HAT) between the hindered phenol 2,4,6-$^t Bu_3C_6H_2OH$ and its phenoxyl radical has been measured by ESR to be 220 M^{-1} s^{-1} [23]. Degenerate PCET between iron–biimidazoline complexes, $Fe^{III}Hbim + Fe^{II}H_2bim$, occurs with $k = 5800$ M^{-1} s^{-1} [16]. A survey of PCET self-exchange reactions shows that H-atom exchange involving O–H or N–H bonds is usually facile ($k = 10^2$–10^6 M^{-1} s^{-1}). However, H-atom self-exchange between carbons is dramatically slower [16]. For instance, HAT between benzyl radical and toluene has $k \cong 4 \times 10^{-5}$ M^{-1} s^{-1} [24], seven orders of magnitude slower than the phenol reaction quoted above. This kinetic pattern has long been known to organic radical chemists: reactions of C–H bonds and carbon radicals are much slower than analogous reactions of RO–H and RO$^\cdot$ at the same driving force. We find that H-atom abstraction from C–H bonds is ~10^4 slower than abstraction from an O–H bond of equal strength by the same reactant. This factor of 10^4 is predicted by the cross-

relation, where the ratio of the cross-reaction rate constant should be the square root of the ratio of the self-exchange reaction rate constants.

The kinetic pattern for PCET, $k(O-H) \gg k(C-H)$, is also the well-known kinetic pattern for PT [25]. Proton transfer between electronegative atoms typically occurs with rate constants close to the diffusion limit in water for reactions that are exoergic, and have rate constants $> 10^8\ M^{-1}\ s^{-1}$ at $\Delta G^\circ \cong 0$. Formation or deprotonation of C–H bonds, however, are typically much slower. In Marcus terminology, PT reactions of C–H bonds have much higher intrinsic barriers (or higher work terms to assemble the reactive precursor complex) than reactions of O–H or N–H bonds [25]. While we use the Marcus language here, the Marcus approach has not proven to be globally successful for PT reactions [25]. To our knowledge, the only successful application of the cross-relation for PT is among a set of three closely related metal hydride compounds [26]. Still, applications of the Marcus equation to PT reactions have been valuable and continue to influence current theoretical approaches [27].

It should be noted that a number of sophisticated quantum mechanical theories of PCET are being developed [28], as discussed elsewhere in this issue. In brief, these treatments do not use the standard transition state theory approach, in which the nuclei move over a barrier on a Born–Oppenheimer potential energy surface that implicitly includes electronic reorganization. Instead, the new approaches treat the transferring proton and electron as quantum particles and include tunneling and non-adiabatic effects. There is a continuum between the semi-classical and quantum pictures and particular reactions could involve both classical and tunneling paths [29]. Experimental studies have indicated the importance of proton tunneling in many PCET processes, most visibly in remarkably large H/D kinetic isotope effects [30]. To our knowledge, the success of the cross-relation for PCET does not follow simply from the current theories.

5. PCET vs. stepwise ET/PT

5.1. Examples and current intuition

Many biological reactions involve transfers of electrons and protons. In this wide-ranging literature, most reactions involving cleavage of C–H bonds are discussed only in terms of HAT, with concerted proton and electron transfer. Stepwise mechanisms are typically not even mentioned in, for instance, vitamin B_{12} reactions, methane monooxygenase mechanisms, fatty acid oxidations by lipoxygenases, or camphor oxidation by cytochrome P450. This is likely due in part to the large thermochemical bias toward PCET for hydrocarbon substrates—methane and camphor are very difficult to oxidize to radical cations or to deprotonate (it is the unactivated 5-methylene of camphor that is oxidized, not the enolizable 3-methylene). A rare exception to this generalization is *N*-dealkylation of alkylanilines by P450s, where there is ongoing debate between HAT and stepwise ET/PT mechanisms [31]. Anilines have relatively low redox potentials so initial ET is reasonable [32].

In contrast, studies of oxidations of O–H and N–H bonds usually invoke stepwise mechanisms (ET/PT or PT/ET) rather than concerted PCET. A recent paper on guanine oxidation states the common intuition: "While these PCET reactions produce the energetically most favorable route, the need to release the proton often increases the kinetic barrier to the overall process." [1a]. This intuition may in part reflect that the thermochemical bias toward PCET is smaller for reactions of O–H and N–H bonds than it is for reactions of C–H bonds. It may also derive from the facile PT reactions available to O–H and N–H bonds. However, the intuition is also in part historical, because some PCET studies grew out of work on ET, for instance the classic studies of Cukier and Nocera [28c] and Nocera et al. [33] probing the influence of hydrogen bonding on ET. The history is evident in the name for the mechanism, *proton-coupled electron transfer*. Since the proton is the heavier, slower moving particle, it might have been more appropriate to call such reactions *electron-coupled proton transfer*.

This is the intuition that Jerry was bucking, in suggesting that tyrosine oxidation of the manganese oxygen-evolving complex occurs by PCET rather than by a stepwise pathway. This and similar issues in PS II and cytochrome *c* oxidase are still being debated (cf., Ref. [5] and other articles in this issue). On the reductive side of the bacterial photosystem PS I, Graige et al. [1c] have shown that reduction of the quinones most likely takes place by a stepwise rather than a PCET path. Stepwise paths are most commonly invoked in the catalase reaction and in superoxide dismutation. However, PCET has been indicated for reduction of O_2^-/HO_2 to H_2O_2 by manganese(II)-aquo species [34]. Ascorbate (vitamin C) has traditionally been viewed as reacting by a series of PT and ET steps, but Njus and Kelley [35] have shown, through thermochemical arguments analogous to those above, that many ascorbate reactions must occur by concerted PCET. One example is ascorbate reduction of the tocopherol (vitamin E) radical, which occurs too fast to be via an uphill electron transfer [35a]. Oxidation of ascorbate by cytochrome b_{561} apparently occurs by PCET, with proton transfer to an essential histidine residue concomitant to electron transfer to the heme [35b–e]. The antioxidant action of vitamin E is in general viewed as concerted HAT [36].

5.2. Stepwise vs. concerted mechanisms based on intrinsic barriers

Understanding whether reactions will occur by stepwise vs. concerted paths requires knowledge of the thermochemistry and the intrinsic barriers. To determine relative intrinsic

barriers, we have examined the ET and PCET self-exchange reactions of iron complexes shown in Eqs. (8) and (9) [16,37]. H_2L is biimidazoline (H_2bim) or tetrahydrobipyrimidine (H_2bip), and the asterisk in the equations simply identifies the different iron centers.

electron self exchange :

$$Fe^{III}(H_2L) + {}^*Fe^{II}(H_2L) \rightleftarrows Fe^{II}(H_2L) + {}^*Fe^{III}(H_2L) \quad (8)$$

PCET self exchange :

$$Fe^{III}(HL) + {}^*Fe^{II}(H_2L) \rightleftarrows Fe^{II}(H_2L) + {}^*Fe^{III}(HL) \quad (9)$$

As noted above, the rate constants for such self-exchange processes are direct measures of the intrinsic barriers ($\lambda = 4\,\Delta G^{\ddagger}_{o}$ at $\Delta G^{\circ} = 0$, ignoring work terms and non-adiabaticity). We find that the rate constants are quite similar for ET and PCET self-exchange, with ET being a factor of 3 greater for the H_2bim compounds and a factor of 10 greater for the H_2bip analogues (differences of less than 1.5 kcal mol^{-1} in $\Delta G^{\ddagger}_{o}$). The similarity of the intrinsic barriers is apparently due to the balancing of two effects [16,38]. It appears to be inherently more difficult to concurrently move two particles, e^- and H^+, rather than just an electron. In the classical picture, the inner-sphere reorganization for PCET requires stretching the X–H bond in addition to the normal ET reorganization [16]. In the quantum treatments involving both proton and electron tunneling, there are two tunneling probabilities that are less than one [38]. On the other hand, PCET has a smaller outer-sphere reorganization energy than ET because there is less charge redistribution and therefore less solvent motion.

The similarity of intrinsic barriers for ET and PCET is not, however, a general result, and more work is needed to define the relationship between ET, PT, and PCET intrinsic barriers (cf., Refs. [37,39]). Our working hypothesis is that systems with large intrinsic barriers to PT will often have λ(PCET)>λ(ET). This would explain why PCET reactions are slower for C–H bonds than for O–H bonds on the basis of the intrinsically slow C–H proton transfer reactions. While it is premature to make broad generalizations, it should be emphasized that for HAT-type PCET reactions, there is no theoretical or experimental evidence to support the intuition that stepwise mechanisms (ET/PT or PT/ET) are kinetically more facile than concerted PCET pathways. In fact, when the intrinsic barriers are similar, the typical thermochemical bias toward PCET will lead to that pathway being favored.

6. Conclusions

Chemical reactions involving transfer of an electron and a proton can occur by concerted or stepwise mechanisms. These are well described by square schemes such as those in Scheme 1. The concerted or one-step mechanism corresponds to the diagonal of the square, and is termed PCET. Understanding why one mechanism is preferred over another requires knowledge of both the thermochemistry and the intrinsic barriers of all five of the individual reaction steps in the square scheme. Thermodynamically, the PCET path is usually more favorable than the stepwise mechanisms, and this thermochemical bias toward PCET can be quite large. In terms of the intrinsic barriers, there seems to be a common intuition that PCET processes will be intrinsically more difficult (higher barriers) than ET reactions. This intuition is not supported by current experimental results on HAT-type PCET reactions. In most of the cases we have examined, the intrinsic barriers for PCET and ET are similar. When the intrinsic barriers are close, the thermodynamic bias toward PCET will make that the kinetically favored mechanism.

Acknowledgements

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