# Thermochemistry of Proton-Coupled Electron Transfer Reagents and its Implications

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*Received March 8, 2010*

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## 1. Introduction

Many, if not most, redox reactions are coupled to proton transfers. This includes most common sources of chemical potential energy, from the bioenergetic processes that power cells to the fossil fuel combustion that powers cars. These proton-coupled electron transfer or PCET processes may involve multiple electrons and multiple protons, as in the $4e^-$, $4H^+$ reduction of dioxygen ($O_2$) to water (eq 1), or can involve one electron and one proton such as the formation of tyrosyl radicals from tyrosine residues (TyrOH) in enzymatic catalysis (eq 2).

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O \quad (1)$$

$$TyrOH \rightarrow TyrO^{\bullet} + e^- + H^+ \quad (2)$$

In addition, many multielectron, multiproton processes proceed in one-electron and one-proton steps. Organic reactions that proceed in one-electron steps involve radical intermediates, which play critical roles in a wide range of chemical, biological, and industrial processes. This broad and diverse class of PCET reactions are central to a great many chemical and biochemical processes, from biological catalysis and energy transduction, to bulk industrial chemical

10.1021/cr100085k 
Published on Web 10/06/2010

Jeff Warren was born in Spokane, WA in 1982. He received his Bachelor of Science Degree in Chemistry from Washington State University in 2005, at which time he joined Professor James M. Mayer's research group at the University of Washington. He earned his PhD in March, 2010 and is currently a Postdoctoral Scholar in Chemistry at Caltech under the mentorship of Harry Gray. He is currently interested in understanding biological redox reactions, especially coupled redox reactions, using a combination of small molecule and biochemical tools.

Tristan Tronic was born in Falls Church, Virginia in 1985. He received his B.S. in chemistry from the College of William and Mary in 2007, performing undergraduate research with Robert Pike. He then joined the group of James Mayer at the University of Washington, where he is currently studying redox reactions related to catalytic dioxygen/water interconversion.

James Mayer was born in New York City in 1958 and did undergraduate research at Hunter College with Edwin Abbott, and with William Klemperer while earning his A.B. at Harvard. He completed a PhD at Caltech under the direction of John Bercaw in 1982, and after two years as a Visiting Scientist at DuPont moved to the University of Washington, where he is now Alvin L. and Verla R. Kwiram Professor of Chemistry. His interests in redox chemical reactions span inorganic, bioinorganic, organometallic, and physical organic chemistry.

processes, to new approaches to solar energy conversion. PCET is therefore of broad and increasing interest, as illustrated by this issue and a number of other recent reviews.[1−3]

Proton-coupled redox reactions are by no means a new concept. The Nernst equation of 1889[4] describes how aqueous redox potentials vary with pH when protons are involved. Physical and organic chemists have been studying hydrogen atom transfer reactions of organic compounds for over a century, and a hydrogen atom is simply a proton and an electron. It has more recently been realized that these areas are connected; organic H-transfer reactions are part of a broader class of reactions in which $1H^+$ and $1e^-$ are transferred. As a result, the ubiquity of $H^+/e^-$ transfers has come to the forefront of chemistry and biology.

The first issue that needs to be addressed in any PCET process is the thermochemistry of the electron transfer, proton transfer, and PCET processes. While many aspects of PCET are of great interest, from hydrogen tunneling and isotope effects to photoinduced processes, they all rely on knowledge of the thermochemistry. The thermochemical description is essentially a map of the system, showing each of the possible reactant, intermediate and product states where the system can reside (for at least a few vibrational periods), and the energies of each of these states. Having such a map is fundamental to understanding any PCET system.

In particular, the free energies of the various species will, in large part, answer one of the central questions in any PCET process: whether the electron and proton transfer "together", in a single kinetic step, or whether the process occurs by a sequence of electron transfer (ET) and proton transfer (PT) steps. In many cases, as described below, there is a large thermochemical bias that favors moving the two particles together, in a concerted process, since this can circumvent high energy intermediates formed in elementary ET or PT steps. While ET and PT are two of the most fundamental chemical reactions, the understanding of how $H^+$ and $e^-$ transfer together is still emerging. In fact, even the concept of "transferring together" can have a number of meanings, as discussed below and in a number of the other reviews in this issue.

This review provides, to the best of our abilities, the current "best" values for the solution thermochemistry of several classes of proton-coupled redox cofactors. Many of these PCET species are either involved in, or have been used to understand, key chemical and biochemical reactions. These thermochemical data can be used, as illustrated below, to analyze the mechanisms of specific $H^+/e^-$ transfer reactions using common "square schemes". Analogous thermochemical data are available for some biochemical small molecules, allowing us to illustrate that the same approach can be used to analyze biochemical transformations. We begin with a discussion of definitions and thermochemical background.

## 2. Scope and Definitions

This review tabulates and analyzes the thermochemical properties of reagents that transfer electrons and protons. Our focus is on processes involving $1e^-$ and $1H^+$, and connecting this proton/electron perspective with hydrogen atom transfers and X−H homolytic bond strengths. We do not deal extensively here with processes involving multiple electron and/or proton transfers and heterolytic bond strengths, such

as hydride ($2e^-/1H^+$) transfers, although the same type of analysis can be applied. A recent and elegant example can be found in the work of DuBois et al. using of the thermochemistry of $H^-$, $H^\bullet$, $H^+$, and $e^-$ transfers to develop new transition metal-hydride catalytic processes.[5]

These $H^+/e^-$ transfer processes all fall under the general term "proton-coupled electron transfer" or PCET. This term has come to encompass any redox process where the rate or energetics are affected by one or more protons, including processes in which protons and electrons transfer among one or more reactants, by concerted or stepwise mechanisms, and processes in which protons modulate ET processes even if they do not transfer.[6] This very broad definition is not what Meyer and co-workers intended when they coined the term in 1981,[7] and many current researchers in the field use 'PCET' to mean something more specific. However, examination of the large literature citing PCET—over 200 papers from 2006 to 2009[8]—shows that the broad usage has taken hold. Therefore in our view, PCET can no longer be used to refer to a single reaction class, and the mechanistic implications of this term have often been diluted. Thus, we support the broad use of PCET given above. We note that Meyer and Costentin have also recently emphasized this broad definition of PCET.[1,3]

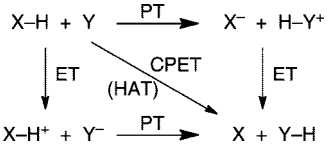
Because PCET has been used to describe many different redox reactions, researchers have coined new and more specific terms, which has led to some confusion in this area. The variety of nomenclature, while unfortunate, reflects the surge of interest in the field by workers from quite different disciplines, and the variety of PCET phenomena that have been investigated.

## 2.1. Concerted Proton−Electron Transfer (CPET) vs Stepwise Pathways

As originally conceived,[7] PCET referred to reactions where a proton and electron are transferred in a single, concerted step. Since PCET has lost this mechanistic connotation, Savéant and co-workers have proposed a new term, concerted proton−electron transfer (CPET), that makes the mechanistic implication explicit.[9] We support using this term to refer to any chemical reaction where one $H^+$ and one $e^-$ are transferred in a single kinetic step. CPET is equivalent to the CEP term (concerted electron/proton) used by Hammarström and co-workers,[10] and the EPT moniker (electron/proton transfer) used by Meyer et al.[1a] CPET (/CEP/EPT) processes contrast with stepwise processes involving either initial ET followed by PT, or PT followed by ET, as shown in Scheme 1. In this and the other schemes in this review, proton transfer processes are horizontal lines, ET processes are vertical lines, and processes that involve protons and electrons are diagonal lines. Readers should be aware that other workers have chosen other representations that better illustrate their particular concerns (cf., ref 5).

The stepwise pathways in Scheme 1 for $1H^+/1e^-$ transfer reactions are proton transfer followed by electron transfer (PT−ET) and ET−PT. Many examples of PT−ET, ET−PT, and concerted reactions are known. For instance, the groups

**Scheme 1. Concerted vs. Stepwise Transfer of $e^- + H^+$**



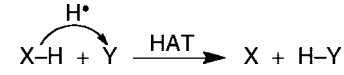

of Ingold and Foti have shown that acidic phenols can react by a PT−ET type mechanism termed sequential proton-loss electron transfer or SPLET (adding to the list of acronyms).[11−13] Hammarström et al. have shown that the aqueous ruthenium−tyrosine complexes can undergo ET−PT, CPET, or PT−ET processes depending on the pH.[10,14] ET−PT pathways are particularly well documented in the electrochemical literature, where they are a type of EC mechanism (electrochemical then chemical).[15] The factors that determine which path is followed are discussed in section 6.

## 2.2. Hydrogen Atom Transfer

Hydrogen atom transfer (HAT) has been studied by physical and organic chemists for over a century.[16] It is key to the rate and selectivity of a variety of free radical reactions, including radical chains as in autoxidation and combustion. The abstraction of $H^\bullet$ from organic compounds by peroxyl radicals has been especially widely discussed and researched because they are important to disease states, aging and food preservation.[17]

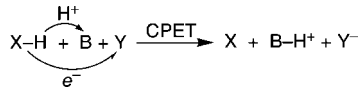
In the older physical−organic literature there was no need to define HAT, as it was self-evident that this referred to reactions involving concerted transfer of $H^\bullet$ from a donor (XH) to an acceptor (Y, Scheme 2).[18] We will use this definition here, noting that "concerted" implies a single kinetic step for transfer of the two particles but does not necessarily imply synchronous transfer. By this definition, HAT is one class of CPET reactions.

**Scheme 2. Hydrogen Atom Transfer**




In the last 25 years, it has been recognized that transition metal coordination complexes and metalloenzymes can undergo HAT reactions, and that there is overlap between traditional HAT reactions and PCET. This has led to the appearance of a number of new definitions and new thinking about HAT.[19−22] For instance, computationally there is a clear orbital distinction between degenerate $H^\bullet$ exchange between toluene and benzyl radical, versus exchange between phenol and phenoxyl radical.[19] In toluene, the $H^+$ and $e^-$ start in the same bond and end in the same bond. In the phenol/phenoxyl reaction, however, the proton is in the molecular plane but the transferring electron is in an orthogonal $\pi$ symmetry orbital.[19] To deal with such distinctions, Meyer et al. have proposed to restrict HAT to reactions where "the transferring electron and proton come from the same bond."[1,20] This contrasts with his earlier definition that "the term 'H-atom transfer' refers to what is transferred between reactants in the net sense and not to the mechanism of the event."[18] However, the restrictive definition is problematic in many cases. For instance, often the two particles come from the same bond but are not in the same bond in the product. One example is hydrogen atom abstraction from C−H bonds by compound I in cytochrome P450 enzymes, where the proton transfers from carbon to the oxygen of the ferryl (Fe=O) group but the electron is transferred to the porphyrin radical cation.[23] Under the restrictive "same bond" definition the reaction would be HAT in the forward direction but not in the reverse, which is a problem. Furthermore, it is often difficult to determine whether the electron and proton are "in the same bond." In removing $H^\bullet$ from phenols, for example, the $e^-$ and $H^+$ are in the same bond when the O−H

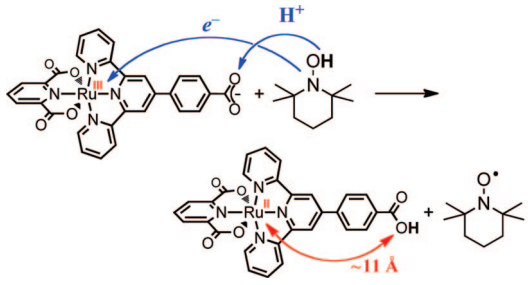
**Scheme 3. Concerted Proton-Electron Transfer That Is Not HAT**




bond lies in a plane perpendicular to the aromatic ring, but they are not in the same bond when the O−H lies in the plane of the aromatic ring. In phenol itself the hydrogen is in the plane, but how would reactions of the common 2,6-di-*tert*-butyl-substituted phenols be classified? Similarly, classification of H• removal from the vanadyl hydroxide complex $[(bpy)_2V^{IV}(O)(OH)]^+$ would depend on the O≡V−O−H torsion angle.[24] In the minimum energy structure, the O−H bond is calculated to have a torsion angle of 45° versus the orbital with the transferring electron, which precludes conclusions about "being in the same bond". To avoid these confusions, we prefer the definition implied in Scheme 2, that hydrogen atom transfer indicates concerted transfer of $H^+$ and $e^-$ from a single donor to a single acceptor.

## 2.3. Separated CPET

There are also concerted transfers of $1e^- + 1H^+$ in which the proton and electron transfer to (or from) different reagents. In Scheme 3, for instance, XH is oxidized with the electron being transferred to oxidant Y while the proton is transferred to base B. One of the more widely discussed biological examples is the photosynthetic oxidation of tyrosine-Z where an electron is transferred to the oxidized chlorophyll $P680^{\bullet+}$ as the phenolic proton is thought to transfer to a nearby H-bonded histidine residue.[25] Babcock's discussion of the thermochemistry of this process is a landmark in the development of biological PCET chemistry.[26] Such "separated CPET" reactions are clearly distinct from HAT reactions. These have also been termed "multisite EPT".[1a] However, there are an increasing number of reactions that fall in a gray area between HAT and separated CPET, such as the reaction in eq 3.[27] This reaction involves concerted transfer of $e^-$ and $H^+$ (H•) from the O−H bond of the hydroxylamine TEMPOH to a ruthenium(III) complex, so this reaction could formally be called HAT. From another perspective, however, the proton is transferred to a carboxylate oxygen that is 11 Å removed from the ruthenium center that accepts the electron, and there is essentially no communication between these sites,[27] so in some ways this is better described as a separated CPET process.

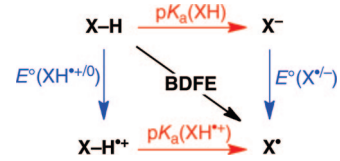



(3)

# 3. Thermochemical Background

The thermochemistry of a $1H^+/1e^-$ PCET reagent XH in a given solvent is described by five parameters, as shown in Scheme 4. These are the acidity/basicity of the oxidized and reduced forms, given by the $pK_a$s of $XH^{\bullet+}/X^\bullet$ and $XH/X^-$ pairs; the reduction potentials of the protonated and deprotonated substrate, $E°[XH^{\bullet+}/XH]$ and $E°[X^\bullet/X^-]$; and the homolytic bond dissociation free energy, the BDFE (see below). All of these parameters are free energies, and it is simple to convert them all into the same units (eqs 4 and 5, where $R$ is the gas constant, $T$ is the temperature, and $F$ is the Faraday constant). The $E°$ is a free energy for the chemical reaction that is the sum of the half reaction of interest, such as $X^\bullet + e^- \rightarrow X^-$, and the half reaction for the standard redox couple (NHE for aqueous values). For a reaction such as $HX + Y \rightarrow X + HY$, the $pK_a$ and $E°$ values for the HX and HY systems determine the free energies of PT, ET, and H• transfer steps.

**Scheme 4. Thermochemical Square Scheme for a PCET Reagent**




$$\Delta G°_{PT} = -RT\ln(K_a) = 2.303RT(pK_a)$$
$$= -(1.37\ \text{kcal mol}^{-1})pK_a = -(5.73\ \text{kJ mol}^{-1})pK_a\ (\text{at } 298\ \text{K}) \quad (4)$$

$$\Delta G°_{ET} = -FE° = -(23.06\ \text{kcal mol}^{-1}\ \text{V}^{-1})E° = -(96.48\ \text{kJ mol}^{-1}\ \text{V}^{-1})E° \quad (5)$$

The $pK_a$ values in many cases can be determined by titration either versus pH (in aqueous media) or versus a standard acid or base (in organic solvents). As discussed below in more detail, there are extensive acid/base data available in organic solvents from the work of Izutsu,[28] Bordwell,[29] and Kütt and others.[30] The redox potentials are typically determined electrochemically. The average of the anodic and cathodic peaks in the cyclic voltammogram, $E_{1/2}$, is typically used as a good measure of the thermodynamic potential $E°$.[31] Parenthetically, we note that it is strongly preferred to reference nonaqueous potentials to the ferrocene ($Cp_2Fe^{+/0}$) couple.[32] Aqueous potentials are referenced to the normal hydrogen (NHE) in this review. Useful conversions between common electrochemical references are available for acetonitrile[33] and water[34] and potentials of $Cp_2Fe^{+/0}$ in organic solvents versus aqueous NHE have been reviewed.[35]

The thermodynamic parameters $E°$ and $pK_a$, if they are to be used in the same scheme or equation, should be determined under conditions that are as similar as possible. For instance, if the electrochemical data are determined using solutions containing supporting electrolyte (as is typical), then the $pK_a$ values should ideally be determined in the presence of the same electrolyte. Because the data tabulated below often come from different sources and different types of measurements, this requirement for similar conditions is not always met, which introduces some (usually relatively small) uncertainty into any composite values. A valuable check on the consistency of the data can be obtained using Hess' law, which states that the energy change is independent of path, and that the energy change around any closed cycle is zero. This means that there are actually only three independent parameters in Scheme 4. It also implies, perhaps counterintuitively, that in free energy terms the change in the $pK_a$ values upon oxidation is identical to the change in redox potential upon deprotonation (eq 6).

$$2.303RT[pK_a(XH^{\bullet+}) - pK_a(XH)] = F[E^\circ(X^{\bullet/-}) - E^\circ(XH^{\bullet+/0})] \quad (6)$$

## 3.1. X−H Bond Dissociation Free Energies

HAT reactions have historically been analyzed using the Bell−Evans−Polyani relation,[36] which uses bond dissociation *enthalpies* (BDEs, which are not exactly the same as bond dissociation energies[37]). It is, however, more appropriate to use bond dissociation *free energies* (BDFEs) because all modern theories of ET, PT, and CPET use free energies rather than enthalpies. Our group has shown, for an iron system where the BDE and BDFE are quite different, that CPET reactivity correlates with the free energy and not the enthalpy.[38,39] The use of BDFEs rather than BDEs is especially important for transition metal complexes because they can have large entropic contributions to the driving force for a PCET reaction.[39,40]

One of the goals of this review is to encourage the use of solution BDFEs because these directly connect with the free energy of reaction which is the correct driving force. We discourage the (common) use of reduction potentials to describe PCET reagents because the $E^\circ$ or $E_{1/2}$ value does not indicate the proton stoichiometry. As noted above, a reduction potential is the free energy for a particular process and it is strictly speaking meaningful only when the stoichiometry of that process is well-defined.

This review tabulates both solution BDFEs and BDEs. Most of the BDFEs are determined from known p$K_a$ and $E^\circ$ following methods developed by Bordwell[41] for organic compounds and later extended by Parker and Wayner[42] and by Tilset[43] (eq 7). The methods are essentially identical, but Bordwell's method focuses more explicitly on BDEs, while Tilset's derivation perhaps more clearly distinguishes between BDEs and BDFEs. Bordwell and co-workers were the first to popularize this approach and apply it to a range of compounds. They provide valuable discussion of the assumptions and potential errors involved,[41] which were later analyzed in more detail by Parker and Tilset[44] and others.[45] It should also be noted that there are examples of the use of p$K_a$ and $E^\circ$ values to derive bond strengths prior to Bordwell's broad use, including work by Breslow as early as 1969[46] and by Wiberg in 1961.[47] Similar thermochemical cycles have also been used in gas-phase thermochemical studies for some time.[37]

This approach to calculating BDFEs uses Hess' Law and the p$K_a$ and $E^\circ$ values on adjacent sides of a square scheme (Scheme 4, eqs 4 and 5). Essentially the same equation can be used for BDEs, with a constant denoted $C_H$ (but see the comments in the next paragraph). The constants $C_G$ and $C_H$ were derived explicitly as described by Tilset,[43] and a similar derivation was given earlier by Parker.[48] A number of slightly different values of $C_H$ can be found in the literature, depending on the assumptions and values used in the derivation.[41−44] The differences between these values are typically smaller than the estimated uncertainties in the bond strengths derived from this analysis, as briefly discussed in section 4.1 below.

$C_G$ in a given solvent is equivalent to the $H^+/H^\bullet$ standard reduction potential in that solvent (see section 5.8.3). Following Tilset,[43] $C_G$ includes the free energy for formation of $H^\bullet$ ($\Delta G_f^\circ(H^\bullet_g) = 48.59$ kcal mol$^{-1}$),[49] the free energy of solvation of $H^\bullet$ ($\Delta G_{solv}^\circ(H^\bullet)$), as well as the nature of the reference electrode. In Parker's early analysis,[48] $\Delta G_{solv}^\circ(H^\bullet)$ was approximated using solvation energies of the noble gases. Roduner has now shown that the solvation of $H^\bullet$ is better approximated as that of $H_2$.[50] On that basis, we have calculated revised values for $C_G$ in several different solvents (Table 1),[39,51] using known values of $\Delta G_{solv}^\circ(H_2)$.[52−54] The values for $C_G$ and $C_H$ in water in Table 1 are also different from those reported previously because we have corrected the standard state for $\Delta G_{solv}^\circ(H^\bullet)$ ($\approx\Delta G_{solv}^\circ(H_2)$) from 1 atm to 1 M.[55] These $C_G$ and $C_H$ values are, to the best of our abilities, the most accurate available, and they have been confirmed by comparison with BDEs and BDFEs derived from other methods such as equilibration or calorimetry. Readers should note that the constants in Table 1 in organic solvents are for redox potentials referenced to $Cp_2Fe^{+/0}$, because we feel that these are more directly useful than those given previously vs the standard hydrogen electrode.[43]

**Table 1. Summary of Constants $C_G$ and $C_H$ in Common Solvents**[a]

| solvent | $C_G$ | $T(\Delta S^\circ)_{solv}$[b] | $C_H$ | electrochemical reference |
|---|---|---|---|---|
| acetonitrile | 54.9 | 4.62 | 59.4 | $Cp_2Fe^{+/0}$ |
| DMSO | 71.1 | 4.60 | 75.7 | $Cp_2Fe^{+/0}$ |
| DMF | 69.7 | 4.56 | 74.3 | $Cp_2Fe^{+/0}$ |
| methanol | 65.3 | 3.81 | 69.1 | $Cp_2Fe^{+/0}$ |
| water | 57.6 | −1.80 | 55.8 | normal hydrogen |

[a] Values in kcal mol$^{-1}$ at 298 K from references.[39,51] [b] $T(\Delta S^\circ)_{solv} = T(S^\circ(H^\bullet)_g + \Delta S_{solvation}^\circ(H_2)_{solv})$.

$$BDFE_{sol}(X-H) = 1.37pK_a + 23.06E^\circ + C_{G,sol} \quad (7)$$

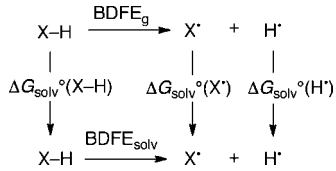
The calculation of bond dissociation *enthalpies* from free energy measurements (p$K_a$ and $E^\circ$) is accurate *only* when there are no significant entropic effects. Specifically, this analysis requires that the entropies of HX and $X^\bullet$ are essentially equal [$S^\circ(HX)_{solv} = S^\circ(X^\bullet)_{solv}$].[39−43] This issue was discussed early on by Bordwell, Parker, and Tilset,[41−43] and entropic contributions were found to be small for the organic and organometallic systems they studied.[37,39−43] With the assumption that $S^\circ(HX)_{solv} = S^\circ(X^\bullet)_{solv}$, the solution BDE can be calculated from p$K_a$ and $E^\circ$ values or from the $BDFE_{sol}$ (eqs 8, 9), with the constant $C_H$ given by $C_G - T\Delta S^\circ(H^\bullet)_{solv}$. Recently, however, it has been shown that $S^\circ(HX)_{solv}$ and $S^\circ(X^\bullet)_{solv}$ can be very different when the compounds contain high-spin transition metal ions.[39,40] For such species, BDEs cannot be determined from p$K_a$ and $E^\circ$ values.

$$\text{Assuming } S^\circ_{sol}(HX) = S^\circ_{sol}(X^\bullet), \text{ then}$$
$$BDE_{sol}(X-H) = 1.37pK_a + 23.06E^\circ + C_{H,sol} \quad (8)$$

$$BDE_{sol}(X-H) = BDFE_{sol}(X-H) + (C_{H,sol} - C_{G,sol}) \quad (9)$$

Equations 7 and 8 use the thermochemical standard potentials $E^\circ$ which are typically very close to the $E_{1/2}$ values measured by cyclic voltammetry. Bordwell has also shown that useful values can also often be obtained using electrochemical peak potentials from irreversible cyclic voltammograms.[41] However, this introduces an additional uncertainty into the derived values (see section 4.1). In the thermochemical tables below, it is explicitly noted when the

**Scheme 5. Relationship between Gas-Phase and Solution Bond Dissociation Free Energies**




BDFE or BDE value has been derived using an irreversible peak potential.

A more direct way to determine a BDFE is by equilibration with a standard reagent, for instance, measurement of $K_{eq}$ for XH + 2,4,6-$^t$Bu$_3$ArO$^•$ ⇄ X$^•$ + 2,4,6-$^t$Bu$_3$ArOH. $RT\ln(K_{eq})$ is then the difference between the BDFEs of XH and the standard reagent. This approach works very well for stable species such as aminoxyl radicals (section 5.1) and transition metal complexes (section 5.10), or for reactions of transients that reach equilibrium faster than they decay. Pedulli and co-workers, for instance, have used this approach to measure the bond strengths in a variety of phenols.[56] Kreevoy et al. used equilibration to measure the relative hydride affinities of $NAD^+$ analogues (a type of heterolytic bond strength).[57]

### 3.1.1. Solution Versus Gas-Phase Bond Strengths

CPET reactivity in solution should be analyzed with solution BDFEs, but common tabulations of bond strengths are gas-phase BDEs (as in many organic chemistry textbooks[58]). A very extensive tabulation of such BDEs can be found in the recent book by Luo.[59] Gas phase BDEs are related to gas phase BDFEs by eq 10, using $S°_g(H^•) = 27.42$ cal K$^{-1}$ mol$^{-1}$.[49] As noted above, for small molecules and organic molecules, $S°(X^•) \cong S°(XH)$ because the species are roughly the same size and structure.[37,40] For instance, $\{S°_g(HO^•) - S°_g(H_2O)\} = -1.2$ cal mol$^{-1}$ K$^{-1}$,[49,60] and $\{S°_g(PhO^•) - S°_g(PhOH)\} = -0.8$ cal mol$^{-1}$ K$^{-1}$,[61] so in both cases the magnitude of the $T\{S°(X^•) - S°(XH)\}$ term is <0.4 kcal mol$^{-1}$. Note that when $S°(X^•) = S°(XH)$, BDFE$_g$(XH) is 8.17 kcal mol$^{-1}$ less than the corresponding BDE$_g$(XH).

$$\mathrm{BDFE_g(XH)} = \mathrm{BDE_g(XH)} - TS°(H^•) - T\{S°(X^•) - S°(XH)\} \quad (10)$$

Gas-phase BDFEs are related to solution BDFEs as shown in Scheme 5 and eq 11. Determining the solution BDFE from the gas phase value requires (i) the free energy of solvation of H$^•$ and (ii) the *difference* in the solvation free energies of X$^•$ and XH. $\Delta G_{solv}°(H^•)$ is approximated as that of $H_2$ (see above).

$$\mathrm{BDFE_{solv}(XH)} = \mathrm{BDFE_g(XH)} + \Delta G_{solv}°(H^•) + \Delta G_{solv}°(X^•) - \Delta G_{solv}°(XH) \quad (11)$$

For hydrocarbons and other relatively nonpolar substrates, the free energies of solvation of X$^•$ and XH are close because the closed shell and radical species are approximately the same size and have the same charge. For this situation, $\Delta G_{solv}°(XH) = \Delta G_{solv}°(X^•)$, the difference between the solution and gas phase BDFEs is $\Delta G_{solv}°(H^•)$ which is $\cong \Delta G_{solv}°(H_2)$ (see above). This is, for example, 5.12 kcal mol$^{-1}$ in MeCN.[52] For substrates with one H-bond donating/accepting group such as phenol, $[\Delta G_{solv}°(X^•) - \Delta G_{solv}°(XH)]$ can be approximated as the difference in solvation of the hydroxyl/oxyl moiety. Following Ingold,[62] this difference in solvation can be accurately estimated using Abraham's empirical hydrogen bonding model.[63−65] This model relates the hydrogen bond acidity ($\alpha_2^H$) and the hydrogen bond basicity ($\beta_2^H$) to the strength of a hydrogen bond (eq 12). Its application to estimate $[\Delta G_{solv}°(R^•) - \Delta G_{solv}°(RH)]$ is given in eq 13. We have shown that this procedure gives accurate solution BDFEs for several monohydroxylic substrates in several solvents.[66] However, given the approximations involved, this method should only be used when the relevant thermochemical data for the solvent of interest are not available. This method has been used sparingly in the Tables below and any BDFE estimated in this fashion is given in (parentheses).

$$\Delta G°_{HB} = -10.02\alpha_2^H\beta_2^H + 1.492 \quad (12)$$

$$\Delta G_{solv}°(R^•) - \Delta G_{solv}°(RH) = -10.02\alpha_2^H(solv)\beta_2^H(RO^•) + 10.02\alpha_2^H(ROH)\beta_2^H(solv) \quad (13)$$

## 3.2. PCET Thermochemistry in Aqueous Solutions

In aqueous solution, proton transfer is extremely rapid and electrochemical measurements often give reduction potentials for half reactions including any proton addition or loss. The potential for a half reaction as a function of pH is given by the Nernst equation (eq 14). The Nernst factor RT/F is 59 mV at 298 K, so the potential of a one-electron, one-proton couple ($n = m = 1$) varies 59 mV per pH unit. For such a 1e$^-$/1H$^+$ couple, the BDFE is simply given by the potential at pH 0 by eq 15, in which the p$K_a$ is not needed because $E°(X^•/XH)$ includes the free energy of addition of the proton. For measurements at other pH's, the BDFE is given by eq 16. The 1.37(pH) term in eq 16 in effect extrapolates a 1e$^-$/1H$^+$ potential at a given pH to the standard state of pH 0.

$$\text{For:}\quad \mathrm{A} + n\mathrm{e}^- + m\mathrm{H}^+ \rightarrow \mathrm{H}_m\mathrm{A}^{(n-m)-}$$

$$E = E^0 - \frac{RT}{nF}\ln\frac{[\mathrm{H}_m\mathrm{A}^{(n-m)-}]}{[\mathrm{A}][\mathrm{H}^+]^m}$$

$$\text{or:}\quad E = E^0 - \frac{RT}{nF}\ln\frac{[H_m\mathrm{A}^{(n-m)-}]}{[\mathrm{A}]} - \frac{RT}{F}\frac{m}{n}\mathrm{pH} \quad (14)$$

For a 1e$^-$/1H$^+$ redox couple using $E°$ at pH = 0:

$$\mathrm{BDFE(XH)} = 23.06[E°(X^•/XH)] + 57.6 \text{ kcal mol}^{-1} \quad (15)$$

For a 1e$^-$/1H$^+$ redox couple using $E°$ at another pH:

$$\mathrm{BDFE(XH)} = 23.06[E_{pH}(X^•/XH)] + 1.37(pH) + 57.6 \text{ kcal mol}^{-1} \quad (16)$$

Pourbaix diagrams, which plot potential versus pH, are one form of the thermochemical map described above, and an elegant application of the Nernst equation. Pourbaix assembled a compendium of these diagrams, describing the aqueous redox chemistry of each element.[67] Figure 1 shows a recent example of a Pourbaix diagram, constructed by Llobet and co-workers for a ligated dimeric ruthenium−aquo complex from electrochemical measurements.[68] Horizontal

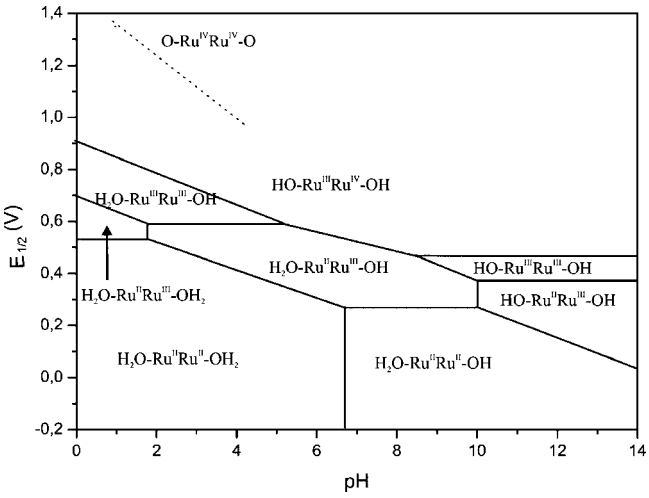



**Figure 1.** Pourbaix diagram for the *in,in*-{[$Ru^{II}$(trpy)($H_2O$)]$_2$($\mu$-bpp)}$^{3+}$ water oxidation catalyst (trpy is 2,2′:6′,2″-terpyridine, bpp is bis(2-pyridyl)-3,5-pyrazolate)). Reprinted with permission from ref 68. Copyright 2009 American Chemical Society.

and diagonal lines on the diagram indicate the potentials separating the *E*/pH regions in which the various stable species predominate. As per eq 14, the lines have the slope of *m*/*n* and therefore indicate the proton/electron stoichiometry of the electrochemical measurements. For the $1e^-/1H^+$ couples, the BDFEs can be determined directly from the Pourbaix diagram from eq 16. Vertical lines indicate the p$K_a$ values of the species to the left of the line.

## 4. Introduction to the Thermochemical Tables

The following sections present an overview of the PCET reactivity of different classes of compounds, such as phenols, hydrocarbons, or transition metal-oxo/hydroxo/aquo complexes. Each section has brief comments about the importance of PCET reactivity of this class of compounds, and then provides an overview and highlights of the data available. Each section concludes with an extensive data Table. To assist the reader looking for a PCET reagent with a particular bond dissociation free energy (BDFE), and to give an overview of the following, this section has a table with selected compounds from each class and their BDFE values (Table 2).

The tables in each of the following sections present thermochemical data for PCET reagents from ascorbate to xanthene. They give, when available, the $E°(XH^{\bullet+}/XH)$, $E°(X^{\bullet}/X^-)$, p$K_a$($XH^{\bullet+}$), p$K_a$(XH), and the solution BDFE and BDE in various solvents (cf., Scheme 4 above). All of the potentials in this review are *reduction potentials*, though arrows in the "square schemes" may appear to indicate oxidation. Unless otherwise noted, the potentials in water are $E°$ (pH 0) versus NHE, and the potentials in organic solvents are $E_{1/2}$ versus the ferrocenium/ferrocene ($Cp_2Fe^{+/0}$) redox couple. When the only redox potentials available are irreversible peak potentials from cyclic voltammetry (CV), the values are indicated by *italics* in the tables. BDFEs and BDEs derived from such irreversible peak potentials should be viewed as more uncertain than those values derived from reversible $E_{1/2}$ measurements. Irreversible peak potentials often depend on the kinetics of the step preceding or following electron transfer and therefore are not necessarily characteristic of the thermodynamics. While this is a concern, Bordwell addressed this issue in his early papers[41,69] and showed that, at least for the systems studied, the use of irreversible potentials gave BDE values in agreement with those from other sources. In some cases, such as for hydrocarbons, gas phase bond strengths are given and the "solvent" is identified as "gas."

**Table 2. Selected PCET Reagents and Their X−H Bond Dissociation Free Energies**[a]

| compound (XH) | solvent | BDFE[b] | table |
|---|---|---|---|
| TEMPOH | $H_2O$ | 71.0 | Table 3 |
| TEMPOH | DMSO | 67.5 | Table 3 |
| TEMPOH | MeCN | 66.5 | Table 3 |
| TEMPOH | $C_6H_6$ | 65.2 | Table 3 |
| PhOH | $H_2O$ | 89.5 | Table 4 |
| 2,4,6-$^t$Bu$_3$PhOH | MeCN | 77.1 | Table 4 |
| hydroquinone ($H_2Q$) | $H_2O$ | first OH: 81.5<br>average: 73.6 | Tables 5, 6 |
| ascorbate | $H_2O$ | 73.6 | Table 7 |
| MeO−H | DMSO | 102.5 | Table 8 |
| OO−H | $H_2O$ | 42.7 | Table 9 |
| HOO−H | $H_2O$ | 91.0 | Table 9 |
| $^t$BuOO−H | $H_2O$ | 91.5 | Table 10 |
| $H_2NNH$−H | $H_2O$ | 83.4 | Table 11 |
| $PhNH_2$ | MeCN | 94.1 | Table 13 |
| tryptophan | $H_2O$ | 90.6 | Table 14 |
| guanosine | $H_2O$ | 106.8 | Table 15 |
| PhS−H | DMSO | 76.9 | Table 16 |
| $C_6H_5CH_2$−H | MeCN | 87 | Table 17 |
| 9,10-dihydroanthracene | DMSO | 76.0 | Table 17 |
| NADH | $H_2O$ | 79.3 | Table 18 |
| N(2,4-$Br_2$−$C_6H_4$)$_3^{\bullet+}$ + 2,6-$Me_2$−pyridine | MeCN | 100.5 | Table 20 |
| $MnO_3(O-H)^-$ | $H_2O$ | 80.4 | Table 21 |
| [(bpy)$_2$py$Ru^{III}$O−H]$^{2+}$ | $H_2O$ | 84.8 | Table 21 |

[a] For more examples, more data, and the origin of these values, see the individual tables below. [b] BDFE values in kcal mol$^{-1}$.

We note that some of the BDEs and BDFEs shown in this review have been revised from those previously reported. This may be due to new values of the p$K_a$ or $E_{1/2}$, or more often to revision of the constants $C_G$ and $C_H$ as discussed above. A few BDFEs measured by equilibration with a standard reagent have been revised because the best BDFE value for the standard has be reevaluated. For instance, BDFEs derived from $K_{eq}$ for XH + 2,4,6-$^t$Bu$_3$ArO$^{\bullet}$ ⇆ X$^{\bullet}$ + 2,4,6-$^t$Bu$_3$ArOH may be revised to reflect the updated solution BDFE for 2,4,6-$^t$Bu$_3$ArOH. Our goal has been to assemble a consistent set of values.

Most of the earlier data are reported as BDEs, but on the basis of our recent discovery of large entropic contributions to PCET, we now encourage the use of BDFEs.[39,40] Readers are urged to pay close attention to this distinction. If only a BDE *or* a BDFE has been reported, the Tables give the other value calculated using the difference between $C_H$ and $C_G$ (eq 9). As described above, this connection of a bond dissociation *enthalpy* (BDE) with measurements of *free energies* (BDFE, $E°$, and p$K_a$) requires the assumption that

**Table 3. PCET Thermochemistry of Hydroxylamines[a]**

| compound (ROH) | solvent | $E(RO^{\bullet/-})$ | $E(ROH^{\bullet+/0})$ | $pK_a(ROH^{\bullet+})$ | $pK_a(ROH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| $H_2NOH$ | $H_2O$ | 0.09[96] | 1.3[96] | [−6.7] | 13.7[97] | 78.4 | 76.7 |
| TEMPOH | $H_2O$ | −0.175[81] | | | 12.9[98,99] | 71.0 | 69.4 |
| TEMPOH | DMSO | *−1.997*[100] | | | 31[100] | 67.5 | 72.1 |
| TEMPOH | MeCN | *−1.95*[82,101] | *0.71*[102] | [−4] | 41[b] | 66.5[c] | 70.6 |
| TEMPOH | $C_6H_6$ | | | | | 65.2[40] | 70.0[40] |
| TEMPOH | hexane | | | | | 64.7 | 69.7[83] |
| TEMPOH | EtOH | | | | | (65.4)[d] | (69)[d] |
| 4-oxo-TEMPOH | hexane | | | | | 62.5 | 67.5[83] |
| 4-oxo-TEMPOH | $CCl_4$ | | | | | 67.3 | 72.0[76] |
| 4-oxo-TEMPOH | MeCN | | | | | 65.6[74] | 70.1 |
| 4-MeO-TEMPOH | MeCN | | | | | 65.0[74] | 69.5 |
| 4-OH-TEMPOH | hexane | | | | | 66.3 | 71.3[83] |
| 4-$NH_2$-TEMPOH | hexane | | | | | 66.0 | 71.0[83] |
| 4-Cl-TEMPOH | hexane | | | | | 66.2 | 71.2[83] |
| $^tBu_2NOH$ | MeCN | [−2][b] | | | 41[100e] | 65.2[74] | 69.7 |
| $^tBu_2NOH$ | DMSO | *−2.070*[100] | | | 31.3[100] | 66.2 | 70.8 |
| $Et_2NOH$ | DMSO | *−1.645*[100] | | | 29.6[100] | 73.7 | 78.3 |
| PhN(Bz)OH[f] | DMSO | *−1.354*[103] | | | 23.87[103] | 72.6 | 77.2 |
| *p*-$BrC_6H_4N(Bz)OH$[f] | DMSO | *−1.259*[103] | | | 22.7[103] | 73.2 | 77.8 |
| *p*-$NCC_6H_4N(Bz)OH$[f] | DMSO | *−0.976*[103] | | | 19.4[103] | 75.2 | 79.8 |
| *c*-$C_5H_{10}NOH$ | DMSO | *−1.610*[103] | | | 26.93[103] | 70.9 | 75.5 |
| NHPI | $H_2O$ | [1] | | | 6.3[88] | 88.8[104] | 87.0 |
| NHPI | DMSO | ≤*−0.079*[105 g] | | | 12.9[88] | ≤87[g] | ≤92[g] |
| NHPI | $^t$BuOH | | | | | 83.3 | 88.1[94] |
| NHPI | MeCN | −0.1[h] | *1.2*[90] | [1.4] | 23.5[88 e] | 84.8 | 89.3 |
| NHPI | $C_6H_6$ | | | | | (83.8) | (88.6) |
| 4-AcO-NHPI | MeCN | | | | | 85.6 | 90.1[i] |
| 3-F-NHPI | MeCN | | | | | 85.3 | 89.8[i] |
| 4-Me-NHPI | MeCN | | | | | 84.9 | 89.4[i] |
| 4-MeO-NHPI | MeCN | | | | | 84.0 | 88.5[i] |
| 3-MeO-NHPI | MeCN | | | | | 84.6 | 89.1[i] |
| 3,6-$(MeO)_2$-NHPI | MeCN | | | | | 83.8 | 88.3[i] |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. $E°$ and $pK_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6, 7). *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. BDFE and BDE in kcal mol$^{-1}$; when neither has a reference the BDFE has been calculated from $E$ and $pK_a$ values (eqs 7, 15, and 16); when one of these has a reference, the other has been calculated from it using eq 9. BDE or BDFE values in (parentheses) have been estimated from a value in another solvent using the Abraham model (eq 13). [b] Estimated in ref 40. [c] The $E$ and $pK_a$ data yield BDFE(TEMPOH) = 66.1 kcal mol$^{-1}$, slightly lower than the preferred value from our recent critical evaluation of BDFE(TEMPOH) in MeCN.[40] [d] Estimated from the value in $C_6H_6$ using Abraham's model. [e] Extrapolated from DMSO to MeCN using the method of Kütt and co-workers.[89] [f] Bz = benzyl ($-CH_2C_6H_5$). [g] Ref 105 states that the CV of deprotonated NHPI in DMSO shows an odd concentration dependence and that the true $E°$ may be lower than the given value, so the BDFE is also an upper limit. [h] Estimated from MeCN electrochemical data with added pyridine bases; see text.[90−93] [i] Determined at −10 °C in MeCN with respect to NHPI in ref 95. Modified relative to our value for $BDE_{MeCN}$(NHPI). The corresponding BDFEs are obtained using eq 9.

the entropies of HX and X$^\bullet$ are equal (eqs 8 and 9). Because this assumption does not hold well for some transition metal complexes, the calculation of BDEs in this fashion has not been done in Table 21, below. In some cases, a BDFE in one solvent has been estimated from a BDFE in a different solvent, using the Abraham model (eq 13); in these cases the BDFE is given in parentheses.

## 4.1. Estimated Errors

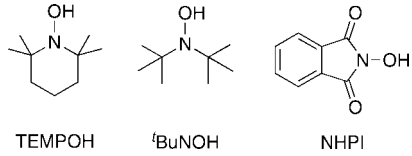
The thermochemical data given here come from a wide variety of sources and are derived from a variety of different measurements. It is beyond the scope of this review to provide error analyses for each value presented (particularly in light of the occurrence of systematic errors that have at times affected measurements of BDEs[70]). Instead, we roughly estimate that typical uncertainties in the solution BDFE values given in this review of ±2 kcal mol$^{-1}$. Accuracies may be better for well-studied, small molecules, particularly in their gas-phase bond dissociation enthalpies. For BDFEs derived from $pK_a$ and $E_{1/2}$ measurements (eq 7 above), our error estimate is based on typical uncertainties in these values, and the uncertainties in the $C_G$ constant. Relative values may be more accurate, as the uncertainty in $C_G$ is eliminated. Bordwell estimated somewhat larger errors (≤ ±3 kcal mol$^{-1}$) when irreversible peak potentials are used.[41] In some cases, these estimated accuracies may be optimistic. We encourage the interested reader to examine the primary literature. All of the bond strengths are reported here to one decimal place to eliminate ambiguity due to rounding.

# 5. Thermochemistry of PCET Reagents

## 5.1. Hydroxylamines

Hydroxylamines and their $1e^-/1H^+$ oxidized partners, aminoxyl radicals, also known as nitroxyl radicals or nitroxides,[71] have received considerable attention in the past 20 years.[72] Thermochemical data for proton, electron, and H$^\bullet$ transfers from hydroxylamines are given in Table 3. This section is focused on three of the most well studied hydroxylamine/aminoxyl radical pairs: 2,2′-6,6′-tetramethylpiperidine-1-ol (TEMPOH), *N,N*-di-*tert*-butylhydroxylamine ($^tBu_2NOH$) and *N*-hydroxyphthalimide (NHPI) (Scheme 6).

**Scheme 6. Hydroxylamines**




### 5.1.1. TEMPO(H) and $^tBu_2NO(H)$

The 2,2′-6,6′-tetramethypiperidine-1-oxyl radical, TEMPO, and related derivatives have been widely used as spin labels, spin traps, MRI contrast agents, free radical polymerization promoters, and 'green' oxidation catalysts.[73] The radicals are typically air-stable, isolable, and commercially available (while the hydroxylamine 2,2′-6,6′-tetramethypiperidine-1-ol, TEMPOH, is reactive with air). The TEMPO/TEMPOH and related redox couples are particularly valuable for PCET studies because of the their low O−H bond strengths, and their strong thermochemical bias toward concerted H• transfer reactions (as discussed in greater detail below). HAT pseudo self-exchange reactions of TEMPO and related alkyl aminoxyl radicals have been found to involve significant hydrogen tunneling (as do some cross reactions), in contrast to the related reactions of aryl aminoxyl radicals.[74,75]

The BDFE and BDE of TEMPOH will serve as benchmarks for some of the following discussion. We have recently critically evaluated the BDE and BDFE of TEMPOH in MeCN and $C_6H_6$ solvents, using both reported calorimetric measurements[76] and $E°$ and $pK_a$ data (Table 3).[40] The calorimetric measurements, for diphenylhydrazine +2 TEMPO → azobenzene +2 TEMPOH, were reinterpreted using the recently revised heat of formation of azobenzene.[77]

The other noteworthy redox reaction of TEMPO is its oxidation to the corresponding nitrosonium cation. The nitrosonium cation has received attention for its superoxide dismutase-type reactivity[78] and catalytic alcohol oxidations,[79] both of which can be described as PCET processes. In water, $E°(TEMPO^{•/+}) = 0.74$ V (vs NHE),[80,81] and in MeCN, $E°(TEMPO^{•/+}) = 0.61$ V[82] (vs SCE; better: 0.24 V vs $Cp_2Fe^{+/0}$ [33]).

Several 4-substituted derivatives of TEMPO have been investigated, including 4-oxo-, 4-methoxy-, 4-amino-, and 4-hydroxy-TEMPO. Bond strengths for these and other aminoxyls in hexane have been reported by Malievskii et al. from kinetic and equilibrium measurements,[83] but little acidity or redox potential data are available for these other TEMPO derivatives.

As noted above, the TEMPO(•/H) $1H^+/1e^-$ couple is an excellent example of a PCET reagent that favors concerted H• transfer over stepwise ET-PT or PT-ET pathways. TEMPOH ($pK_a = 41$ in MeCN) is a very poor acid and TEMPO ($pK_a \approx -4$) is a poor base. Likewise, it is difficult to oxidize TEMPOH to $TEMPOH^{•+}$ ($E_{p,a} = 0.71$ V vs $Cp_2Fe^{+/0}$) and quite difficult to reduce TEMPO to $TEMPO^-$ ($E_{p,c} = -1.95$ V). These data indicate that under typical conditions, $TEMPO^-$ and $TEMPOH^{•+}$, the species at the top right and bottom left of the TEMPO square scheme (see Scheme 4), are high-energy species. These same arguments also hold for other alkyl hydroxylamines, such as $^tBu_2NOH$.

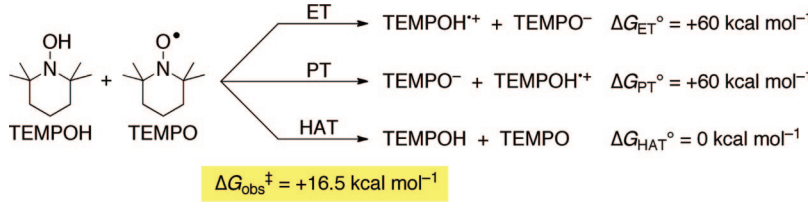
The preference for concerted transfer of H• in reactions of TEMPO and TEMPOH can be illustrated by examining the energetics for the different pathways for the TEMPOH + TEMPO self-exchange reaction (Scheme 7). HAT from TEMPOH to TEMPO has $\Delta G° = 0$ because it is a degenerate process. In MeCN, initial PT from TEMPOH to TEMPO gives $TEMPO^-$ + $TEMPOH^{•+}$. This reaction has an equilibrium constant of $10^{-45}$ based on the $pK_a$s of 41 and ∼−4, respectively (Table 3), indicating a very unfavorable free energy, $\Delta G°_{PT} \approx +60$ kcal mol$^{-1}$. Initial ET from TEMPOH to TEMPO is uphill by the same amount (∼2.7 V from the redox potentials). Note that for the unique case of a self-exchange reaction XH + X, these two values must be the same, because initial PT and ET both make the same intermediate state, $XH^+ + X^-$.[84] Thus, there is a very large (60 kcal mol$^{-1}$) bias favoring concerted transfer of $e^-$ and $H^+$. The self-exchange reaction occurs readily, proceeding on the stopped flow time scale with an Eyring barrier $\Delta G^‡ = 16.5$ kcal mol$^{-1}$ in MeCN.[38,74] On this basis, the self-exchange cannot be proceeding through an intermediate state that is 60 kcal mol$^{-1}$ above the ground state; the two particles must transfer together. This type of thermochemical argument, probably first applied to PCET by Meyer and co-workers,[1] is quite powerful and is discussed in more detail for cross reactions in section 6.

### 5.1.2. N-hydroxyphthalimide (NHPI)/Phthalimide−N-Oxyl Radical (PINO)

The PINO radical has been broadly explored in organic free radical oxidations,[85,86] especially as a "green" alternative to the bromide cocatalyst in transition metal-catalyzed autoxidations.[87] Catalytic oxidations in PINO-containing systems are thought to proceed through a series of H-atom abstraction steps. Despite the wide attention that NHPI/PINO has received, relatively few thermochemical data are available. Koppel and co-workers have determined $pK_a$ values for NHPI in water and DMSO,[88] and the DMSO value can be used to estimate a $pK_a$ in MeCN.[89] NHPI is much more acidic than dialkyl hydroxylamines, as would be expected for a phthalimide.

There is little consensus between the published electrochemical studies of NHPI. In MeCN in the absence of base, a broad quasi-reversible oxidation is observed at +1.2 V versus $Cp_2Fe^{+/0}$.[90] Addition of pyridine bases caused a shift to much lower potentials, which was attributed to the oxidation of deprotonated NHPI (the $NHPI^{•/-}$ couple).[90−93] However, this assignment is unlikely since the pyridine bases used ($pK_a = 12-16$ in MeCN[30]) are not basic enough to deprotonate NHPI to any great extent ($pK_a = 23.5$ in MeCN; see Table 3). Furthermore, the potentials vary with the strength of the added base, with stronger bases leading to lower potentials, by roughly 59 mV per unit change in the

**Scheme 7. Thermochemical Analysis of Stepwise vs. Concerted Pathways for the TEMPO + TEMPOH Self-Exchange Reaction**



pyridine p$K_a$,[90−93] as would be expected for a PCET reaction. These data all suggest that the electrochemical process removes $1H^+$ and $1e^-$ from NHPI, not simply an electron. We estimate, based on the reported electrochemical data extrapolated to p$K_a$(NHPI) = 23.5 (59 mV per p$K_a$), $E°$(NHPI$^{\bullet/-}$) = −0.1 V and BDFE = 84.8 kcal mol$^{-1}$ in MeCN.

Lucarini, Pedulli, and co-workers have employed their EPR radical equilibration technique to determine bond strengths (BDEs) of NHPI, substituted NHPI derivatives and other related hydroxylamines.[94,95] The BDE of NHPI was determined to be 88.1 kcal mol$^{-1}$ in $^t$BuOH solvent.[94] Later, bond strengths for substituted NHPI derivatives were determined in $CH_3CN$ with respect to the parent NHPI, again using the EPR equilibration technique.[95] The reference BDE used in that study was 88.1 kcal mol$^{-1}$, the BDE of NHPI in $^t$BuOH. However, based on the $E°$ and p$K_a$ data for NHPI in MeCN, we conclude that the BDE$_{MeCN}$ of NHPI is 1.2 kcal mol$^{-1}$ higher than the corresponding BDE in $^t$BuOH. Thus, BDEs for substituted NHPI derivatives have been adjusted upward by 1.2 kcal mol$^{-1}$ such that they are relative to the BDE of NHPI in MeCN determined here. One of the great advantages of the EPR equilibration technique is that the BDEs are usually very accurate with respect to each other, so that the uncertainty in the absolute BDE is essentially only dependent upon the accuracy of the reference compound BDE.

## 5.2. Phenols, Hydroquinones, Catechols, and Ascorbate

This section presents thermochemical data for hydroxylic compounds where the OH group is attached to an unsaturated ($sp^2$) carbon. The redox chemistry of such compounds—phenols, quinones, ascorbate, etc.—has been the subject of intense interest for more than a half century. To give just a few examples, PCET reactions of these compounds are integral to biological energy production (e.g., quinone cycling in photosystems I and II and the $bc_1$ complex; tyrosine Z in photosystem II),[106−108] biosynthesis (ribonucleotide reductases),[109] antioxidant activity (tocopherols),[110,111] and food preservation (butylated hydroxytoluene).[112] The coverage in this section is not intended to be complete, but is rather focused on representative cases where there are extensive p$K_a$, $E$, and bond strength data. A reader interested in a particular substituted derivative that does not appear in Table 4 is encouraged to check the references cited there, and reference,[56] as many of the primary papers cover a range of substituents.

### 5.2.1. Phenol (PhOH)

Phenol has been widely studied as the simplest of the aromatic hydroxylic compounds. The gas-phase O−H BDE in phenol has been a subject of much discussion.[62,113,114] Heats of formation from the NIST Chemistry WebBook, $\Delta H_f°_{gas}$(PhO$^\bullet$) = 13 ± 1 kcal mol$^{-1}$ and $\Delta H_f°_{gas}$(PhOH = −23.03 ± 0.14 kcal mol$^{-1}$, give BDE$_g$(PhOH) = 88.0 ± 1 kcal mol$^{-1}$.[49,70] This value is in between alternative values of 86.7 kcal mol$^{-1}$ [114] and 88.7 kcal mol$^{-1}$.[62] A clearer value for this important benchmark compound would be valuable.

A wealth of thermochemical data is available for phenols, in particular their acidity [p$K_a$(ArOH)] and the phenoxyl radical/phenoxide reduction potential [$E°$(ArO$^{\bullet/-}$)]. Protonated phenoxyl radicals are typically high energy species with aqueous p$K_a$ values >0.[115] The most extensive studies of $E°$(ArO$^{\bullet/-}$) are by Bordwell et al. for DMSO solutions[116] and by Lind et al. and Steenken and Neta in aqueous media.[117,118] The aqueous measurements take advantage of the phenol potential becoming independent of pH above its p$K_a$ (see section 3.2).

Phenols readily react by hydrogen atom transfer (HAT) and this pathway is implicated in the antioxidant properties of phenols both in vivo and in vitro (see below).[119] For the more acidic phenols, or under basic conditions, a mechanism of sequential proton loss then electron transfer (SPLET) can occur.[11−13] It is less common for phenols to react by initial outer-sphere electron transfer because of the high $E°$(PhOH$^{\bullet+/0}$) potentials. The ArO$^\bullet$/ArOH potentials (or, better, BDFEs) are often above the thermodynamic requirement for water oxidation, as is necessary for the function of Tyrosine Z in photosystem II, mediating hole transfer from the chlorophyll radical cation to the oxygen evolving complex.

### 5.2.2. 2,4,6-Tri-tert-butylphenol ($^t$Bu$_3$PhOH)

4-Substituted-2,6-di-*tert*-butyl-phenols are widely used in the research lab and as food preservatives, especially 'butylated hydroxytoluene' (BHT, 4-Me) and 'butylated hydroxyanisole' (BHA, 4-MeO). 2,4,6-$^t$Bu$_3$PhOH is an especially interesting and useful reagent for studies of PCET reactions because of the exceptional stability of the phenoxyl radical ($^t$Bu$_3$PhO$^\bullet$).[120] The radical is easily prepared from the corresponding phenol using NaOH and $K_3Fe(CN)_6$, and can be isolated as dark blue crystals.[120] As discussed for TEMPOH above, we have recently reevaluated the solution BDE of $^t$Bu$_3$PhO$^\bullet$ in $C_6H_6$ to account for recent revision of the thermochemistry of the originally used diphenylhydrazine/azobenzene couple.[40] Our preferred value is 81.6 ± 0.4 kcal mol$^{-1}$.

The $^t$Bu$_3$PhO($^\bullet$/H) PCET couple is a very useful benchmark for the determination of bond strengths in other phenols. The clearest example is Pedulli and co-workers' EPR method to measure equilibrium constants for ArOH + $^t$Bu$_3$PhO$^\bullet$.[121] Please note that here and in Table 4, we have slightly adjusted Pedulli's reported BDEs to reflect our recent critical evaluation of the BDE (and the BDFE) of $^t$Bu$_3$PhOH.[40] The EPR equilibration method provides a high degree of precision and the values are, in general, internally consistent.[122] The values obtained agree very well with those from other methods, such as from $E°$ and p$K_a$ measurements. For example, the adjusted Pedulli values for BDFE(PhOH) and BDFE(2,6-$^t$Bu$_2$PhOH) in $C_6H_6$, = 83.8 and 78.3 kcal mol$^{-1}$ (Table 4), agree very closely with our conversion of Bordwell's BDFEs in DMSO (from $E°$ and p$K_a$ values)[116] to $C_6H_6$ using the Abraham method, 83.7 and 78.1 kcal mol$^{-1}$, respectively.

### 5.2.3. Tyrosine

Redox reactions of the amino acid tyrosine are involved in biological energy transduction, charge transport, oxidative stress, and enzymatic catalysis.[123] The $1H^+/1e^-$ oxidized form, the tyrosyl radical, has been implicated in a variety of enzymatic systems, including ribonucleotide reductases,[109] photosystem II,[106] galactose oxidase,[124] prostaglandin-H-synthase,[125] and perhaps cytochrome *c* oxidase.[126] Furthermore, tyrosine oxidation products are thought to play deleterious roles in various disease states, including atherosclerosis and aging.[127]

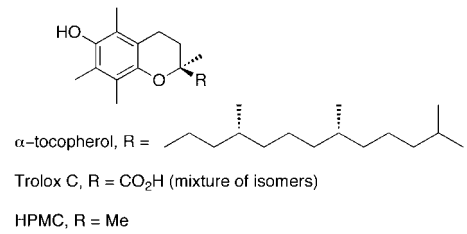
**Table 4. PCET Thermochemistry of Phenols[a]**

| compound | solvent | $E(RO^{\bullet/-})$ | $E(ROH^{\bullet+/0})$ | $pK_a(ROH^{\bullet+})$ | $pK_a(ROH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| PhOH | gas | | | | | 79.8[49] | 88.0[49] |
| PhOH | $H_2O$ | 0.79[117] | 1.5[136] | [−2][115] | 10.0[137] | 89.5 | 87.7 |
| PhOH | DMSO | *−0.325*[116] | *1.2*[116] | [−7.7] | 18.0[116] | 88.3 | 92.7 |
| PhOH | $C_6H_6$ | | | | | 83.8 | 88.6[121 b] |
| 4-Me−PhOH | $H_2O$ | 0.68[117] | 1.4[136] | [−2][115] | 10.3[137] | 87.4 | 85.6 |
| 4-Me−PhOH | DMSO | *−0.428*[116] | *1.1*[116] | [−4] | 18.9[116] | 87.1 | 91.7 |
| 4-Me−PhOH | $C_6H_6$ | | | | | 81.7 | 86.5[121 b] |
| 4-MeO−PhOH | $H_2O$ | 0.54[117] | 1.1[136] | [0.7] | 10.1[137] | 83.9 | 82.1 |
| 4-MeO−PhOH | DMSO | *−0.618*[116] | *0.85*[116] | [−5.6] | 19.1[116] | 83.0 | 87.6 |
| 4-MeO−PhOH | $C_6H_6$ | | | | | 78.3 | 83.1[121 b] |
| 4-$NO_2$−PhOH | $H_2O$ | 1.22[117] | | | 7.1[137] | 95.5 | 93.7 |
| 4-$NO_2$−PhOH | DMSO | *0.314*[116] | *1.9*[116] | [−9.5] | 10.8[116] | 93.1 | 97.7 |
| 4-F−PhOH | $H_2O$ | 0.76[117] | | | 9.9[137] | 88.7 | 86.9 |
| 4-Cl−PhOH | $H_2O$ | 0.80[117] | | | 9.4[137] | 88.9 | 87.1 |
| 4-Cl−PhOH | DMSO | *−0.232*[116] | *1.4*[116] | [−11] | 16.75[116] | 88.7 | 93.3 |
| 4-Br−PhOH | $H_2O$ | 0.82[117] | | | 9.4[137] | 89.4 | 87.6 |
| 4-Br−PhOH | DMSO | *−0.19*[116] | *1.3*[116] | [−8.7] | 16.36[116] | 89.1 | 93.7 |
| 4-I−PhOH | $H_2O$ | 0.82[117] | | | 9.3[137] | 89.3 | 87.5 |
| 4-$CO_2^-$-PhOH | $H_2O$ | 0.90[117] | | | 9.4[137] | 91.2 | 89.4 |
| 4-Me(O)C-PhOH | $H_2O$ | 1.00[117] | | | 8.0[137] | 91.6 | 89.8 |
| 4-Me(O)C-PhOH | DMSO | *0.04*[116] | *1.6*[116] | [−12] | 14.0[116] | 91.2 | 95.8 |
| 4-CN−PhOH | $H_2O$ | 1.12[117] | | | 7.9[137] | 94.3 | 92.5 |
| 4-CN−PhOH | DMSO | *0.15*[116] | *1.7*[116] | [−13] | 13.2[116] | 92.6 | 97.2 |
| 4-$NH_2$−PhOH | $H_2O$ | 0.217[117] | | | 10.4[137] | 76.9 | 75.0 |
| 4-$NH_2$−PhOH | DMSO | −1.031[116] | *−0.065*[116] | [4.5] | 20.75[116] | 75.8 | 80.4 |
| 4-$NMe_2$-PhOH | $H_2O$ | 0.174 | | | 10.1[137] | 75.4 | 73.6 |
| 4-$NMe_2$-PhOH | DMSO | *−0.847*[116] | *−0.045*[116] | [6.3] | 19.8[116] | 78.7 | 83.3 |
| 1-naphthol | $H_2O$ | 0.59[138] | | | 9.3[138] | 83.9 | 82.1 |
| 1-naphthol | DMSO | *−0.473*[116] | *0.95*[116] | [−7.8] | 16.2[116] | 82.4 | 87.0 |
| 2-naphthol | $H_2O$ | 0.69[138] | | | 9.6[138] | 86.7 | 84.9 |
| 2-naphthol | DMSO | *−0.353*[116] | *1.0*[116] | [−5.7] | 17.1[116] | 86.4 | 91.0 |
| tyrosine | $H_2O$ | 0.71[117] | [1.4] | ∼ −2[115] | 10.1[137] | 87.8 | 86.0 |
| Trolox C[c] | $H_2O$ | 0.192[118] | | | 12[139] | 78.5 | 76.7 |
| HPMC[d] | $C_6H_6$ | | | | | 73.7 | 78.5[121 b] |
| TocOH[e] | DMSO | *−0.87*[140] | | | 20.2[140] | 78.7 | 83.3 |
| TocOH[e] | MeCN | *−0.90*[141] | *0.6*[141] | [4.7] | 30[140 f] | 75.2 | 79.7 |
| TocOH[e] | $C_6H_6$ | | | | | 73.7 | 78.5,[121 b] |
| 2,4,6-$^t$Bu$_3$PhOH | $H_2O$ | 0.21[142] | 1.28[142] | [−5][142] | 13[142,143] | 80.3 | 78.5 |
| 2,4,6-$^t$Bu$_3$PhOH | DMSO | −0.645[116] | *1.0*[116] | [−10] | 17.8[116] | 80.6 | 85.2 |
| 2,4,6-$^t$Bu$_3$PhOH | MeCN | −0.70[144−146] | *1.18*[147] | [−3] | 28[116 f] | 77.1 | 81.6 |
| 2,4,6-$^t$Bu$_3$PhOH | $C_6H_6$ | | | | | 76.7 | 81.6[40] |
| 2,4,6-$^t$Bu$_3$PhOH | $CCl_4$ | | | | | 77.2 | 82.0[40] |
| 2,6-$^t$Bu$_2$PhOH | DMSO | *−0.619*[116] | | | 17.3[116] | 80.5 | 85.1 |
| 2,6-$^t$Bu$_2$PhOH | $C_6H_6$ | | | | | 78.3 | 83.1[121 b] |
| 4-Me-2,6-$^t$Bu$_3$PhOH | DMSO | −0.755[140] | | | 17.7[140] | 77.9 | 82.5 |
| 4-Me-2,6-$^t$Bu$_3$PhOH | $C_6H_6$ | | | | | 76.9 | 81.7[121 b] |
| 4-MeO-2,6-$^t$Bu$_3$PhOH | DMSO | −0.806[140] | | | 18.2[140] | 77.4 | 82.0 |
| 4-MeO-2,6-$^t$Bu$_3$PhOH | $C_6H_6$ | | | | | 73.8 | 78.6[121 b] |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. $E°$ and $pK_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6, 7). *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. BDFEs (kcal mol$^{-1}$) are from the cited reference or calculated from $E$ and $pK_a$ values (eqs 7, 15, 16); BDEs (kcal mol$^{-1}$) are typically calculated from BDFEs using eq 9. [b] The values reported in ref 121 are relative to $^t$Bu$_3$PhOH. The values given here have been adjusted to reflect our critical re-evaluation of BD(F)E of $^t$Bu$_3$PhOH in reference.[40] [c] Trolox C = (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid. [d] HPMC = 6-hydroxy-2,2,5,7,8-pentamethylchroman. [e] TocOH = α-tocopherol. [f] Extrapolated from DMSO to MeCN using the method of Kütt and co-workers.[89]

The proton-coupled redox chemistry of tyrosine (TyrOH) and related compounds has been widely reported.[128−131] In aqueous solutions, the Pourbaix diagram shows a clear 59 mV per pH dependence for the oxidation of tyrosine below pH 10, indicative of a $1e^-/1H^+$ redox couple. As for phenol, above $pK_a$(tyrosine), the redox potential does not depend on pH because this is the proton-independent $TyrO^{\bullet}/TyrO^-$ redox couple. Other, more detailed, discussions of aspects of proton-coupled redox chemistry of tyrosine can be found in other contributions to this issue. As an aside, we encourage biochemical studies of PCET to use a nomenclature that explicitly shows the proton, such as "TyrOH" for tyrosine, to avoid ambiguity. For instance, the commonly used "Y•" for tyrosyl radicals could refer either to neutral radical $TyrO^{\bullet}$ or to the typically high-energy radical cation $TyrOH^{\bullet+}$.

**Scheme 8. α-Tocopherol (Vitamin E) and Analogues Trolox C and HPMC**




### 5.2.4. α-Tocopherol and Related Phenols

α-Tocopherol (a main component of vitamin E) is thought to be a key chain-breaking antioxidant in biological systems. Since its discovery in 1922,[132] vitamin E has received considerable attention from chemists, biologists, and clinicians, among others.[110] Because of its insolubility in water, several small water-soluble analogues such as Trolox C ((±)-

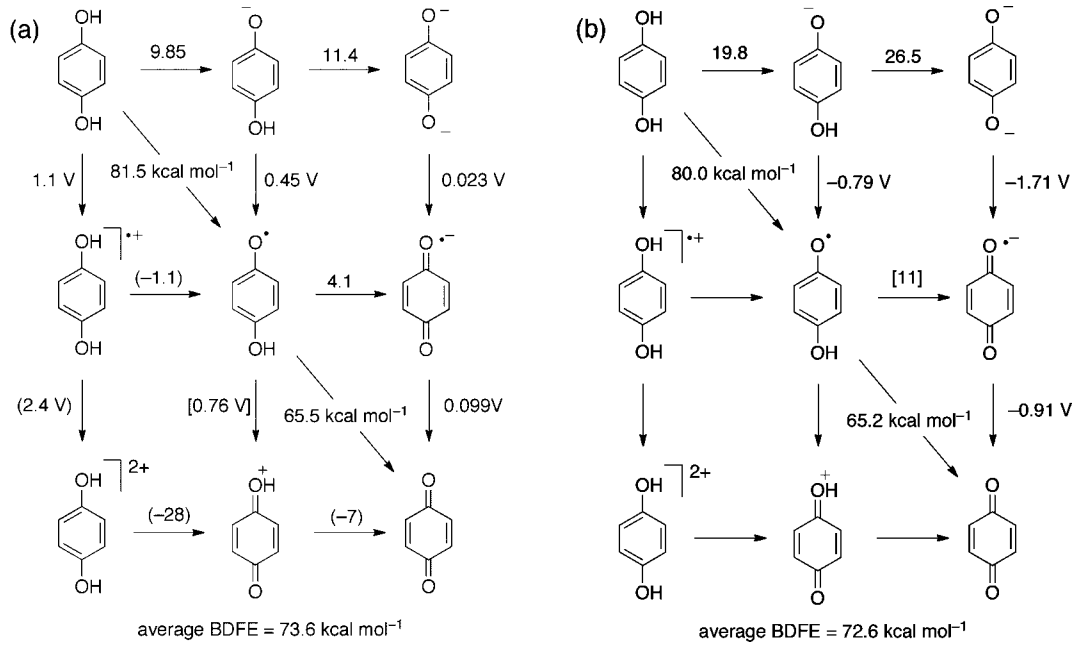



**Figure 2.** Thermochemistry of the hydroquinone/benzoquinone system (a) in water[117,152,158,159] and (b) in DMSO,[116] (see Table 6). Numbers above horizontal arrows give p$K_a$ values; numbers beside vertical arrows give electrochemical potentials (vs NHE in water and vs $Cp_2Fe^{+/0}$ in DMSO); numbers bisecting diagonal lines are BDFEs in kcal mol$^{-1}$. In (a), the values in parentheses were estimated by Laviron;[152] in (a) and (b) the values in square brackets are estimated using eq 7 and Hess' Law.

6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) and HPMC (6-hydroxy-2,2-5,7,8-pentamethylchroman) have been developed (Scheme 8; see refs 133 and 134). As shown in Table 4, these three phenols show similar thermochemistry in the same solvent. This is in good agreement with their solution kinetic behavior and indicates that the analogues lacking the greasy phytyl tails are good models for the redox chemistry of tocopherol. The BDFEs of these phenols are much lower than those of other phenols, by >10 kcal mol$^{-1}$ vs unsubstituted phenol and by ~2 kcal mol$^{-1}$ vs $^t$Bu$_3$PhOH in the same solvent. This relatively weak bond is the origin of the good biological reducing power of vitamin E. The weak bond is a result of the electron-donating substituents, which also reduces the acidity of these phenols. The combination of a weak O−H bond, low acidity, and a high outer-sphere redox potential [$E°$(ArOH$^{\bullet+/0}$)] give these molecules a strong preference to react by concerted transfer of e$^-$ and H$^+$ (HAT). Njus and Kelley used such reasoning to conclude that vitamin E donates H$^\bullet$ as opposed to e$^-$ in biological reactions.[135] A characteristic of these and other systems that prefer to transfer H$^\bullet$ rather than react by stepwise paths (cf., TEMPOH above) is the very large shift of the p$K_a$ upon redox change and (equivalently) the large shift of $E°$ upon protonation: for α-tocopherol, the p$K_a$ changes by 25 units and $E°$ changes by 1.5 V.

### 5.2.5. Quinones, Hydroquinones, and Catechols

The PCET chemistry of hydroquinones and catechols (1,4- and 1,2-dihydroxybenzenes, respectively) is somewhat similar to that of substituted phenols, but more extensive because there are two transferable hydrogen atoms and removal of both leads to stable quinones. This means that, instead of the four species of the standard square scheme for HX (Scheme 4), there are nine species derived from hydroquinone ($H_2Q$), as shown in Figure 2. This is also the case for flavins, which are discussed below. In practice, the cationic forms, $H_2Q^{\bullet+}$, $H_2Q^{2+}$, and $HQ^+$, are not involved in typical PCET reactivity because they are high-energy species under normal conditions.

In the reactions of the first O−H bond, hydroquinones follow the patterns outlined above for phenols. In general, the p$K_a$ values for $H_2Q$ and the oxidation potential of $HQ^-$ fit on Hammett correlations with other 4-substituted phenols, both in aqueous[117] and in organic media.[116] For example, the BDFE of the first O−H bond in hydroquinone is 2−3 kcal mol$^{-1}$ weaker than that of *p*-methoxyphenol. With hydroquinones and catechols, however, loss of H$^\bullet$ yields the semiquinone radical that has a high propensity to lose a second H$^\bullet$.[148] Semiquinones and related species were among the first free radicals to be investigated in detail: Michaelis' 1935 review in this journal points out that many systems commonly understood as 1e$^-$ systems can actually undergo 1e$^-$ or 1H$^+$/1e$^-$ redox chemistry, and that the redox properties of semiquinone-type radicals are dependent upon pH. This was a very early recognition of the importance of PCET in biology.[149]

While hydroquinones have reactivity patterns that are in part similar to phenols, with preferential loss of H$^\bullet$, quinones have a different PCET behavior, especially in water. Quinones are typically easily reduced to semiquinone radical anions in water, without the assistance of protons, and the Q$^{\bullet-}$ anions are not particularly basic (Table 6). Therefore quinone cofactors can readily mediate stepwise PCET reactions, with initial electron transfer followed by proton transfer. Q/Q$^{\bullet-}$ interconversion is well understood using semiclassical ET theory.[150] Such stepwise mechanisms have been discussed,[151] and an example of stepwise PT−ET of quinones in biology is discussed in section 6 below.

The aqueous 2H$^+$/2e$^-$ potentials of many quinones have been reported, because they are easily measured and because they are important biological cofactors (ubiquinone, for instance, is so named because it is ubiquitous). Their electrochemistry is generally well behaved,[153] although there is still much to be learned in this area.[154] The electrochemical

**Table 5. Average O−H BDFEs and BDEs of Substituted 1,4-Hydroquinones in Water[a]**

| quinone | $E^{155}$ | avg. BDFE | avg. BDE | quinone | $E^{155}$ | avg. BDFE | avg. BDE |
|---|---|---|---|---|---|---|---|
| benzoquinone (BQ) | 0.700 | 73.6 | 71.8 | methyl−BQ | 0.644 | 72.5 | 70.7 |
| chloro−BQ | 0.712 | 74.0 | 72.2 | 2,5-dimethyl−BQ | 0.596 | 71.3 | 69.5 |
| 2,6-dichloro−BQ | 0.721 | 74.2 | 72.4 | 2,3-dimethyl−BQ | 0.588 | 71.2 | 69.4 |
| 2,5-dichloro−BQ | 0.723 | 74.3 | 72.5 | 2,3,5-trimethyl−BQ | 0.527 | 69.8 | 68.0 |
| 2,3-dichloro−BQ | 0.706 | 73.9 | 72.1 | 2-Me-5-$^{i}$Pr−BQ | 0.589 | 71.2 | 69.4 |
| bromo−BQ | 0.715 | 74.1 | 72.3 | 2,5-$Me_2$-3-Cl−BQ | 0.595 | 71.3 | 69.5 |
| 2-Br-5-Me−BQ | 0.656 | 72.7 | 70.9 | 2,5-dimethoxy−BQ | 0.590 | 71.2 | 69.4 |
| 2-Cl-5-Me−BQ | 0.654 | 72.7 | 70.9 | 2,6-dimethoxy−BQ | 0.514 | 69.5 | 67.7 |
| tetrachloro−BQ | 0.68 | 73.3 | 71.5 | tetramethyl−BQ | 0.48 | 68.7 | 66.9 |
| naphthoquinone (NQ) | 0.48 | 68.7 | 66.9 | 2,3-dimethyl−NQ | 0.34 | 65.4 | 63.6 |
| 2-methyl−NQ | 0.415 | 67.2 | 65.4 | | | | |

[a] BQ = 1,4-benzoquinone; NQ = 1,4-naphthoquinone. Potentials in V versus NHE. BDFE and BDE are in kcal $mol^{-1}$. The BDFEs are derived from the $E^{\circ}$ values using an analogue of eq 15, and the BDEs are 1.8 kcal $mol^{-1}$ lower than the BDFEs according to eq 9.

**Table 6. PCET Thermochemistry of 1,4-Hydroquinones[a]**

| hydroquinone | solvent | $E(HQ^{\bullet/-})$ | $E(H_2Q^{\bullet+/0})$ | $pK_a(H_2Q^{\bullet+})$ | $pK_a(H_2Q)$ | $pK_a(HQ^-)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|---|
| hydroquinone ($H_2Q$) | $H_2O$ | 0.45[117] | 1.1[158] | −1.1[152] | 9.85[159] | 11.4[159] | 81.5 | 79.7 |
| hydroquinone ($H_2Q$) | DMSO | *−0.79*[116] | | | 19.8[116] | 26.5[116] | 80.0 | 84.6 |
| methyl−HQ | $H_2O$ | [0.40] | | | 10.1[159] | 11.6,[159] 12.1[160] | 80.7 | 78.9 |
| 2,3-dimethyl−$H_2Q$ | $H_2O$ | [0.36] | | | 10.4[161] | 12.6[161] | 80.1 | 78.3 |
| 2,5-dimethyl−$H_2Q$ | $H_2O$ | [0.36] | | | 10.4[161] | 12.5[161] | 80.2 | 78.4 |
| 2,3,5-$Me_3$−$H_2Q$ | $H_2O$ | [0.28] | | | 10.8[161] | 12.9[161] | 79.0 | 77.2 |
| tetramethyl−$H_2Q$ | $H_2O$ | [0.075] | | | 11.3[161] | 13.2[161] | 74.8 | 73.0 |
| 2-methyl−$H_2NQ$ | $H_2O$ | | | | | | 75.5 | 73.7 |
| 2,3-MeO−$H_2NQ$ | $H_2O$ | | | | | | 72.8 | 71.0 |
| semiquinone | solvent | $E(Q^{0/\bullet-})$ | $E(HQ^{+/\bullet})$ | $pK_a(HQ^+)$ | $pK_a(HQ^{\bullet})$ | | BDFE | BDE |
| $HQ^{\bullet}$ | $H_2O$ | 0.099[162] | [0.76] | −7[152] | 4.1[163,164] | | 65.5 | 63.7 |
| $HQ^{\bullet}$ | DMSO | *−0.91*[116] | | | [11] | | 65.2 | 69.8 |
| methyl−$HQ^{\bullet}$ | $H_2O$ | 0.023[162] | | | 4.5[165] | | 64.3 | 62.5 |
| 2,3-dimethyl−$HQ^{\bullet}$ | $H_2O$ | −0.074[162] | | | 4.7[165] | | 62.3 | 60.5 |
| 2,5-dimethyl−$HQ^{\bullet}$ | $H_2O$ | −0.067[162] | | | 4.6[165] | | 62.4 | 60.6 |
| 2,3,5-$Me_3$−$HQ^{\bullet}$ | $H_2O$ | −0.165[162] | | | 5.0[165] | | 60.6 | 58.8 |
| tetramethyl−$HQ^{\bullet}$ | $H_2O$ | −0.235[166] | | | 5.0[165] | | 59.0 | 57.2 |
| 2-methyl−$HNQ^{\bullet}$ | $H_2O$ | −0.203[166] | | | 4.4[165] | | 58.9 | 57.1 |
| 2,3-$Me_2$−$HNQ^{\bullet}$ | $H_2O$ | −0.240[162] | | | 4.3[165] | | 58.0 | 56.2 |

[a] $H_2Q$ = 1,4-hydroquinone; $H_2NQ$ = 1,4-naphthalenediol; $HQ^{\bullet}$ and $HNQ^{\bullet}$ are the monoprotonated semiquinones derived from these two hydroquinones. Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in DMSO. *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. $E^{\circ}$ and $pK_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6 and 7). BDFE and BDE are in kcal $mol^{-1}$, the former calculated from eq 7 and converted to the latter using eq 9.

data directly give an average BDFE/BDE for each quinone system (Table 5). Interestingly, the average bond strength for most quinones lies in the relatively narrow range of 68−75 kcal $mol^{-1}$.

The *average* O−H bond strengths in Table 5 do not, however, always parallel the individual O−H bond strengths. Using the known $pK_a$ values and reduction potentials for the quinones and semiquinones, the BDFEs (and BDEs) for many hydroquinones can be calculated (Table 6). The power of the thermochemical cycles (Hess' Law) is illustrated by the calculation of the values shown in square brackets in Figure 2, which are difficult to obtain directly because of the rapid disproportionation of semiquinone radicals.[116,156] It should also be noted that the BDFEs of these quinones do not necessarily reflect the $1e^-$ quinone/semiquinone radical anion reduction potentials. For example, tetrachloro-*p*-benzoquinone is 0.5 V more oxidizing than *p*-benzoquinone,[157] even though the average BDFEs are not too different. One-electron potentials for a variety of quinones in several different organic solvents are available in ref 157.

The *ortho*-substituted quinone/catechol redox couple has reactivity and thermochemistry that is somewhat distinct from the *para*-quinone/hydroquinone couple. *Ortho*-quinones and catechols (1,2-hydroxybenzenes) are also key biological cofactors, the most widely known of which are the catecholamines dopamine, epinephrine, and norepinepherine.[167] The antioxidant and anticancer activities of *ortho*-quinone derivatives, known as "catachins", have recently received considerable attention.[168] Unfortunately, the thermochemical data available for catechols are more limited than those for hydroquinones, and thus, the double square scheme in Figure 3 cannot be completely filled in. Still, sufficient results are available to show the important differences between hydroquinones and catechols.

The aqueous $2H^+/2e^-$ potential of catechol[155] indicates an average O−H BDFE of 75.9 kcal $mol^{-1}$, slightly higher than that of 1,4-hydroquinone (73.6 kcal $mol^{-1}$). From the known $pK_a$ of the semiquinone[169] and the one-electron potential of *ortho*-benzoquinone, the second BDFE is 65.4 kcal $mol^{-1}$, using eq 7. Thus, the first BDFE in catechol must be 86.2 kcal $mol^{-1}$ in water. The second O−H BDFEs for the hydroquinone and catechol semiquinones are very similar, 65.5 and 65.4 kcal $mol^{-1}$, respectively.

The thermochemistry of catechols is different from hydroquinones partially due to the availability of an internal hydrogen bond (Scheme 9). The first $pK_a$ of catechol (9.26[170]) is not too different from the first $pK_a$ in hydroquinone (9.85), and for both, the second $pK_a$ is larger, as expected for deprotonation of an anion. However, the second $pK_a$ for catechol (13.4[170]) is 2 $pK_a$ units larger than that of hydro-

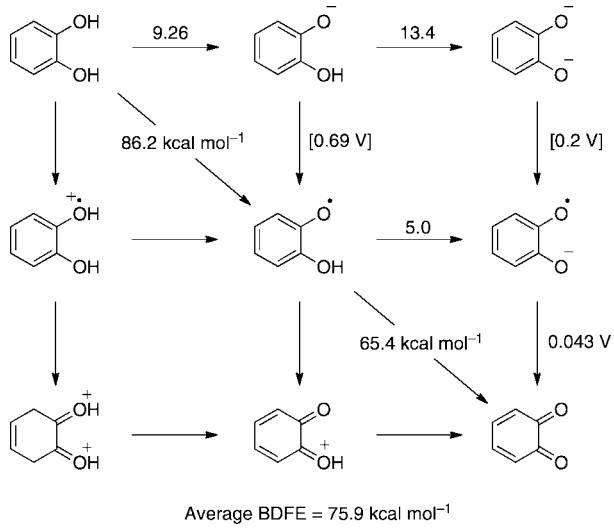
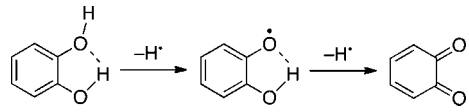



**Figure 3.** Thermochemistry of the catechol/*ortho*-quinone system in water, with p$K_a$ values above horizontal arrows, redox potentials (in V vs NHE) beside vertical arrows, and BDFE values (in kcal mol$^{-1}$) bisecting diagonal lines (see text for references). The values in square brackets are estimates using eq 7 and Hess' Law.

**Scheme 9. H$^\bullet$ Loss and Intramolecular H-Bonding in *ortho*-Quinones**




quinone (11.4), because the catecholate is stabilized by the strong intramolecular hydrogen bond.

The *intra*molecular hydrogen bond appears to be more important in the gas phase and in non-hydrogen bond accepting solvents where it does not compete with hydrogen bonding to solvent. Theoretical work indicates that the intramolecular hydrogen bond in catechol has a free energy of about −4 kcal mol$^{-1}$ and, importantly, that the analogous H-bond in the monoprotonated semiquinone radical is about twice as strong (Scheme 9).[171,172] Thus, the reactivity of catechols can be quite different in non-hydrogen bond-accepting solvents versus water. Lucarini et al.[173] and Foti et al.[174] have each shown that in non-hydrogen bond-accepting solvents, compounds with intramolecular hydrogen bonds are better H$^\bullet$ donors than analogous species without intramolecular hydrogen bonding. This is opposite to the thermochemistry in water where BDFE(catechol) > BDFE-(hydroquinone).

### 5.2.6. Ascorbate

Ascorbic acid (vitamin C) is a ubiquitous biological cofactor that is necessary for human health.[175] Ascorbate has traditionally been thought of as a one-electron reductant, but redox reactions of ascorbate almost always involve the loss of an electron and a proton (or a hydrogen atom), so it is really a PCET reagent. Njus et al.[176] and Tsubaki and co-workers[177] have shown that ascorbate donates hydrogen atoms in its reactions with cytochrome $b_{561}$. Njus and Kelley have also demonstrated this for other ascorbate-utilizing enzyme systems.[178] Ascorbate is also likely oxidized by loss of $H^+ + e^-$ in the catalytic cycle of ascorbate peroxidase (APX).[179] HAT from ascorbate may play a role in regeneration of vitamin E (tocopherol) radicals.[135,180] 5,6-Isopropylidene ascorbate, a convenient, commercially available organic-soluble analogue of ascorbate, reacts with TEMPO, $^t$Bu$_3$PhO$^\bullet$, and iron−porphyrin models via concerted transfer of H$^\bullet$.[181,182]

The aqueous thermochemistry of ascorbate is well understood (Figure 4).[135,183,184] In principle, a nine-membered square could be constructed for ascorbic acid because two electrons and two protons can be removed to make dehydroascorbate. However, similar to hydroquinones, the oxidized forms that have not lost a proton are high-energy species (very acidic) and are not relevant to ascorbate chemistry. Ascorbic acid becomes a stronger reducing agent at higher pH as it is converted to ascorbate (AscH$^-$) and then the doubly deprotonated form (Asc$^{2-}$).[184,185] At physiological pH, AscH$^-$ is the predominant species and the ascorbyl radical (Asc$^{\bullet-}$) is deprotonated (the p$K_a$ of AscH$^{\bullet+}$ is −0.45). Therefore, the most important reaction is AscH$^-$ → Asc$^{\bullet-}$ + H$^+$ + e$^-$. The thermochemical data for ascorbate and isopropylidene ascorbate in a few different solvents is given in Table 7. The ascorbyl radical rapidly disproportionates with consumption of a proton to give 1 equiv of dehydroascorbate (Asc) and ascorbate,[186] so the very weak

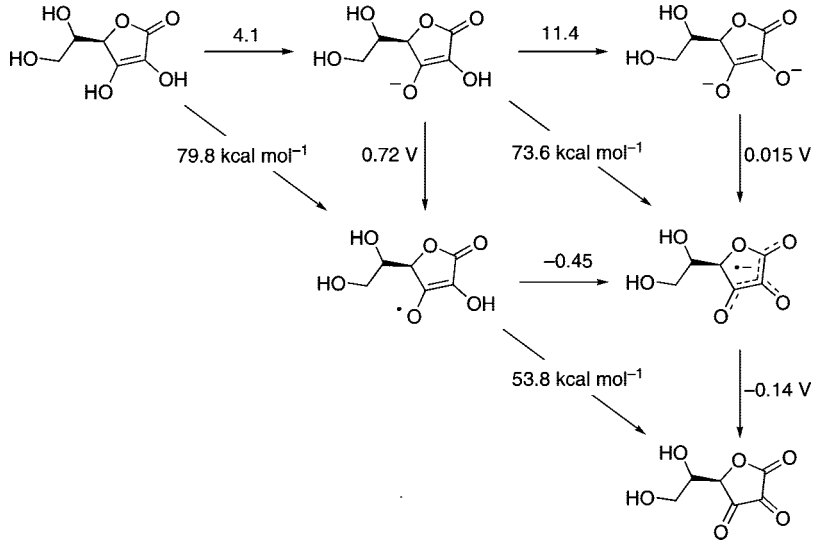



**Figure 4.** Aqueous thermochemistry of ascorbic acid, with p$K_a$ values above horizontal arrows, redox potentials (in V vs NHE) beside vertical arrows, and BDFE values (in kcal mol$^{-1}$) bisecting diagonal lines. Data from refs 135, 183, 184, and 187 (see Table 7).

**Table 7. PCET Thermochemistry of Ascorbates[a]**

| compound | solvent | $E(Asc^{\bullet -/2-})$ | $E(AscH^{\bullet/-})$ | $pK_a(Asc^{\bullet})$ | $pK_a(AscH^{-})$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| $AscH^{-}$ | water | 0.015[183,184] | 0.72[183,184] | −0.45[187] | 11.4[183,184] | 73.6 | 71.8 |
| $AscH^{-}$ | MeCN | | | | | 67.7 | 72.3 |
| $AscH^{-}$ | DMSO | | | | | 67.6 | 72.2 |
| *i*$AscH^{-}$ | MeCN | −1.30[182] | −0.41[182] | 14[b] | 26.8[182] | 65.4[c] | 70.0 |
| *i*$AscH^{-}$ | DMSO | | | | | 67.5 | 72.1[c] |
| compound | solvent | $E(AscH_2^{\bullet +/0})$ | $E(AscH^{\bullet/-})$ | $pK_a(AscH_2)$ | $pK_a(AscH_2^{\bullet +})$ | BDFE | BDE |
| $AscH_2$ | water | | 0.72[183,184] | 4.1[183,184] | | 79.8 | 78.0 |
| *i*$AscH_2$ | MeCN | | −0.41[182] | 18.3[182] | | 70.5 | 75.1 |
| compound | solvent | $E(Asc^{0/\bullet -})$ | NA | $pK_a(Asc^{\bullet})$ | NA | BDFE | BDE |
| $Asc^{\bullet -}$ | water | −0.14[183,184] | | −0.45[187] | | 53.6 | 52.0 |

[a] Potentials are in V versus NHE for aqueous measurements and versus $Cp_2Fe^{+/0}$ in MeCN. The BDFEs (kcal mol$^{-1}$) are calculated from $E°$ and $pK_a$ values (eqs 7, 15, and 16), and the BDEs are calculated from them using eq 9. [b] Calculated from a thermochemical cycle (Hess' Law). [c] For the BDFE of 5,6-isopropylidene ascorbate in MeCN, we prefer the use of the BDFE obtained from equilibration with TEMPO, BDFE(*i*$AscH^{-}$) = 66.4 kcal mol$^{-1}$ and BDE = 71.0 kcal mol$^{-1}$.

**Table 8. PCET Thermochemistry of Water and Common Alcohols[a]**

| compound (ROH) | solvent | $E(RO^{\bullet/-})$ | $pK_a$(ROH) | BDFE | BDE |
|---|---|---|---|---|---|
| HO−H | gas | | | 111.0[b] | 118.8[200] |
| HO−H | $H_2O$ | 1.89[209] | 15.7[209] | 122.7 | −[c] |
| $^{\bullet}O-H^{-}$ | gas | | | 96.2[b] | 102.8[200] |
| $^{\bullet}O-H^{-}$ | $H_2O$ | 1.43[209] | 11.9[209] | 106.9 | −[c] |
| $O-H^{-}$ | gas | | | 103.1[b] | 110.2[37] |
| $O-H^{-}$ | $H_2O$ | | | 117.5[f] | −[c] |
| MeOH | gas | | | 96.4 | 104.6[37] |
| MeOH | DMSO | *−0.368*[100] | 29.1[201] | 102.5 | 107.1 |
| EtOH | gas | | | 96.5 | 104.7[37] |
| EtOH | DMSO | *−0.483*[100] | 29.8[201] | 100.8 | 105.4 |
| $^{i}$PrOH | gas | | | 97.5 | 105.7[37] |
| $^{i}$PrOH | DMSO | *−0.471*[100] | 30.3[201] | 101.7 | 106.3 |
| $^{i}$BuOH[d] | DMSO | *−0.512*[100] | 32.2[201] | 103.4 | 108.0 |
| $^{t}$BuOH | gas | | | 98.1 | 106.3[37] |
| $^{t}$BuOH | DMSO | [−0.40] | 32.2[201] | (106) | (111) |
| $^{t}$BuOH | $H_2O$ | [≤1.2] | ≥15.5[137,202 e] | (107) | (105) |

[a] Potentials are in V, vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in DMSO. *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. BDEs (kcal mol$^{-1}$) are from the cited reference or are calculated from the BDFEs using eq 9. BDFEs (kcal mol$^{-1}$) are from the gas-phase BDEs using $S°_{gas}(H^{\bullet})$ or are calculated from $E$ and $pK_a$ values (eqs 7, 15, and 16). BDE or BDFE values in (parentheses) have been estimated from a value in another solvent using the Abraham model (eq 13). [b] BDFEs for these species are calculated using $S°_{gas}(X-H)$ and $S°_{gas}(X^{\bullet})$ from ref 49. [c] BDEs are not given for these species because it is not clear that eq 9 holds for very small molecules in water where the solvation of the closed shell and radical species may be complicated. [d] $^{i}$BuOH = isobutyl alcohol, $(CH_3)_2CHCH_2OH$. [e] $pK_a(^{t}BuOH)$ is taken to be at least that of MeOH or EtOH. [f] Calculated from $E°(OH^{\bullet/-})$ = 1.89 and the $pK_a(^{\bullet}O-H)$ = 11.9 given above.

O−H BDFE of the ascorbyl radical is typically not relevant. However, disproportionation is much slower in anhydrous solvents with low proton activity.[182]

## 5.3. Alcohols and Water

Aliphatic alcohols and water have quite different PCET chemistry than the "enols" discussed above (phenols, hydroquinones, catechols, and ascorbate). O−H bonds in alcohols are much stronger than those in phenolic compounds (because the enolic $\pi$-resonance stabilizes the oxyl radical much more than the $\sigma$-bond hyperconjugation). Thus, the gas-phase O−H BDE in methanol (96.4 kcal mol$^{-1}$)[188] is ca. 8 kcal mol$^{-1}$ stronger that the analogous BDE in phenol (88 kcal mol$^{-1}$). The alcohol O−H bond is usually stronger than the C−H bonds in the same molecule. Again using methanol as an example, the O−H BDE is >8 kcal mol$^{-1}$ stronger than the C−H $BDFE_g$ for H−$CH_2OH$, 87.9 kcal mol$^{-1}$.[37] For this reason, hydrogen atom abstractors react with alcohols to give a hydroxyalkyl radical such as $^{\bullet}CH_2OH$, rather than the alkoxyl radical ($CH_3O^{\bullet}$).

### 5.3.1. tert-Butanol and tert-Butoxyl Radical

The *tert*-butoxyl radical ($^{t}BuO^{\bullet}$) has received considerable attention, in part because it does not have any easily abstracted α-C−H bonds. $^{t}BuO^{\bullet}$ radicals can be generated via photolysis of $^{t}BuOO^{t}Bu$ in the gas phase[189] or in solution,[190] and by photolysis or thermal decomposition of *tert*-butylhyponitrite ($^{t}BuONNO^{t}Bu$),[191] *tert*-butylhypochlorite,[192] or *tert*-butylperoxalate.[193] The O−H bond in *tert*-butanol ($^{t}BuOH$) is quite strong, with a gas-phase BDE of 106.3 kcal mol$^{-1}$,[37] so $^{t}BuO^{\bullet}$ is a quite reactive H-atom abstractor. Photochemically generated $^{t}BuO^{\bullet}$ is therefore useful to rapidly form other oxyl radicals, such as phenoxyls, often within the duration of a nanosecond laser pulse.[194−196] A large number of rate constants are available for HAT from various substrates to $^{t}BuO^{\bullet}$.[197] With less reactive X−H bonds, however, HAT must compete with $\beta$-scission of $^{t}BuO^{\bullet}$ to give methyl radical and acetone.[198] In neat acetonitrile, for instance, only $\beta$-scission is observed, because of the low reactivity of the H−$CH_2CN$ bonds.[198]

BDFEs for $^{t}BuOH$ in water and DMSO have been estimated using Abraham's empirical method, described in

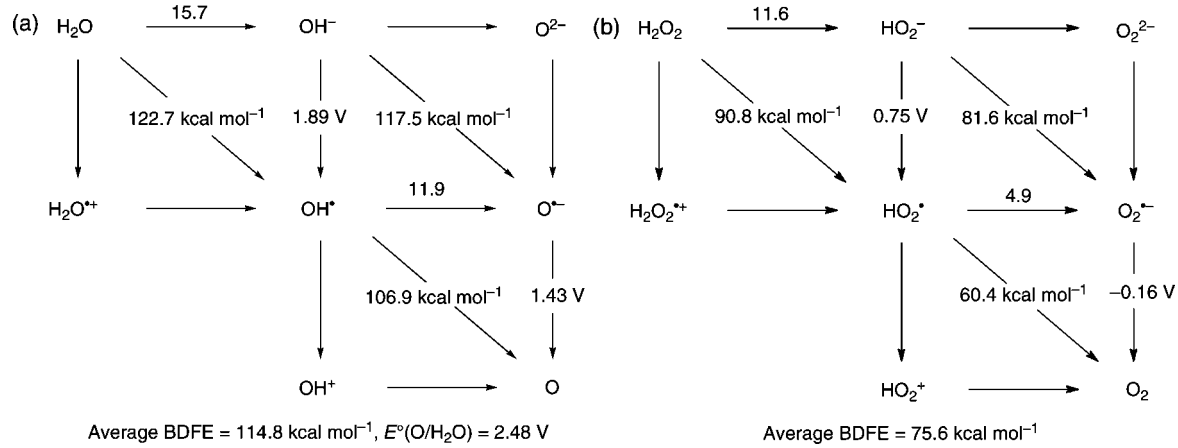



**Figure 5.** Aqueous PCET thermochemistry of (a) aqueous $H_2O$ and (b) aqueous hydrogen peroxide, with p$K_a$ values above horizontal arrows, redox potentials (in V vs NHE) beside vertical arrows, and BDFE values (in kcal mol$^{-1}$) bisecting diagonal lines. Data are from Tables 8 ($H_2O$) and 9 ($H_2O_2$).

section 3.1.1. Combining these values with the known p$K_a$ values provides estimates of the 1e$^-$ reduction potentials of $^t$BuO$^\bullet$ in these solvents. The estimated $E(^t\text{BuO}^{\bullet/-})$ in DMSO is in reasonable agreement with Bordwell and Liu's estimate,[100] from the complex electrochemical response of $^t$BuO$^-$ in DMSO (Table 8). In water, $^t$BuO$^\bullet$ is very oxidizing, substantially more than phenoxyl (1.2 versus 0.78 V for the RO$^{\bullet/-}$ couple). Electron transfer reactions of $^t$BuO$^\bullet$ have been briefly discussed,[199] although the product of these reactions is $^t$BuOH, apparently formed by protonation of the quite basic *tert*-butoxide anion.

### 5.3.2. Water/Hydroxyl Radical

The first O−H bond in water is, to our knowledge, the strongest known O−H bond. It has a gas-phase BDFE of 110.64 kcal mol$^{-1}$ (a BDE$_g$ of 118.81 kcal mol$^{-1}$).[37,200] In aqueous solution, we calculate the BDFE(HO−H) to be 122.7 kcal mol$^{-1}$ based on the OH$^{\bullet/-}$ redox potential and the p$K_a$. The very high HO−H bond strength is due, at least in part, to the absence of any resonance or hyperconjugative stabilization in OH$^\bullet$. The hydroxyl radical is therefore a very high energy species capable of extracting H-atoms from essentially all aliphatic C−H bonds (C−H bonds with an sp$^3$-hybridized carbon). OH$^\bullet$ is also a potent 1e$^-$ oxidant and can add to unsaturated organic compounds, for instance converting benzene to phenol. The O−H bond in the hydroxyl radical (the second O−H bond in water) is significantly weaker, as given in Table 8 and shown in the square scheme in Figure 5a.

## 5.4. Compounds with O−O Bonds

### 5.4.1. Overview of Dioxygen PCET Chemistry

PCET reactions involving dioxygen are of considerable research interest. The four-electron/four-proton reduction of $O_2$ to water is key to biological aerobic metabolism[203] and is the "oxygen reduction reaction" (ORR) in fuel cells.[204] The oxidation of water to dioxygen is an important component in many proposals for storage of electrical energy.[205] The abundance and low environmental impact of dioxygen make it an attractive oxidant in industrial chemical processes.[206] However, all 4e$^-$ and 4H$^+$ cannot be added or removed at the same time, so the intermediate species of dioxygen reduction are also of great importance. These species, $O_2^{\bullet-}$, $HO_2^\bullet$, $HO_2^-$, $H_2O_2$, HO$^\bullet$, and O$^{\bullet-}$, are all high-energy intermediates, as can be seen in the Frost diagrams in Figure 6, and are known collectively as reactive oxygen species (ROS). In biology, ROS damage lipids, proteins, nucleic acids, and carbohydrates and have been implicated in various diseases and aging.[203,207,208] Many of these species are highly reactive with organic molecules, making it difficult to study their chemistry in nonaqueous solvents. However, the aqueous thermochemistry of oxygen species has been studied extensively and has been reviewed by Sawyer[209] and Afanas'ev.[210] The properties of the species without an O−O bond have been summarized above; the PCET thermochemistry of the O−O bonded species are given in Table 9 and Figures 5b and 6a,b.

The Pourbaix diagram for water (Figure 6c) does not show most of the reactive oxygen species. This is because, other than $H_2O_2$ and $HO_2^-$, the ROS are not the most thermodynamically stable species at any point in the diagram, at any pH or redox potential. The standard (pH 0) potential for the 4e$^-$/4H$^+$ reduction of $O_2$ is always given as 1.23 V (eq 17), but from some perspectives, it can be better to think about $O_2$ reduction or water oxidation as transferring hydrogen atoms. The free energy in these terms, following eqs 15 or 16 above, is given in eq 18 both for the full 4e$^-$/4H$^+$ process and per hydrogen atom, as an effective BDFE. Thus, oxidizing water to $O_2$ requires a "system" with an effective BDFE of >86 kcal mol$^{-1}$. Such a system could be a hydrogen atom abstracting reagent or a combination of an oxidant and a base (section 5.9 below). In photosystem II, the oxidizing equivalents pass through the tyrosine/tyrosyl radical couple, which in aqueous solution has a BDFE of 87.8 kcal mol$^{-1}$ from Table 4. While this BDFE could be different within the protein, it shows that the tyrosyl radical has just enough free energy to accomplish water oxidation and shows the remarkable catalytic activity of the oxygen-evolving complex at low overpotential.

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O \quad E^\circ = 1.23\ \text{V} \quad (17)$$

$$O_2 + 4H^\bullet \rightarrow 2H_2O \quad -\Delta G^\circ = 344\ \text{kcal mol}^{-1}$$
$$\text{or } \text{BDFE}_{\text{average}} = 86\ \text{kcal mol}^{-1} \quad (18)$$

### 5.4.2. Dioxygen

Whereas the overall proton-coupled reduction of $O_2$ to water is quite favorable, transfer of the first electron is far

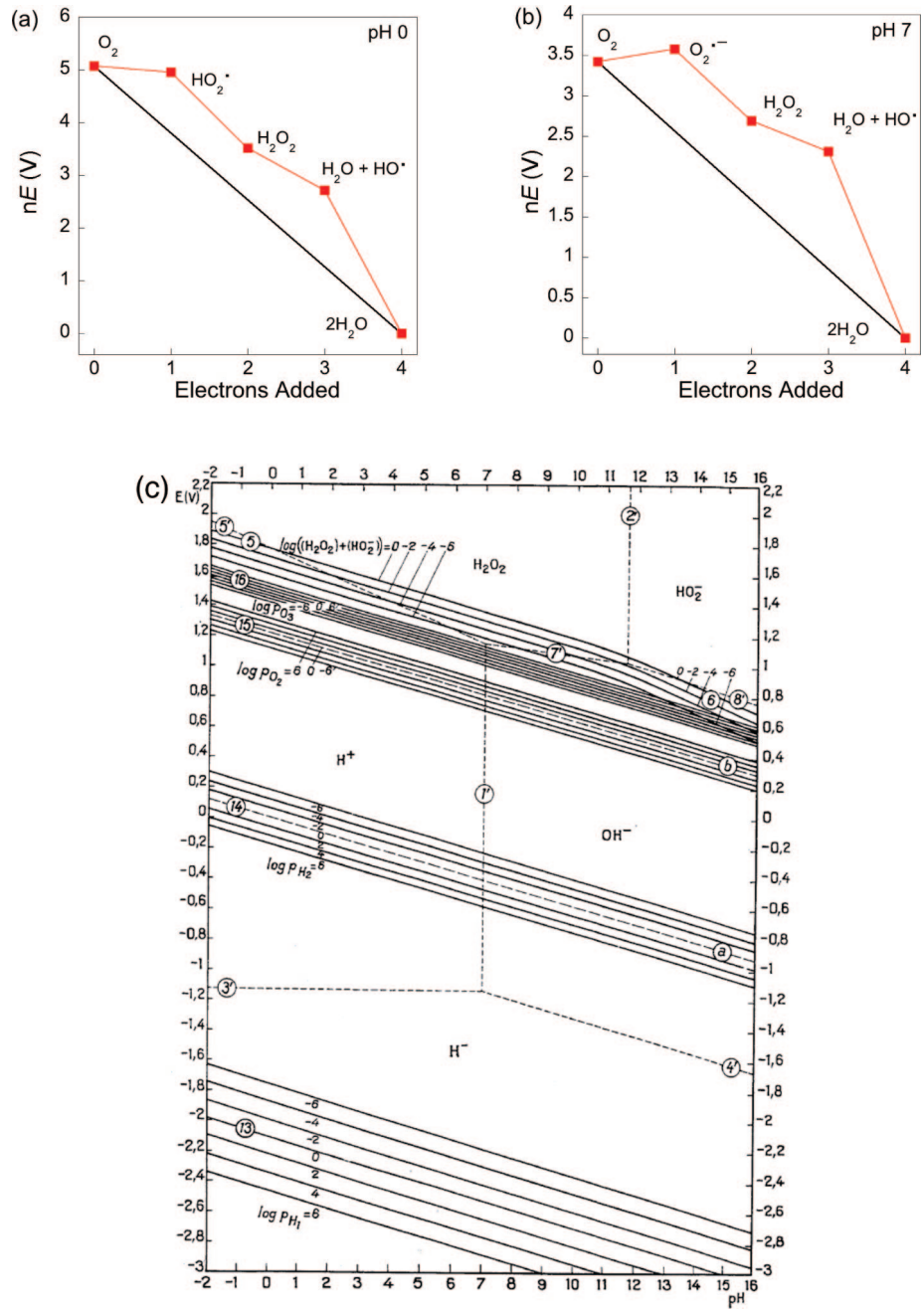



**Figure 6.** Frost diagram for dioxygen reduction to water showing the free energy (*nE*) of the various reactive oxygen species at (a) pH 0 and (b) pH 7. (c) Pourbaix diagram for water, showing the potentials for oxidation to $O_2$ and reduction to $H_2$ as a function of pH and the pressure of $O_2$ and $H_2$. The large white region in the lower center of the diagram is for $H_2$, and the region for $O_2$ is the thin white area above $H^+$ and $OH^-$. Reprinted with permission from M. Pourbaix, *Atlas of Electrochemical Equilibria in Aqueous Solutions*, ref 67. Copyright 1974 NACE International.

less favorable. Dioxygen is a poor one-electron outer-sphere oxidant, with $E°$ for reduction to superoxide ($O_2^{\bullet-}$) = −0.16 V vs NHE in $H_2O$.[209] Superoxide is also not very basic (aqueous p$K_a$ = 4.9), so this combination of a low potential and low p$K_a$ means that $HO_2^{\bullet}$ (hydroperoxyl) has a very low O−H BDFE, 60.4 kcal mol$^{-1}$ in water. Because of this low BDFE, $O_2$ is not an effective H-atom abstractor (so the large majority of organic molecules are "air-stable"). It should be emphasized that H-atom abstracting ability typically correlates with the X−H BDFE that an oxidant can form and does not correlate with the "radical character".[211] Thus, dioxygen is a triplet diradical but is quite unreactive toward HAT, while permanganate ($MnO_4^-$) with no unpaired spins is a reactive H-atom abstractor because it can form an O−H bond with a BDFE of 80.7 kcal mol$^{-1}$ (section 5.10). In contrast, oxene (O), a neutral triplet radical like $O_2$, is a far more potent H-atom abstractor because of the high BDFE of $^{\bullet}$O−H, 106.9 kcal mol$^{-1}$ (Table 8).

### 5.4.3. Superoxide/Hydroperoxyl

Superoxide radical anion ($O_2^{\bullet-}$) and its protonated form (the neutral perhydroxyl radical, $HO_2^{\bullet}$) are considered reactive oxygen species but do not undergo the chemistry typical of oxygen radicals.[212] Superoxide generally does not act as a direct one-electron oxidant because of the relatively high energy of the solvated peroxide dianion ($O_2^{2-}$).[213] Similarly, $O_2^{\bullet-}$ does not usually react as a direct H-atom

**Table 9. PCET Thermochemistry of Dioxygen, Superoxide, And Hydrogen Peroxide[a]**

| $HO_2^{\bullet}$/HOOH | solvent | $E$(HOOH$^{\bullet+/0}$) | $E$(HOO$^{\bullet/-}$) | p$K_a$(HOOH$^{\bullet+}$) | p$K_a$(HOOH) | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| $HO_2^{\bullet}$/HOO−H | gas | | | | | 79.6 | 87.5[228] |
| $HO_2^{\bullet}$/HOO−H | $H_2O$ | | 0.76[b] | | 11.6[220] | 91.0 | −[c] |
| $O_2$/$^{\bullet}$OOH | solvent | $E$(HOO$^{+/\bullet}$) | $E$($O_2^{\bullet/-}$) | p$K_a$($HO_2^{+}$) | p$K_a$($HO_2^{\bullet}$) | BDFE | BDE |
| $O_2$/$^{\bullet}$OO−H | gas | | | | | 42.7 | 49.2[228] |
| $O_2$/$^{\bullet}$OO−H | $H_2O$ | | −0.16[209] | | 4.9[209] | 60.6 | −[c] |
| $O_2$/$^{\bullet}$OO−H | DMSO | | −1.27[209] | | ~12[229] | ~58 | ~63 |
| $O_2^{\bullet-}$/$^{-}$OO−H | solvent | $E$(HOO$^{\bullet/-}$) | $E$($O_2^{\bullet-/2-}$) | p$K_a$($HO_2^{\bullet}$) | p$K_a$($HOO^{-}$) | BDFE | BDE |
| $O_2^{\bullet-}$/$^{-}$OO−H | $H_2O$ | 0.76[b] | | 4.9[209] | | 81.6 | −[c] |

[a] Potentials are in V versus NHE for aqueous measurements and versus $Cp_2Fe^{+/0}$ in DMSO. BDFEs and BDEs are in kcal mol$^{-1}$. Gas-phase BDFEs are calculated from gas-phase BDEs, and $S°_{gas}$(H$^{\bullet}$), $S°_{gas}$(X−H), and $S°_{gas}$(X$^{\bullet}$) are from ref 49. Solution BDFEs are calculated from $E$ and p$K_a$ values (eqs 7, 15, and 16). [b] Calculated using the 1H$^+$/1e$^-$ potential (1.44 V versus NHE at pH 0[209]) and extrapolating to pH = p$K_a$($H_2O_2$) assuming a 59 mV per pH unit dependence. [c] BDEs are not given for these species because it is not clear that eq 9 holds for very small molecules in water where the solvation of the closed shell and radical species may be complicated.

abstractor since it forms a relatively weak O−H bond (aqueous BDFE($^{-}$OO−H) = 81.6 kcal mol$^{-1}$). The neutral perhydroxyl radical $HO_2^{\bullet}$ is a more reactive oxidant, in part because it forms a stronger O−H bond: $E$($HO_2^{\bullet/-}$) = 0.76 V and BDFE$_{aq}$(HOO−H) = 91.0 kcal mol$^{-1}$ (Table 9). Thus, it is perhydroxyl, present in small quantities at biological pH (p$K_a$ $HO_2^{\bullet}$ = 4.9),[209] that is responsible for much of the oxidative damage associated with biological fluxes of superoxide. Some of this damage also results from the $H_2O_2$ produced by superoxide dismutation or by HAT to $HO_2^{\bullet}$. Perhydroxyl, because of its high BDFE, can abstract H-atoms from weak C−H bonds such as the allylic C−H's in cyclohexadiene[214,215] or linoleic acid.[216] Superoxide HAT reactions have also been reported with H-atom donors such as ascorbic acid[217] and di-*tert*-butylcatechol.[218]

Superoxide is fairly stable to disproportionation in the absence of protons because the peroxide ($O_2^{2-}$) product is a high-energy species. In the presence of protons, however, it rapidly decays to $H_2O_2$ and $O_2$ ($k = 1.0 \times 10^8$ M$^{-1}$ s$^{-1}$ at pH 7). This reaction likely occurs by the reaction of superoxide with perhydroxyl radicals to give hydroperoxide and dioxygen, which is a highly favorable process (eq 19).[219] This reaction has been described as the reduction of $HO_2^{\bullet}$ by superoxide, in other words as an ET reaction, but it could also occur by HAT from $HO_2^{\bullet}$ by superoxide, a net oxidation of $HO_2^{\bullet}$ that gives the same products. Superoxide disproportionation forms $HO_2^{-}$, which is a moderate base (p$K_a$ 11.6),[220] so aqueous superoxide in effect acts as a base despite its relatively low dissociation constant.

$$HO_2^{\bullet} + O_2^{-} \rightarrow HO_2^{-} + O_2 \qquad K = 4 \times 10^{20} \text{ in water at pH 7} \quad (19)$$

### 5.4.4. Hydrogen Peroxide

Peroxides are two-electron reduced from dioxygen. The peroxide dianion ($O_2^{2-}$) is found in ionic solids but is very basic, such that the two-electron electrochemical reduction of oxygen in DMSO produces deprotonated DMSO (p$K_{a,DMSO}$ = 35[29]) and hydroperoxide.[221] Hydroperoxide ($HO_2^{-}$) is moderately basic in water [p$K_a$($H_2O_2$) = 11.6]. In typical organic solvents such as DMSO, DMF, or acetonitrile, the p$K_a$ of $H_2O_2$ cannot be directly measured because $HO_2^{-}$ readily reacts with sulfoxides, amides, and nitriles.[221,222]

Hydrogen peroxide is increasingly attractive as a green oxidant and is being produced on a very large scale.[223] It is almost always used as an aqueous solution.[224] $H_2O_2$ is unstable with respect to disproportionation to water and dioxygen, but this is slow in the absence of light or a catalyst. The most famous example is the Fenton reaction, in which iron salts catalyze the decomposition in part by the inner-sphere reduction of $H_2O_2$ by Fe(II) (eq 20), which yields the very reactive hydroxyl radical (HO$^{\bullet}$).[225,226] This and related reactions are a connection between the compounds with O−O bonds discussed in this section and the water/hydroxyl radical PCET chemistry described earlier. The proton-coupled reduction of $H_2O_2$ to $H_2O$ + OH$^{\bullet}$ is thermodynamically quite favorable (eq 21). In practice, however, cleavage of $H_2O_2$ by outer-sphere electron donors and hydrogen atom donors often has a large kinetic barrier, likely associated with the cleavage of the O−O bond.[227]

$$\text{Fe(II)} + H_2O_2 \rightarrow \text{Fe(III)OH} + OH^{\bullet} \quad (20)$$

$$H_2O_2 + e^- + H^+ \rightarrow H_2O + OH^{\bullet} \quad E° = 0.80 \text{ V}$$
$$H_2O_2 + H^{\bullet} \rightarrow H_2O + OH^{\bullet} \quad \Delta G° = -76 \text{ kcal mol}^{-1} \quad (21)$$

### 5.4.5. Organic Hydroperoxides

Organic hydroperoxides have received considerable attention for their roles in synthesis, catalysis, and biochemical processes. Like $H_2O_2$, the free radical chemistry of ROOH-containing systems can proceed either by O−O or O−H homolysis. Here we only discuss the chemistry of the O−H bond; the interested reader is pointed to a review of the radiation and photochemistry of peroxides, which discusses a variety of O−O bond homolysis reactions.[230] PCET reactions of organic peroxyl radicals have almost always been understood as HAT reactions, especially the chain-propagating step in autoxidation.[17] This makes sense because of the strong ROO−H bonds, while PT−ET or ET−PT pathways are disfavored by the low basicity of ROO$^{\bullet}$ and the moderate ROO$^{\bullet/-}$ potentials (Table 10).

The most commonly employed organic hydroperoxide is *tert*-butyl hydroperoxide. The gas-phase thermochemistry of organic peroxides has been widely discussed. Simmie et al.[231] recently gave $\Delta H_f°$($^t$BuOO$^{\bullet}$) = −24.69 kcal mol$^{-1}$, which, together with $\Delta H_f°$(H$^{\bullet}$) = 52.103 kcal mol$^{-1}$ [232] and $\Delta H_f°$($^t$BuOOH) = −56.14 kcal mol$^{-1}$,[233] gives BDE$_g$($^t$BuOOH) = 83.6 kcal mol$^{-1}$.[234]

The p$K_a$ values of several alkyl hydroperoxides and peracids have long been known,[235] and p$K_a$ values for several peroxybenzoic acids have been reported.[236] However, until recently,

**Table 10. PCET Thermochemistry of Organic Hydroperoxides[a]**

| compound | solvent | $E(ROOH^{\bullet+/0})$ | $E(ROO^{\bullet/-})$ | $pK_a(ROOH^{\bullet+})$ | $pK_a(ROOH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| MeOOH | gas | | | | | 79.6 | 87.8[234a] |
| MeOOH | $H_2O$ | [1.62][b] | 0.94[237] | [0][b] | 11.5[235] | 95.0 | 93.2 |
| EtOOH | gas | | | | | 76.6 | 84.8[234a] |
| EtOOH | $H_2O$ | [1.57][b] | 0.91[237] | [0][b] | 11.8[235] | 94.8 | 93.0 |
| $^{i}$PrOOH | gas | | | | | 76.9 | 85.1[231] |
| $^{i}$PrOOH | $H_2O$ | [1.51][b] | 0.81[237] | [0][b] | 12.1[235] | 92.8 | 91.0 |
| $^{t}$BuOOH | gas | | | | | 76.1 | 84.3[234a] |
| $^{t}$BuOOH | $H_2O$ | [1.47][b] | 0.71[237] | [0][b] | 12.8[235] | 91.5 | 89.7 |
| HC(O)OOH | gas | | | | | 86.8 | 95.0[241] |
| HC(O)OOH | $H_2O$ | | [>1][c] | | 7.1[235] | [>90.4] | [>88.6] |
| $CH_3C(O)OOH$ | gas | | | | | 82.3 | 90.5[242] |
| $CH_3C(O)OOH$ | $H_2O$ | | [1.14][d] | | 8.2[235] | 95.1 | 93.3 |
| $^{n}$PrC(O)OOH | $H_2O$ | | | | 8.1[235] | | |
| $^{n}$BuC(O)OOH | $H_2O$ | | | | 8.2[235] | | |
| *m*-CPBA | $H_2O$ | | | | 7.5[236] | | |

[a] Potentials are in V vs NHE and BDFE and BDE are in kcal mol$^{-1}$. Gas-phase BDFEs are calculated from gas-phase BDEs and $S°_{gas}(H^{\bullet})$ from ref 49. Aqueous BDFEs calculated from $E°$ and $pK_a$ values (eqs 15 and 16) and the solution BDEs are estimated from those values using eq 9. [b] From ref 237 assuming that $pK_a$ $ROOH^{\bullet+} \approx 0$. [c] Minimum value, see text. [d] Estimated from electron transfer kinetic data (see text).[240]

the reduction potentials of the corresponding peroxyl radicals have remained elusive. Neta and co-workers indirectly measured the $ROO^{\bullet/-}$ couple for several peroxyl compounds in water (Table 10).[237] Their value for $E°(^{t}BuOO^{-/\bullet})$ is in good agreement with an earlier estimate made using kinetic and $pK_a$ data.[238] In contrast, very little data exist on the redox potentials of percarboxylate anions. Peracids have gas-phase BDFEs that are a little higher, and they are more acidic than the corresponding alkyl peroxides, which indicate that the $RC(O)OO^{\bullet/-}$ potentials are probably more oxidizing ($\geq 1$ V).[239] Jonsson's estimate of $E°(CH_3C(O)OO^{\bullet/-}) = 1.14$ V[240] is in agreement with this analysis. Jonsson has also estimated thermochemical data for a variety of other peroxides, but these need to be used with caution as they were extracted from electron transfer kinetic data[240] and some of these values do not agree with those determined via more direct methods (e.g., Jonsson gives $E°(Cl_3COO^{\bullet/-}) = 1.17$ V while Neta and co-workers report $E°(Cl_3COO^{\bullet/-}) = 1.44$ V[237]).

## 5.5. Simple Nitrogen Compounds: Dinitrogen to Ammonia, Amines, and Arylamines

The previous sections all focused on reagents with reactive O−H bonds. With this section, we shift to N−H bonds, and further sections deal with S−H and C−H bonds. While the same principles apply, there are some important differences. N−H bonds are less acidic than comparable O−H bonds, and in general, *N*-lone pairs are higher in energy so nitrogen compounds are more basic and more easily lose an electron to form the radical cation. Therefore, stepwise PCET reactions of amines typically involve aminium radical cations ($R_3N^{\bullet+}$), particularly for arylamines, whereas those of alcohols and phenols involve alkoxides and phenoxides. We start with the simple gas-phase species from $N_2$ to ammonia, then progress to alkyl and aryl amines, and finally to more complex aromatic heterocycles of biological interest.

### 5.5.1. Dinitrogen, Diazine, and Hydrazine

Dinitrogen ($N_2$) is one of the most abundant compounds on earth, making it an almost unlimited feedstock for the production of reduced nitrogen species such as ammonia. The overall reduction of dinitrogen to ammonia by dihydrogen is thermodynamically favorable under standard conditions both in the gas phase and in aqueous solution. However, this is a $6H^+/6e^-$ reaction and cannot occur in one step.[243] The energetics of the intermediates are therefore important. Industrially, dinitrogen is reduced to ammonia via the Haber-Bosch process, which is carried out at high temperatures and high pressures by an iron catalyst. The high temperature is needed to overcome the kinetic barrier but makes the reaction less favorable so high pressures are needed. Combining the production of the $H_2$ and the operation of the Haber-Bosch process, it is said that industrial $N_2$ fixation accounts for 1% or more of the total human energy consumption.[244] In biology, $N_2$ fixation is accomplished by nitrogenase enzymes in solution at room temperature using reduced ferredoxins and ATP.[243] Most biochemical studies and biomimetic models for nitrogen fixation propose sequential single-electron and single-proton transfers to metal-bound nitrogen species, but the thermochemistry of these steps is not experimentally known (only in the Schrock/Yandulov cycle is there good evidence for each of the various intermediates).[245,246] Much less is known about the solution thermochemistry of simple $N_xH_y^{z\pm}$ species compared with the oxygen analogues. The known aqueous values are provided by Stanbury,[247] and Koper and co-workers have recently reviewed electrochemical studies.[248]

Dinitrogen is one of the most inert chemical compounds. The addition of a proton or an electron is not very favorable: $N_2$ has a gas-phase proton affinity of 5.12 eV, slightly less than methane, and its electron affinity is negative (−1.8 eV).[243] The BDE of NN−H is estimated to be close to or less than 0 kcal/mol (Table 11).[249] These values make it unlikely that reduction of free dinitrogen can proceed through a free one-electron reduced species. The two H-atom reduced species of dinitrogen is diazene (HN═NH), also called diimide. Diazene is unstable, as it is a powerful H-atom transfer agent with a first BDE of only ~60 kcal/mol.[49] The average gas-phase BDFE for *Z*-diazene to $N_2 + 2H^{\bullet}$ is only 19.5 kcal mol$^{-1}$ (average BDE = 26.7 kcal mol$^{-1}$), so decomposition to $N_2$ and $H_2$ is very favorable.[49] Moreover, diazene is thought to transfer both hydrogens in a concerted fashion to alkenes and alkynes, a very rare example of a $2e^-/2H^+$ reaction.[250] Diazene, like dinitrogen, is a very poor base, with a $pK_a$ of the conjugate acid of <0.[251]

The reduction of diazene by one H-atom gives the hydrazyl radical ($HNNH_2$), a high-energy species with a very weak N−H bond. Hydrazyl is capable of abstracting a H-atom to yield the more stable hydrazine ($H_2NNH_2$) with $BDFE_{aq}(H_2NNH_2) = 83$ kcal mol$^{-1}$. In the gas phase, the

**Table 11. PCET Thermochemistry for $N_2H_x$ Derivatives[a]**

| compound | solvent | $E°(-NH^{\bullet+/0})$[a] | $pK_a(-NH^{\bullet+})$ | $pK_a(-NH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|
| NN−H | gas | | | | | $\sim -4$[b,249] |
| HNN−H | gas | | | | 52.6 | 60.8[49] |
| HNN−H | $H_2O$ | | | 34.3[255] | | −[c] |
| HNNH−H | gas | | | | 35.6 | 43.8[256] |
| HNNH−H | $H_2O$ | [−0.22][d] | −1.5[247] | | 50.5 | −[c] |
| $H_2$NNH−H | gas | | | | 72.6 | 80.8[256] |
| $H_2$NNH−H | $H_2O$ | 0.69 | 7.2[257] | | 83.4 | −[c] |

[a] Potentials in V referenced to NHE. Gas-phase BDFEs (kcal $mol^{-1}$) calculated from gas-phase BDEs and $S°_{gas}(H^{\bullet})$ from ref 49. Solution BDFEs calculated from $E°$ and $pK_a$ values (eqs 7, 15, and 16). [b] Approximate value based on density functional theory (DFT) calculations. [c] BDEs are not given for these species because it is not clear that eq 9 holds for very small molecules in water where the solvation of the closed shell and radical species may be complicated. [d] Calculated from the $1e^-/1H^+$ potential of −0.31 V vs. NHE.

**Table 12. PCET Thermochemistry of Ammonia and Alkylamines[a,b]**

| compound | solvent | $E(RR'NH^{\bullet+/0})$ | $pK_a(RR'NH^{\bullet+})$ | BDFE | BDE |
|---|---|---|---|---|---|
| $H_3N-H^+$ | gas | | | 116.9 | 125.1[263,264] |
| $^+H_2N-H$ | gas | | | 121.9 | 130.1[263] |
| $H_2N-H$ | gas | | | 99.4 | 107.6[265] |
| $MeNH_2$ | gas | | | 93.4 | 101.6[266] |
| $PrNH_2$ | MeCN | 1.12[267] | [5.7] | 88.6 | 93.1[262] |
| $PrNH_2$ | $C_6H_6$ | | | 86.2 | 91.0[262] |
| $PrNH_2$ | MeCN | 1.10[267] | [7.6] | 90.7 | 95.5[262] |
| $PrNH_2$ | $C_6H_6$ | | | 86.0 | 90.5[262] |
| $Me_2N-H$ | gas | | | 86.4 | 94.6[266] |
| $Me_2N-H$ | $H_2O$ | 1.27[268] | 6.8[268] | 96.2 | 94.4 |
| $Et_2N-H$ | $H_2O$ | 1.36[268] | 5.3[268] | 96.2 | 94.4 |
| $Et_2N-H$ | MeCN | 0.97[269] 0.75[268] | [5.0] [8.7] | 84.1 | 88.6[262] |
| $Et_2N-H$ | $C_6H_6$ | | | 82.2 | 87.0[262] |
| piperidine | $H_2O$ | 1.34[268] | 5.8[268] | 96.5 | 94.6 |
| $^nBu_2N-H$ | $C_6H_6$ | | | 86.0 | 90.8[262] |
| $^nBu_2N-H$ | MeCN | 0.83[269] | [7.6] | 84.4 | 88.9[262] |
| $^tBuNH_2$ | $C_6H_6$ | | | 90.2 | 95.0[262] |
| $^tBuNH_2$ | MeCN | 1.13[267] | [5.7] | 88.8 | 93.3[262] |

[a] Potentials are in V vs NHE for aqueous values and vs $Cp_2Fe^{+/0}$ in MeCN; BDFE and BDE are in kcal $mol^{-1}$. Gas-phase BDFEs are calculated from gas-phase BDEs, and $S°_{gas}(H^{\bullet})$ is from ref 49 [assuming $S°_{gas}(XH) = S°_{gas}(X^{\bullet})$]. Solution BDFEs are calculated from $E$ and $pK_a$ values (eqs 7, 15, and 16), and the solution BDEs are calculated from those values using eq 9. [b] We have found no values for $E°(RR'N^{\bullet/-})$ or $pK_a(RR'NH)$ for simple amines.

average BDFE for $H_2NNH_2$ to *Z*-diazene + $2H^{\bullet}$ is 58.7 kcal $mol^{-1}$ (average BDE = 66.2 kcal $mol^{-1}$).[49] Like peroxides, hydrazine has a weak N−N bond (BDE = 66.2 kcal $mol^{-1}$) and can undergo homolytic N−N bond cleavage as well as PCET reactions. Hydrazine's lone pairs make it moderately basic, with a first $pK_a$ of the conjugate acid similar to the $pK_a$ of ammonium, though the addition of a second proton is very unfavorable.[247] Electron transfer oxidation of tetraalkylhydrazines has been examined by Nelsen and others.[252] Hydrazine is a powerful, but kinetically slow, oxidant, undergoing $2e^-/2H^+$ reduction to give two molecules of ammonium with $E° = 1.2$ V in acidic aqueous solution.[253] Hydrazine has also been used as a mild reducing agent in aprotic media, though the proton-containing products are not clear.[254]

### 5.5.2. Ammonia and Alkylamines

Ammonia is the simplest amine and a critical commodity chemical; in 2005, global ammonia production was estimated at 168 million tons.[258] Ammonia is a good base ($pK_a(NH_4^+)_{H_2O} = 9.24$[259]), so it primarily exists as ammonium salts at normal physiological conditions. The gas-phase N−H homolytic bond strengths for $NH_3$, $NH_4^+$, and $NH_3^{\bullet+}$ are very high (Table 12). H-abstraction from $NH_3$ requires very high energy species, such as hydroxyl radical.[260] The $pK_a$ of $NH_3$ has been estimated to be 38,[261] similar to that for $H_2$ (see below).

As indicated above, alkylamines can often be oxidized by one $e^-$ to the protonated aminium radical cation $R_2NH^{\bullet+}$ (Table 12), which is substantially less acidic than a protonated alkoxyl radical. As with alcohols, the N−H bonds in alkylamines are significantly stronger than the α-C−H bonds (because of dative stabilization of the carbon radical by the nitrogen lone pair). This is evident, for instance, in the N−H and C−H alkylamine BDEs in MeCN and $C_6H_6$ reported by Lalevée and co-workers.[262]

### 5.5.3. Arylamines and Arylhydrazines

Arylamines are more easily oxidized to radical cations than phenols, because $-NH_2$ is a more electron-donating substituent to the aromatic ring than −OH (in both cases, the electron is lost from a $\pi$-symmetry orbital in large part on the aromatic ring). Therefore, for anilines, the potential for oxidation of the neutral $ArNH_2$ is experimentally accessible $E°(ArNH_2^{\bullet+/0})$, whereas for phenols the accessible outer-sphere potential involves the phenoxide $E°(PhO^{\bullet/-})$. Monoaryl and diaryl aminium radical cations are transient, but triarylaminium radical cations with *para*-substituents are isolable and very useful, for instance as chemical reagents[254] and as "hole-transport" electronic materials.[270] Bordwell et al. have tabulated data for complete square schemes for several substituted anilines and diphenylamines.[271] Furthermore, Jonsson, Lind, Merényi, and co-workers have determined reduction potentials for anilinium radical cations and $pK_a$ values for the corresponding radical cations in water.[268,272,273] Selected data are shown in Table 13, but other examples are available in both DMSO and water in each respective reference.

The N−H BDE of aniline ($PhNH_2$) in $C_6H_6$ has been measured by MacFaul et al. using photoacoustic calorimetry (PAC), and they calculated the gas-phase BDE using estimated solvation enthalpies.[274] These values are consistent with the BDE derived from the reported $E°$ and $pK_a$ data in DMSO when we extrapolate it to $C_6H_6$ using Abraham's model.[275,276] For diphenylamine, a number of slightly different BDEs have been reported,[274,277,278] as summarized by Pratt et al.;[278] at this time, we see no clear reason to favor one value.[122]

The stable, isolable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) has long been used to study the antioxidant properties of organic compounds.[11,12,279] DPPH−H (1,1-diphenyl-2-picrylhydrazine) has a bond strength ca. 80 kcal $mol^{-1}$, making it well suited for studies of many antioxidants, such as phenols and thiols. The BDFE of DPPH−H is

**Table 13. PCET Thermochemistry of Arylamines**[a]

| compound | solvent | $E(R_2N^{\bullet/-})$ | $E(R_2NH^{\bullet+/0})$ | $pK_a(R_2NH^{\bullet+})$ | $pK_a(R_2NH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| $PhNH_2$ | gas | | | | | 81.5 | 89.7[274] |
| $PhNH_2$ | $H_2O$ | | 1.02[272] | 7.05[272] | | 90.8 | 88.0 |
| $PhNH_2$ | DMSO | *−0.992*[271] | *0.5*[271] | 6.4[271] | 30.6[271] | 90.1 | 94.7 |
| $PhNH_2$ | MeCN | [−1.1] | 0.66[268] | 17.5[b] | 44[b] | 94.1 | 98.6 |
| $PhNH_2$ | $C_6H_6$ | | | | | 87.4 | 92.2[274] |
| 4-$MePhNH_2$ | $H_2O$ | | 0.92[272] | 8.5[272] | | 90.9 | 89.1 |
| 4-$MePhNH_2$ | DMSO | *−1.072*[271] | *0.305*[271] | 8.5[271] | 31.7[271] | 89.8 | 94.4 |
| 4-$MePhNH_2$ | $C_6H_6$ | | | | | 85.2 | 90.0[274] |
| 4-$MeOPhNH_2$ | $H_2O$ | | 0.79[272] | 9.6[272] | | 89.0 | 87.2 |
| 4-$MeOPhNH_2$ | DMSO | *−1.188*[271] | *0.125*[271] | 10[271] | 32.5[271] | 87.6 | 92.2 |
| 4-$ClPhNH_2$ | $H_2O$ | | 1.01[272] | ~7 | | 90.5 | 88.7 |
| 4-$ClPhNH_2$ | DMSO | *−0.915*[271] | *0.535*[271] | 5.0[271] | 29.4[271] | 90.3 | 94.9 |
| 4-$CNPhNH_2$ | $H_2O$ | | 1.32[272] | 4[272] | | 93.5 | 91.7 |
| 4-$CNPhNH_2$ | DMSO | *−0.550*[271] | *0.795*[271] | 2.6[271] | 25.3[271] | 93.0 | 97.6 |
| 4-$CF_3PhNH_2$ | $H_2O$ | | 1.38[272] | 4.8[272] | | 96.0 | 94.2 |
| 4-$CF_3PhNH_2$ | DMSO | *−0.597*[271] | *0.723*[271] | 4.7[271] | 27.0[271] | 94.3 | 98.9 |
| $Ph_2NH$ | $H_2O$ | | 1.0[268] | 3.8[268] | | 85.9 | 84.1 |
| $Ph_2NH$ | DMSO | *−0.865*[271] | *0.455*[271] | 2.7[271] | 25.0[271] | 85.3 | 89.9 |
| $Ph_2NH$ | MeCN | [−0.82] | 0.61[268] | 13.5[b] | 37.5[b] | 87.5 | 92.0 |
| | | [−0.92] | 0.51[281] | | | 85.2 | 89.7 |
| $Ph_2NH$ | $C_6H_6$ | | | | | 84.4 81.3 | 89.2[274] 86.2[c] |
| $(4\text{-}MePh)_2NH$ | DMSO | *−0.923*[271] | *0.415*[271] | 2.9[271] | 25.5[271] | 84.8 | 89.4 |
| $(4\text{-}MePh)_2NH$ | MeCN | [−1.0] | 0.40[281] | 13.7[b] | 38[b] | 82.9 | 87.4 |
| DPPH−H[d] | $H_2O$/EtOH | 0.52[282] | | | 8.6[283] | 81[e] | 83[e] |
| DPPH−H[d] | DMSO | −0.093[280] | | | | | |
| DPPH−H[d] | $C_6H_6$ | | | | | 75.2 | 80.0[76 f] |
| DPPH−H[d] | hexane | | | | | 77[f] | 82[g] |
| $2,4\text{-}(NO_2)C_6H_3NHNPh_2$ | DMSO | −0.292[280] | | | 12.1[280] | 80.9 | 85.5 |
| $PhNHNPh_2$ | DMSO | −1.117[280] | | | 24.5[280] | 78.9 | 83.5 |
| PhNHNHPh | DMSO | −1.730[280] | | | 26.2[280] | 67.1 | 71.7 |
| $PhNHNH_2$ | DMSO | *−1.740*[280] | | | 28.8[280] | 70.4 | 75.0 |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. $E°$ and $pK_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6, 7). *Italicized* values are irreversible potentials ($E_{p,a}$) measured by cyclic voltammetry. BDFE and BDE are in kcal $mol^{-1}$. When neither has a reference, the BDFE has been calculated from $E$ and $pK_a$ values (eqs 7, 15, and 16); when one of these has a reference, the other has been calculated from it using eq 9. [b] Extrapolated from DMSO to MeCN using the method of Kütt and co-workers.[89] [c] The value reported in ref 277 is relative to $^tBu_3PhOH$. The value given here has been adjusted to reflect our critical reevaluation of BD(F)E of $^tBu_3PhOH$ in ref 40. [d] DPPH−H = 1,1-diphenyl-2-picrylhydrazine. [e] Assumes that $C_G(H_2O/EtOH) \approx C_G(H_2O)$ (and similarly for $C_H(H_2O)$). [f] Corrected for the revised heat of formation of azobenzene as described in ref 40. [g] BDFE(DPPH) in hexane is +1.17 kcal $mol^{-1}$ larger than BDFE($^tBu_3PhOH$) in hexane,[284] which we have estimated to be 76 kcal $mol^{-1}$ using the Abraham model and the data in Table 4.

perhaps best known in benzene from the calorimetric determination by Ingold and co-workers.[76] Thermochemical data in other solvents are also shown in Table 13. From the work of Bordwell in DMSO,[280] the bond strengths of aryl hydrazines are less than the BDFEs of arylamines, presumably because of stabilization of the radical by the delocalized $\pi$-system.

## 5.6. Tryptophan, Flavins, and Nucleosides

The nitrogen-containing heterocycles tryptophan, flavin, and the nucleotide guanine are important in biological redox chemistry. Tryptophan is thought to be important in long-range electron transfer in proteins,[123,285] and its oxidation products are often observed in oxidatively stressed proteins.[286] Guanine is the most easily oxidized nucleoside and is therefore implicated in the much-studied long-range hole transfer through DNA. Guanine oxidation is also thought to be important in DNA damage/repair.[287] Flavins are critical biological cofactors that mediate charge transfer in a variety of proteins.[288,289] Although these cofactors are widely discussed in terms of electron transfer, their pH-dependent redox potentials indicate that they should be viewed as PCET reagents, at least in certain circumstances.

### 5.6.1. Indole and Tryptophan

The biological importance of electron transfer reactions of tryptophan has prompted thorough studies of its solution thermochemistry (Table 14). Merényi and co-workers have reported aqueous redox potentials and $pK_a$ values for a series of indoles,[290] although their measurement of $E°(TrpH^{\bullet+/0})$ is different from the value reported by both Harriman[128] and DeFelippis et al.[131] (Table 14 does not give the $pK_a$ values for the amine or the carboxylate moieties of tryptophan.) Indoles and tryptophan are more acidic than alkylamines and anilines but are still less acidic than phenols [in DMSO, $pK_a$(indole) = 20.9[291] while $pK_a$(phenol) = 18.0[116] (see Tables 4 and 14 for more extensive data)]. The more striking difference between indole and phenol is the acidity of the radical cation: $PhOH^{\bullet+}$ is a very strong acid (aqueous $pK_a = -2$[115]) while $indole^{\bullet+}$ is a weak acid (aqueous $pK_a$ = 4.9[290]). Thus, oxidations of indoles and tryptophan often form the radical cation (like the amines discussed above), while oxidations of phenols typically form the neutral phenoxyl radical.

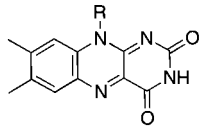
This comparison of indole and phenol is particularly interesting because tryptophan and tyrosine are the most important redox-active amino acids, and their thermochemistry proves the framework for understanding their roles in biological catalysis and charge transfer. Tyrosine radical cations ($TyrOH^{\bullet+}$) are too high in energy to be involved in

**Table 14. Thermochemical Data for Indoles and Tryptophan[a]**

| compound | solvent | $E(R_2N^{\bullet/-})$ | $E(R_2NH^{\bullet+/0})$ | $pK_a(R_2NH^{\bullet+})$ | $pK_a(R_2NH)$ | BDFE | BDE |
|---|---|---|---|---|---|---|---|
| indole | DMSO | *−0.35*[291,293] | | | 20.94[291] | 91.7 | 96.3 |
| indole | $H_2O$ | [0.52] | 1.24[290] | 4.9[290] | 17.0[294] | 92.9 | 91.1 |
| tryptophan | $H_2O$ | [0.43] | 1.15[128] | 4.7[128] | 16.8[294] | 90.6 | 88.8 |
| | | | 1.24[290] | | | 92.6 | 90.8 |
| 2-$CH_3$−indole | $H_2O$ | | 1.10[290] | 5.7[290] | | 90.8 | 89.0 |
| 3-$CH_3$−indole | $H_2O$ | [0.38] | 1.07[290] | 5.0[290] | 16.6[294] | 89.1 | 87.3 |
| 2,3-$CH_3$−indole | $H_2O$ | | 0.93[290] | 6.1[290] | | 87.4 | 85.6 |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in DMSO; BDFE and BDE values are in kcal $mol^{-1}$. *Italicized* values are irreversible potentials ($E_{p,a}$) measured by cyclic voltammetry. The BDFEs are calculated from the $E$ and $pK_a$ values using eqs 7, 15, and 16; BDEs are calculated from the BDFEs using eq 9.

**Scheme 10. Nomenclature and Structures of Biologically Relevant Flavins**



6,7-dimethyl-isoalloxazine

R = H (lumichrome)
Me (lumiflavin)
$CH_2(CHOH)_3CH_2OH$ (riboflavin)
$CH_2(CHOH)_3CH_2O(PO_3^-)$ (flavin mononucleotide, FMN)
$CH_2(CHOH)_3CH_2O(PO_3^-)_2$-adenine (flavin adenine dinucleotide (FAD)

a biological system, even in photosystem II, which is said to contain the strongest oxidant in biology.[292] Thus, in biological systems (and in the large majority of chemical systems as well), tyrosine and other phenols are oxidized to the neutral phenoxyl radical. However, $TrpH^{\bullet+}$ is a much more accessible species, being much less acidic than $TyrOH^{\bullet+}$ and having a reduction potential 0.25 V lower than that of $TyrOH^{\bullet+}$. Therefore, oxidations of tryptophan (and indoles) often involve the radical cation, but not always.[453] In this way, indoles resemble the alkylamines and anilines discussed in section 5.5.3. While tryptophan is easier to oxidize by outer-sphere electron transfer, tyrosine is easier to oxidize by PCET because its BDFE is ∼3 kcal $mol^{-1}$ weaker than the N−H BDFE in tryptophan. Again, given the critical importance of the proton in these chemical transformations, we strongly encourage those working on redox-active amino acids to not just refer to the oxidized forms as, for instance, $Y^{\bullet}$ or $W^{\bullet}$, but to explicitly show the proton, for instance as $TyrO^{\bullet}$ versus $TrpH^{\bullet+}$.

### 5.6.2. Flavins

Flavin is the common name for a family of 7,8-dimethyl-substituted isoalloxazines (isoalloxazine = 10-substituted alloxazine). The reader should be warned that the current IUPAC flavin numbering scheme is different from much of the flavin literature published before ca. 1980.[295] There are four biologically relevant flavins, which differ only in the nature of the alkyl substituent at N10: lumiflavin, riboflavin, flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD) (Scheme 10).[296] These cofactors exhibit essentially identical redox[155] and acid/base chemistry (Figure 7). Both the fully oxidized and fully reduced forms are stable and are typically referred to using nomenclature analogous to quinones/hydroquinones.[289] For example, the fully reduced form can be referred to as the "flavohydroquinone". Flavins also exhibit stable "flavosemiquinone" radicals.[289] Like the other nitrogen centered radicals discussed above, the flavosemiquinones are basic, so they are predominantly protonated at physiological pH. Also like hydroquinones, flavins can undergo $2H^+/2e^-$ chemistry; thus, a 9-membered square scheme is needed to describe the PCET thermodynamics.

The proton-coupled redox chemistry of flavins has long been known. Michaelis and co-workers in the late 1930s[297,298] and Lowe and Clark in 1956[299] reported that lumiflavin, FMN, and FAD all have the Nernstian dependence of the redox potential on pH (∼60 mV per pH unit) below the $pK_a$ of the flavohydroquinone, which indicates that they can undergo $1e^-/1H^+$ and $2e^-/2H^+$ PCET reactions. Starting from the reduced anion, flavins can also mediate $1H^+/2e^-$ (hydride) transfer to give the fully oxidized form. The net hydride transfer from NAD(P)H to a flavin is a fundamental biological reaction that can be found in nearly any biochemistry text book. PCET chemistry of NADH and related compounds is discussed below. There is evidence that the mechanism of such net hydride transfers can be concerted in some instances.[300] A recent study of the enzyme glucose oxidase, using chemically modified flavin-type cofactors, concluded that glucose is most likely oxidized by concerted hydride ($2e^-/H^+$) transfer.[301] Flavins can also mediate single electron transfer reactions, such as has been implicated in the electron transport chain of NADPH oxidase, to name just one example.[302] The flavin cofactor in glucose oxidase has been shown to react with $O_2$ by electron transfer, showing the power of using a series of modified flavins in mechanistic studies.[303] The interested reader is directed to these references for the thermochemical properties of flavins, deazaflavins, and related derivatives. While electron and hydride transfer reactions of flavins are well-known, to our knowledge single hydrogen atom transfer reactions of flavins have not been widely discussed.

The acid/base chemistry of flavohydroquinones has been extensively studied. The first $pK_a$s of flavohydroquinones are generally much lower than that of many hydroquinones, and are below neutral pH, so that they are mostly ionized under biological conditions. The $pK_a$ for the flavohydroquinone and the flavosemiquinone have not been drastically revised since their first reports in the early 20th century.[289,297,299] Land and Swallow reported a $pK_a$ of 0.25 for protonation of oxidized riboflavin and $pK_a = 2.3$ for protonation of the flavin semiquinone.[304] We note that $pK_a$ values of the transient flavosemiquinones, like those of most transient radicals, are not simple to determine; the values quoted here are the most widely employed. Many reports of pH 7 midpoint one-electron potentials for flavins have emerged, but perhaps the most widely accepted values were reported by Anderson.[305] Those data were later used to fit $E$ versus pH data for flavins and obtain $1H^+/1e^-$ potentials at pH 0.[306] Using the known dissociation constants (Figure 7), we have calculated the standard $1e^-$ (not proton-coupled) reduction potentials shown along the vertical arrows in Figure 7. The derived bond strengths are in excellent agreement with the average bond

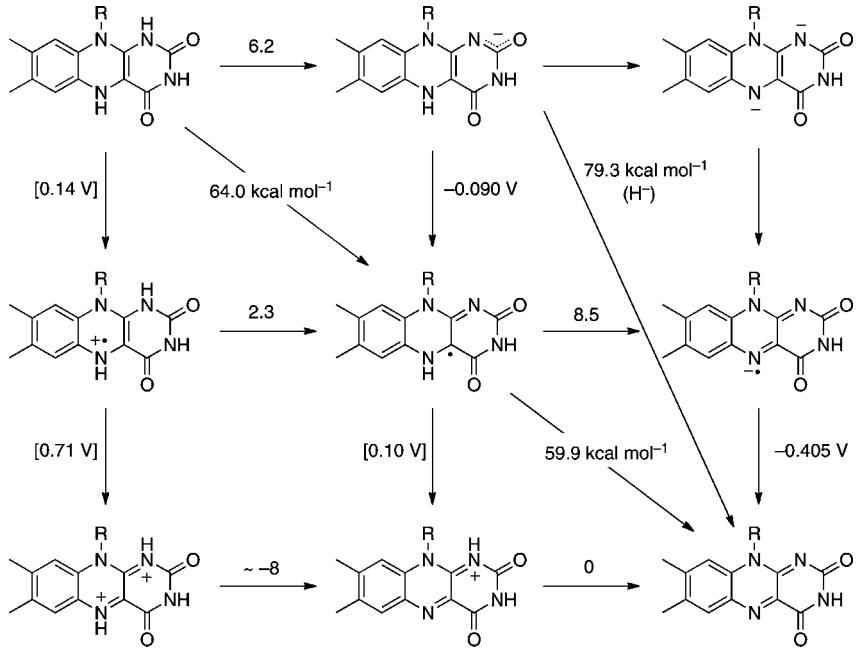



**Figure 7.** Double square scheme showing the PCET thermochemistry of flavins. While only one resonance form is drawn for each species, many are better described by multiple structures. Numbers above horizontal arrows give p$K_a$ values; numbers beside vertical arrows give electrochemical potentials vs NHE in water; numbers bisecting diagonal lines are BDFEs in kcal mol$^{-1}$; and the value beside the steep diagonal is a hydride affinity. The $E°$ values in square brackets are estimates using eq 7 and Hess' law. For definitions of R, see Scheme 10. References for the values in this scheme, and descriptions of how they were derived, are given in the text.

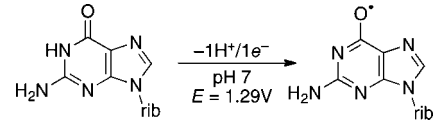
strength calculated from the pH 7 midpoint potential (−0.21 V,[155] equivalent to +0.2 V at pH 0 upon extrapolation with the Nernstian 59 mV per pH).

The free energy to lose $1H^+/2e^-$ (or $H^-$) is also shown in Figure 7, as the long steep diagonal. As with BDFEs, hydride affinities can be determined from thermodynamic square schemes.[5] In a given solvent, the hydride affinity is calculated from the sum of two free energies for reduction/oxidation (23.06$E°$), the free energy for protonation/deprotonation (1.37p$K_a$), and 23.06$E°(H^{+/-})$ (= 23.06($E°(H^{+/\bullet}) + E°(H^{\bullet/-})$), see Table 19 and section 5.8.3).[5] By Hess' law, it does not matter which two reduction potentials and p$K_a$ values are used to calculate a hydride affinity so long as together they connect the two species differing by $H^-$.

The $2H^+/2e^-$ potentials for nonbiological substituted flavins do not vary drastically with respect to substitution,[155,307] ranging from $E° = 0.30$ V to $E° = 0.19$ V (the latter for the biological flavins discussed previously). This implies a range of average N−H BDFEs from 64.5 to 62 kcal mol$^{-1}$. Unfortunately, there are no individual p$K_a$/$E°$ data for many of these compounds, precluding construction of complete thermochemical cycles.

As noted above, the thermochemistry of flavins allows them to mediate a wide range of redox reactions, including hydride transfers and single-electron transfers. The ability of flavins to transfer $H^-$ is in contrast with hydroquinones, which do not normally react by hydride transfer presumably because the hydroquinone anion ($HQ^-$) is a high-energy species and difficult to generate under typical conditions (see above). In contrast, the reduced flavin anion is much lower in energy. In this way, flavins are also unique from the other nitrogen-containing compounds discussed previously. Inspection of Figure 7 shows that the thermochemical landscape for flavins is more "flat" than those for other compounds discussed here. Because the redox potentials of flavins are less sensitive to their acid/base chemistry (and vice versa), they are able to mediate a wider range of reactions do not strongly favor $H^\bullet$ transfer like phenols or ascorbate.

**Scheme 11. $1H^+/1e^-$ Reaction of Guanosine**




### 5.6.3. Nucleosides

The redox chemistry of nucleotides, nucleosides, and nucleobases has been of great interest because of its relevance to the effects of free radicals, oxidants, and ionizing radiation on DNA, as well as to the understanding of long-range change transport along DNA.[308] This section summarizes the PCET thermochemistry of individual nucleosides. These data are a foundation for understanding the redox chemistry of DNA, although the properties of the nucleosides can be different within the DNA helix. There is some evidence that charge transport along DNA can be a PCET process.[308f,309]

Guanine is the most easily oxidized nucleobase and therefore has received the most attention. At pH 7, one-electron oxidation of guanine occurs with loss of the N1 proton (Scheme 11; the radical density in the product is mostly at O6, as drawn). The most authoritative value for this redox potential is 1.29 V at pH 7.[310] It should be emphasized that *this is the potential for a $1H^+/1e^-$ transfer process* and *cannot* be used in analyses of pure electron transfer—although this has been done. The nature of the charge carrier in oxidized DNA is still a matter of debate, as summarized in a very recent review:[308e]

> "in the context of hopping and drift, the nature of the states that mediate charge transport vary with the sequence and sequence-dependent dynamics. What these states are, localized radical cations, localized neutral radicals, large polarons, delocalized domains, or a

**Table 15. PCET Thermochemistry of Nucleosides in Water[a]**

| compound | $E(RN^{\bullet}/RNH)$[a] | $pK_a(RNH^{\bullet+})$ | $pK_a(RNH)$ | BDFE | BDE |
|---|---|---|---|---|---|
| guanosine | 1.29[310] | 3.9[311] | 9.3[310] | 96.9 | 95.1 |
| adenosine | 1.42[310] | ≤1[312] | 12.5[310] | 99.9 | 98.1 |
| cytidine | 1.6[310] | | | 104.0 | 102.2 |
| thymidine | 1.7[310] | | | 106.3 | 104.5 |

[a] Potentials are in V vs NHE at pH 7; BDFE and BDE values are in kcal mol$^{-1}$. The BDFEs are calculated from the $E$ values using eq 16; BDEs are calculated from the BDFEs using eq 9.

combination, will be different on the basis of the properties of the specific donor, DNA bridge, and acceptor."

Table 15 gives the PCET thermochemical data for the four nucleosides at pH 7 and the bond strengths derived from these values. Steenken and Jovanovic also extrapolated these measured pH 7 potentials for guanosine and adenosine to standard pH 0 $E°$ values, accounting for the complex pH dependence of the neutral and radical species.[310] The bond strengths are quite high and highlight the propensity of the nucleobases to undergo reactions other than HAT with powerful oxidants, such as $OH^{\bullet}$ addition to guanosine to produce 8-oxo-guanosine. Reagents that abstract hydrogen atoms tend to react with the weak C−H bonds in the ribose portion of DNA. The nucleobase N−H bonds may also be kinetically unreactive because those hydrogen atoms are in strong hydrogen bonds, a possible effect analogous to Ingold's kinetic solvent effect for HAT from O−H bonds in small molecules in solution.[11]

## 5.7. Thiols

The redox chemistry of thiols is important in many areas of biology. The oxidation of the thiol side chain of the amino acid cysteine, $^{-}O_2CCH(NH_3^{+})CH_2SH$, forms disulfide linkages that are critical to the proper folding and function of peptides and proteins. Thiols are also important to the function of the hormone insulin, to catalysis by ribonucleotide reductases, to the structure of keratin in hair and other biomaterials. Thiols are important biological antioxidants, with the prototypical example being glutathione (GSH), a tripeptide of glycine, cysteine, and glutamic acid.[313] GSH has long been understood as an important biological antioxidant, and it has more recently been shown to have other important biological roles.[314] The redox chemistry of thiols typically involves net $H^{\bullet}$ loss to give the thiyl radical $RS^{\bullet}$, with subsequent disulfide formation or oxidation to sulfenic (RSOH), sulfinic [RS(O)OH], and/or sulfonic acids [$RS(O)_2OH$].

Thiols are in general more acidic than corresponding alcohols, are more easily oxidized, and have weaker X−H bonds. For example, in DMSO, thiophenol is 7.7 $pK_a$ units more acidic and $PhS^{-}$ is 35 mV easier to oxidize than phenol and phenoxide, which results in an 11 kcal mol$^{-1}$ weaker BDFE (Tables 4 and 16). In water, the differences are less because $PhS^{-}$ is not as strongly solvated as $PhO^{-}$: the differences are 3.4 $pK_a$ units, 0.1 V in $E°(PhE^{\bullet/-})$, and 7 kcal mol$^{-1}$ in BDFE (E = S or O). Extensive $pK_a$ data available for thiols[315] but fewer redox potentials are known, presumably because of the rapid dimerization of thiyl radicals. Representative available data are given in Table 16 for selected compounds. We can find no data for thiol radical cations, which suggests that these are high-energy species with $E°(RSH^{\bullet+/0}) > 1$ V and $pK_a(RSH^{\bullet+}) < 0$ in water.

**Table 16. PCET Thermochemistry of Thiols[a]**

| compound | solvent | $E(RS^{\bullet/-})$ | $pK_a$(RSH) | BDFE | BDE |
|---|---|---|---|---|---|
| HS−H | gas | | | 83.0 | 91.2[37] |
| HS−H | $H_2O$ | 1.15[316] | 7.0[137] | 93.7 | 91.9 |
| MeS−H | gas | | | 79.2 | 87.4[321] |
| MeS−H | $H_2O$ | 0.73[b] | 10.3[137] | 88.6 | 86.8 |
| EtS−H | gas | | | 79.1 | 87.3[322] |
| EtS−H | $H_2O$ | 0.74[b] | 10.6[137] | 89.3 | 87.5 |
| $^{t}$BuS−H | gas | | | 78.4 | 86.6[323] |
| $HOCH_2CH_2S$−H | $H_2O$ | [0.77] 0.75[317] | 9.5[c] | 88.3[d] | 86.5 |
| cysteine | $H_2O$ | 0.73[318] | 8.5[319 e] | 86.2[e] | 84.4[e] |
| | | | 9.1[319 f] | 87.0[f] | 85.2[f] |
| glutathione | $H_2O$ | 0.81[324] | 9.3[325] | 89.0 | 87.2 |
| PhS−H | gas | | | 75.3 | 83.5[326] |
| PhS−H | $H_2O$ | 0.69[327] | 6.6[137] | 82.6 | 80.8 |
| PhS−H | DMSO | *−0.36*[41] | 10.3[41] | 76.9 | 81.5 |
| PhS−H | $C_6H_6$ | | | 81.6 | 86.4[326] |
| 4-MePhS−H | $H_2O$ | 0.64[327] | 6.8[137] | 83.9 | 82.1 |
| 4-MeOPhS−H | $H_2O$ | 0.57[327] | 6.8[137] | 80.1 | 78.3 |
| 4-BrPhS−H | $H_2O$ | 0.71[327] | 6.0[137] | 82.2 | 80.4 |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in DMSO. *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. The $E$ value in [square brackets] is calculated from the other values in the row using Hess' law (eqs 6, 7). BDFEs (kcal mol$^{-1}$) are calculated from $E$ and $pK_a$ values (eqs 7, 15, and 16) or (for gas-phase values) from the BDE(g) using eq 10. Solution BDEs (kcal mol$^{-1}$) are calculated from the corresponding BDFEs using eq 9. The application of either eqs 9 or 10 requires the assumption that $S°(RS^{\bullet}) = S°(RSH)$. [b] Calculated using the relevant gas-phase BDFE following Surdhar and Armstrong in ref 316. [c] Average of several reported values; see ref 315. [d] Calculated from the $1H^{+}/1e^{-}$ potential (1.33 V) reported in ref 317. [e] $pK_a$ (and therefore BDFE and BDFE) for zwitterionic form of cysteine. [f] $pK_a$ (and therefore BDFE and BDE) of $HSCH_2CH(CO_2Et)NH_2$.

Surdhar and Armstrong used gas-phase RS−H BDEs, estimated heats of solution, and the $pK_a$ values to calculate $RS^{\bullet/-}$ redox couples in water.[316] They used BDE(RS−H) = 81.2 kcal mol$^{-1}$, but more recently these values have been determined to be larger, ca. 87 kcal mol$^{-1}$ (Table 16). Using Armstrong's thermochemical cycle with the revised gas-phase BDFEs shown in Table 16 gives $E°(MeS^{\bullet/-}) = 0.73$ V and $E°(EtS^{\bullet/-}) = 0.74$ V. These values are in good agreement with later estimates of $E°(RS^{\bullet/-})$ for deprotonated $\beta$-mercaptoethanol ($HOCH_2CH_2SH$)[317] and cysteine.[318]

$\beta$-mercaptoethanol has better solubility in water than other alkyl thiols and serves as a reasonable model of aqueous thiol chemistry because the thiol and alcohol moieties are not too near to each other. The aqueous potential for $HOCH_2CH_2S^{\bullet} + H^{+} + e^{-} \rightarrow HOCH_2CH_2SH$ is $E° = 1.33 \pm 0.02$ V.[317] Applying eq 15 gives $BDFE_{H_2O}(HOCH_2CH_2S-H) = 88.3$ kcal mol$^{-1}$ (and $BDE_{H_2O}(HOCH_2CH_2S-H) = 86.5$ kcal mol$^{-1}$ with the assumption that $S°_{H_2O}(HOCH_2CH_2S^{\bullet}) = S°_{H_2O}(HOCH_2CH_2SH)$, see above). This value is in excellent agreement with the bond strengths calculated above from thermochemical cycles.

The $pK_a$ of the S−H group in cysteine has long been known[319] and was recently determined as a function of temperature and ionic strength.[320] It is very similar to the $pK_a$ of other alkyl thiols,[315] which is not surprising since the side chain is fairly separated from the amine and carboxylate groups. The $RS^{\bullet} + H^{+} + e^{-} \rightarrow RSH$ redox potential of cysteine, determined by Prütz and co-workers, is also very similar to the values determined by Surdhar and Armstrong. Thus, the PCET thermochemistry of cysteine, glutathione, and alkyl thiols are very similar. Like phenols and ascorbate, outer sphere oxidation of RSH to give the radical cation is unfavorable, so the oxidations of thiols preferentially lose

H• under normal physiological conditions, or are oxidized by other means, such as oxygen atom transfer.

## 5.8. C−H Bonds and $H_2$

Bell, Evans, and Polanyi showed in the 1930s that the facility of hydrogen atom abstraction from hydrocarbons parallels the gas-phase homolytic BDE of the C−H bond being cleaved. Ever since then, BDEs have been central to organic free radical chemistry and have been widely used for solution as well as gas-phase radical reactions: the gas-phase BDE is the typical starting point for understanding the reactivity of C−H bonds. However, it should be noted that other factors besides C−H bond strength affect radical reactivity. For instance, the polar effect[328] of electron-withdrawing substituents makes C−H bonds much less reactive toward electrophilic radicals such as $^t$BuO•, as illustrated above in the lack of reactivity of acetonitrile solvent with this radical.[198]

This portion of the review is divided into three subsections. The first presents selected thermochemical data for simple hydrocarbons and small alkylaromatic compounds. Readers interested in a wider range of compounds are referred to specialized reviews on the acidities, redox potentials, and bond dissociation energies of organic compounds. In particular, Bordwell and co-workers measured p$K_a$ values in DMSO for many compounds with weak C−H bonds, as well as a number of redox potentials of the corresponding anions.[29,69,329] One version of this is available online.[29] Kochi and others have discussed outer-sphere electron transfer reactions of organic compounds,[330] and Eberson's book on electron transfer in organic chemistry is particularly useful.[331] Recently, Luo has assembled an excellent and very extensive monograph on bond dissociation energies (which is also in part available online).[59] The second section below discusses the thermochemistry of nicotinamide derivatives and analogues, which are perhaps the most important biological PCET reagents with reactive C−H bonds. There are a number of other redox-active C−H bonds in biology that we would like to include, such as the glycine that is oxidized to a glycyl radical in the catalytic cycle of pyruvate formate−lyase activating enzyme[332] and the adenosine methyl C−H bond that is formed and cleaved in the catalytic cycles of vitamin $B_{12}$ and radical−SAM enzymes.[333] However, little experimental thermochemistry is available for these systems; the interested reader is referred to computational studies.[334] Finally, this section concludes with a discussion of the PCET thermochemistry of $H_2$.

### 5.8.1. Hydrocarbons

Gas-phase C−H BDEs of hydrocarbons have been repeatedly reviewed, but the reader is cautioned that the "best" values have changed over time (the reasons for this are nicely explained by Tsang[70]). Two of the more valuable current sources are a review by Blanksby and Ellison of gas-phase BDEs of common organic and inorganic compounds[37] and Luo's monograph mentioned previously.[59] Table 17 presents some of these data for hydrocarbons (and xanthene), as well as a few p$K_a$ and $E$ values. For a number of entries in the

**Table 17. PCET Thermochemistry of C−H Bonds in Selected Compounds**

| compound | solvent | $E(R^{\bullet/-})^a$ | $E(RH^{\bullet+/0})^a$ | p$K_a(RH^{\bullet+})^a$ | p$K_a$(RH)$^a$ | BDFE$^b$ | BDE$^b$ |
|---|---|---|---|---|---|---|---|
| $CH_4$ | gas | | | | | 96.8 | 105.0[336] |
| $CH_4$ | $H_2O$ | [−0.75] | | | ∼48[259] [c] | (106) | (104) |
| $CH_4$ | DMSO | [−2] | | | ∼56[29] | (102) | (107) |
| $CH_3CH_2$−H | gas | | | | | 92.9 | 101.1[337] |
| $(CH_3)_2$CH-H | gas | | | | | 90.4 | 98.6[337] |
| $(CH_3)_3$C−H | gas | | | | | 88.3 | 96.5[337] |
| $CH_2$=CH−H | gas | | | | | 102.5 | 110.7[338] |
| HC≡C−H | gas | | | | | 125.2 | 133.3[339] |
| *cyclo*-$C_5H_6$[d] | gas | | | | | 73.2 | 81.4[340] |
| *cyclo*-$C_5H_6$[d] | $H_2O$ | [0.11] | | | 16[341] | (82) | (80) |
| *cyclo*-$C_5H_6$[d] | DMSO | *−0.778*[329] | | | 18.0[329] | 77.8 | 82.4 |
| 1,4-cyclohexadiene | gas | | | | | 67.8 | 76.0[342] |
| $C_6H_5$−H | gas | | | | | 104.7 | 112.9[338] |
| $C_6H_5CH_2$−H | gas | | | | | 81.6 | 89.8[343] |
| $C_6H_5CH_2$−H | $H_2O$ | [−0.93] | | | ∼40[259] [e] | (91) | (89) |
| $C_6H_5CH_2$−H | DMSO | [−1.9] | | | ∼43 | (87) | (92) |
| $C_6H_5CH_2$−H | MeCN | *−1.85*[344] | *1.87*[335] | [∼ −8][f] | [∼54][f] | (87) | (92) |
| $(CH_3)_6C_6$ | MeCN | | *1.11*[335] | 2.0[345] | | 83.2 | 87.7 |
| *p*-$(CH_3)_2C_6H_4$ | MeCN | *−2.0*[346] | *1.45*[335] | [−4.3] | 53.8[346] | 82.5 | 87.0 |
| $(CH_3)_5C_6H$ | MeCN | | *1.19*[335] | 2.0[345] | | 85.1 | 89.6 |
| 1,2,4,5-$Me_4C_6H_2$ | MeCN | | *1.20*[335] | 3.0[345] | | 86.8 | 91.3 |
| indene | DMSO | *−0.952*[329] | | | 20.1[329] | 76.7 | 81.3 |
| fluorene | DMSO | *−1.069*[329] | | | 22.6[329] | 77.4 | 82.0 |
| fluorene | MeCN | *−1.16*[344] | *1.16*[335] | [∼ −3][f] | [∼35][f] | (77) | (82) |
| DHA[g] | DMSO | *−1.575*[329] | | | 30.1[329] | 76.0 | 80.6 |
| xanthene | DMSO | *−1.685*[329] | | | 30.0[329] | 73.3 | 77.9 |
| $Ph_3CH$ | DMSO | *−1.486*[329] | | | 30.6[329] | 78.8 | 83.4 |
| $Ph_2CH_2$ | DMSO | *−1.54*[329] | | | 32.2[329] | 79.7 | 84.3 |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. $E$ and p$K_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6 and 7). [b] BDFEs (kcal mol$^{-1}$) are calculated from $E$ and p$K_a$ values (eqs 7, 15, and 16) or (for gas-phase values) from the BDE(g) using eq 10. Solution BDEs (kcal mol$^{-1}$) are calculated from the corresponding BDFEs using eq 9. The application of either eqs 9 or 10 requires the assumption that $S°(R^{\bullet}) = S°(RH)$. BDE or BDFE values in (parentheses) have been estimated from a value in another solvent using the Abraham model (eq 13). [c] Given in ref 259, calculated from data in ref 347. [d] *cyclo*-$C_5H_6$ = 1,3-cyclopentadiene. [e] Given in ref 259, from data in ref 348. [f] For toluene and fluorene, p$K_a$'s in MeCN could be estimated from p$K_a$ measurements in DMSO (43[29a] and 22.6,[329,344] respectively) using the method of Kütt and co-workers,[89] but we believe that it is likely to be more accurate to estimate the p$K_a$s from the $E°$ and BDFE values. [g] DHA = 9,10-dihydroanthracene.

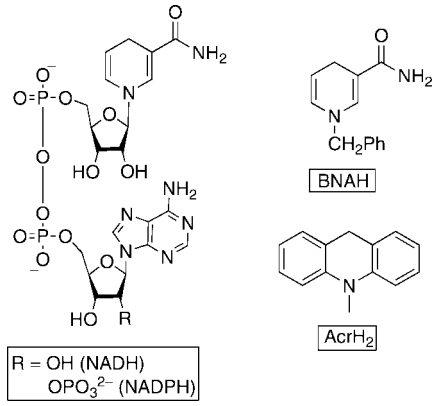



**Figure 8.** Structures of nicotinamide adenine nucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADPH), and the model complexes *N*-benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9,10-dihydroacridine ($AcrH_2$).

table, the solution bond strength has been calculated from the gas-phase value using Abraham's model, which is expected to work well here. In the absence of strong hydrogen bonding, the energies of solution are small and the differences in these energies should be very small [e.g., $\Delta G_{solv}°(R^{\bullet}) - \Delta G_{solv}°(RH) \approx 0$]. This means that the solution bond strengths differ from the gas-phase values primarily by the different solvation energies of $H^{\bullet}$ (see eq 11 above). Using this method, we estimate $BDFE(H_3C-H) \approx 106$ kcal $mol^{-1}$ in water and, using eq 16, $E°(CH_3^{\bullet/-}) = -0.7$ V vs NHE.

For several aromatic hydrocarbons, redox potentials $E(R^{\bullet+/0})$ are available in MeCN solvent.[335] For toluene, *p*-xylene, and fluorene, there are also data for the reduction of the neutral radical $R^{\bullet}$, and estimates can be made of the p$K_a$ values in MeCN. Thus, a complete cycle can be made for these reagents. However, readers should be cautioned that potentials and p$K_a$ values that are very high or very low are difficult to measure and may have larger errors.

These hydrocarbons, as exemplified by toluene, are extreme examples of reagents that prefer to react by $H^{\bullet}$ transfer rather than the stepwise paths of ET−PT or PT−ET. Few reagents are basic or oxidizing enough to mediate single-electron or single-proton transfers with toluene and other alkyl aromatics, yet the toluene C−H is of modest strength and is relatively easily abstracted. As discussed in more detail later, toluene is oxidized by a variety of transition metal complexes, and most of these reactions must proceed via concerted transfer of $H^{\bullet}$ because the stepwise electron transfer or proton transfer intermediates are simply too far uphill. However, an interesting exception involving stepwise ET−PT is also discussed in section 6. As noted above for hydroxylamines and phenols, one of the hallmarks of a reagent that prefers to transfer an electron and proton together is that the p$K_a$ changes dramatically upon redox change (and, equivalently, the $E°$ changes dramatically upon deprotonation). For toluene, the p$K_a$ values of $PhCH_3$ and $PhCH_3^{\bullet+}$ in MeCN differ by >50 orders of magnitude!

### 5.8.2. Nicotinamide Derivatives

One of the archetypal biological redox reactions of C−H bonds is the $H^+/2e^-$ couple in reactions of nicotinamide adenine nucleotide ($NAD^+$/H) and nicotinamide adenine dinucleotide phosphate ($NADP^+$/H, Figure 8). As noted above, NADH and NADPH commonly transfer hydride to flavins in many different enzyme catalytic cycles. Kreevoy and co-workers have beautifully explored the hydride transfer chemistry of NADH analogues and shown that the kinetics of these reactions are related to the thermochemistry of hydride transfer.[57] More recently, other cellular roles of nicotinamides have been uncovered.[349] In vitro, nicotinamide derivatives and analogues can undergo electron transfer, hydrogen atom transfer, and hydride transfer reactions (similar to flavins), as has been shown in a number of studies.[350]

The reactivities of NADH and related compounds, such as *N*-benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9,10-dihydroacridine ($AcrH_2$), have been widely studied, and there are a few reports of the redox potential and p$K_a$ data necessary to draw thermochemical schemes (Table 18). Nicotinamides are oxidized by two electrons with loss of one proton, to give the corresponding pyridinium ion, so a double square scheme is needed to describe each system

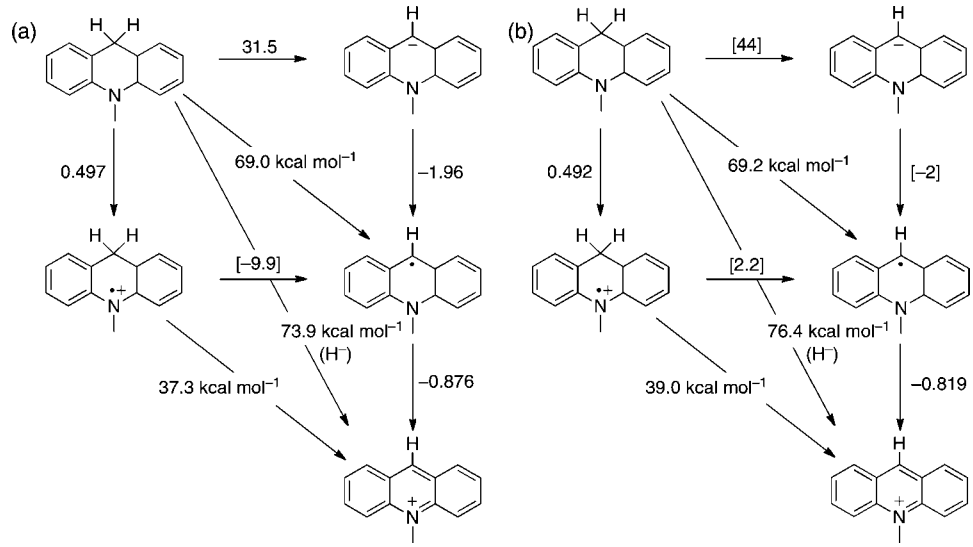



**Figure 9.** Square schemes showing the PCET thermochemistry of 10-methyl-9,10-dihydroacridine ($AcrH_2$) in (a) DMSO and (b) MeCN from Cheng and co-workers;[352,353] see text. Values above horizontal arrows give p$K_a$ values; numbers beside vertical arrows give electrochemical potentials vs $Cp_2Fe^{+/0}$; numbers bisecting diagonal lines are BDFEs in kcal $mol^{-1}$; and numbers along the steep diagonals are hydride affinities. The values in square brackets are estimates using eq 7 and Hess' law.

**Table 18. PCET Thermochemistry of Nicotinamides and Related Compounds[a]**

| compound | solvent | $E(R^{\bullet/-})$ | $E(RH^{\bullet+/0})$ | $E(R^{+/\bullet})$ | $pK_a(RH^{\bullet+})$ | $pK_a(RH)$ | BDFE(RH)[b] | BDFE($RH^{\bullet+}$)[b] | $\Delta G°(H^-)$ |
|---|---|---|---|---|---|---|---|---|---|
| $AcrH_2$ | DMSO | −1.96[352] | 0.497[352] | −0.876[352] | [−9.9] | 31.5[352] | 69.0 | 37.3 | 73.9 |
| $AcrH_2$ | MeCN | [−2] | 0.492[353] | −0.819[353] | 2.2[353] | 44[c] | 69.2[353] | 39.0 | 76.4 |
| $AcrH_2$ | MeCN | | 0.475[355] | −0.845[355] | 0.8[355] | 44[c] | 67.0 | 36.5 | 74.5 |
| BNAH | DMSO | | 0.182[352] | −1.53[352] | −3.3[352] | | 70.8 | 31.3 | 55.0 |
| BNAH | MeCN | | 0.406[355] | −1.49[355] | 4.7[355] | | 86.9 | 43.2 | 62.3 |
| NADH | $H_2O$ | | 0.94[356,357,d] | −0.92[357] | −3.5[357] | | 74.3 | 31.4 | 56.8 |
| | | | | | | | 79.3[351 e] | 36.3[351 e] | 53.6[351 e] |

[a] Drawings of the compounds are shown in Figure 8. Potentials are in V vs NHE for aqueous values and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. $E$ and $pK_a$ values in [square brackets] have been calculated from the other values in the row using Hess' law (eqs 6 and 7). [b] Only BDFEs (in kcal $mol^{-1}$) are given in this table because of space constraints. Assuming $S°(RH) = S°(R^{\bullet})$, the BDE is obtained from the BDFE by adding 4.6 (MeCN or DMSO), or −1.8 ($H_2O$) kcal $mol^{-1}$. [c] Estimated using the method of Kütt and co-workers.[89] [d] $E(NADH^{\bullet+/0}) = 1.05$ V in propanol/water.[357] [e] Values are bond dissociation *enthalpies*, from thermochemical cycles and calorimetric measurements in ref 351.

**Table 19. PCET Thermochemistry of Hydrogen[a]**

| solvent | $E(H^{\bullet}/H^+)$ | $E(H^{\bullet}/H^-)$ | $pK_a(H_2)$[b] | BDFE[c,d] | BDE[d] |
|---|---|---|---|---|---|
| gas | | | | 97.2 | 104.2[361] |
| water | −2.50[51] | 0.18[363] | [32] | 106.2 | 103.2 |
| DMSO | −3.08[51] | −1.09[363] | [42] | 102.8 | 106.2 |
| MeCN | −2.38[51] | −1.13[363] | [54] | 102.3 | 105.8 |
| MeOH | −2.83[51] | | | 102.4 | 105.0 |

[a] Potentials are in V vs NHE for aqueous measurements and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. BDFEs and BDEs are in kcal $mol^{-1}$. Ref 364 has proposed alternative values. [b] $pK_a$ values calculated from reduction potentials and BDFEs according to eq 22. [c] Gas-phase BDFE calculated from BDE and gas-phase $S°(H^{\bullet})$ and $S°(H_2)$ from ref 49. [d] Solution BDFEs and BDEs calculated from gas-phase values according to eq 11 assuming $\Delta G_{solv}°(H^{\bullet}) = \Delta G_{solv}°(H_2)$.[50]

(Figure 9). Nicotinamide radical cations are quite acidic, like the hydrocarbon radical cations discussed previously, and the closed shell (reduced) nicotinamides are very poor acids, highlighting the typical preference of these compounds to undergo PCET rather than ET or PT. Cheng and co-workers have presented thermochemical data for aqueous NADH[351] and for 10-methyl-9,10-dihydroacridine ($AcrH_2$) in DMSO[352] and MeCN (Figure 9),[353] although questions have been raised about some of these results.[354] For $AcrH_2$ in MeCN, there is reasonable agreement between the values of Cheng and co-workers and those reported earlier by Savéant, Neta, and co-workers, but there is a substantial disagreement in the values for BNAH.[355] There is also a discrepancy between the data of Cheng and co-workers[351] and other literature values[356,357] for NADH in water. The $E°$ and $pK_a$ data can be converted to BDFEs and hydride affinities ($\Delta G°(H^-)$), as discussed previously. The derived hydride affinities for $AcrH_2$ and benzyl nicotinamide BNAH (Figure 8) in MeCN are in reasonable agreement with those obtained from equilibrium measurements,[358] and the difference between them similarly agrees with the relative hydride affinities reported by Wayner and co-workers.[359] Methylated BNAH derivatives show thermochemistry that is similar to the parent compound in MeCN.[360]

### 5.8.3. Hydrogen

The H−H bond in dihydrogen is in many ways very similar to the C−H bond in methane. The gas-phase BDE[361] and BDFE[49] of $H_2$ are known (Table 19). These gas-phase values are within 1 kcal $mol^{-1}$ of methane. These BDEs and BDFEs, along with the known enthalpies and entropies of solution, are used to calculate BDEs and BDFEs in various solvents, using Roduner's 2005 demonstration that the solvation of $H^{\bullet}$ is energetically roughly equal to that of $H_2$.[50] As described in section 3.1, use of this approximation has led to revision of the $H^+/H^{\bullet}$ reduction potentials in different solvents. The $H^{\bullet}/H^-$ reduction potentials in water[362] and in DMSO and MeCN[363] have been reported, allowing the $pK_a$ of $H_2$ to be estimated by eq 22. $H_2$ is very weakly acidic, though significantly more acidic than methane. Recently, Kelly and Rosseinsky have proposed new values for $pK_a(H_2)$ and $E°(H^{\bullet/-})$, some of which are very different from the values that have long been used.[364]

$$pK_a(H_2)_{(solv)} = [BDFE(H_2)_{solv} - F[E°(H^{\bullet}/H^+)_{solv} + E°(H^{\bullet}/H^-)_{solv}]]/1.37 \quad (22)$$

## 5.9. Separate Proton and Electron Donors/Acceptors

This review primarily deals with PCET reagents, that is, individual chemical compounds that can donate or accept proton(s) and electron(s). *From a thermodynamic perspective*, this is equivalent to two reagents, one of which accepts or donates proton(s) and the other of which accepts or donates electrons. For instance, ferrocene−carboxylic acid is a single PCET reagent that can donate $e^- + H^+$ ($H^{\bullet}$) to give the zwitterionic ferrocene carboxylate, with an effective BDFE of 68 kcal $mol^{-1}$ in 80/20 MeCN/$H_2O$ solvent [assuming that $C_G(MeCN) \approx C_G(MeCN/H_2O)$].[365] Similarly, the combination of ferrocene and benzoic acid can donate $e^- + H^+$. One can even define a formal BDFE for the $Cp_2Fe$ + benzoic acid combination in MeCN, 83.3 kcal $mol^{-1}$, using the same eq 7 as used above for a single PCET reagent. The thermodynamic calculation is independent of whether the proton and electron come from a single reagent or two reagents. The most famous example of a separate outer-sphere oxidant and a base accomplishing a PCET reaction is the oxidation of tyrosine Z in photosystem II, in which the proton is transferred from tyrosine Z to a nearby histidine while the electron is transferred to the chlorophyll radical cation $P680^{+\bullet}$ about 14 Å away.[108]

The use of a "BDFE" for two separated reagents is perhaps a bit peculiar, because there is no X−H bond that is being homolytically cleaved. It is, however, a very useful way to characterize the thermochemistry of a PCET system, and it emphasizes the thermodynamic equivalence of $H^+/e^-$ acceptors and $H^{\bullet}$ acceptors [$H^+/e^-$ donors and $H^{\bullet}$ donors]. The literature for water oxidation, for example, typically quantifies the free energy required as a minimum redox potential of $E° = 1.23$ V (pH 0). However, this puts emphasis on the electron, while the thermochemistry depends equally on the $e^-$ and the $H^+$. What is needed to convert $H_2O$ to $O_2$ is a PCET reagent *or PCET system* with an average BDFE of ≥86 kcal $mol^{-1}$ (eq 18, described above). This free energy can be obtained with a single PCET reagent or with a

**Table 20. PCET Thermochemistry of a Few Oxidant/Base or Reductant/Acid Pairs in MeCN for Separated CPET**

| oxidant | $E_{1/2}$[a,b] | base | p$K_a$[c] | BDFE[d] |
|---|---|---|---|---|
| N(4-MeO−$C_6H_4$)$_3^{\bullet+}$ | 0.16 | pyridine | 12.5 | 75.7 |
| N(4-MeO−$C_6H_4$)$_3^{\bullet+}$ | 0.16 | 2,6-$Me_2$−pyridine | 14.1 | 77.9 |
| N(4-Me−$C_6H_4$)$_3^{\bullet+}$ | 0.40 | pyridine | 12.5 | 81.3 |
| N(4-Me−$C_6H_4$)$_3^{\bullet+}$ | 0.40 | 2,6-$Me_2$−pyridine | 14.1 | 83.5 |
| N(4-Me−$C_6H_4$)$_3^{\bullet+}$ | 0.40 | 4-N($Me_2$)−pyridine | 18.0 | 88.8 |
| N(4-Br−$C_6H_4$)$_3^{\bullet+}$ | 0.67 | pyridine | 12.5 | 87.5 |
| N(4-Br−$C_6H_4$)$_3^{\bullet+}$ | 0.67 | 2,6-$Me_2$−pyridine | 14.1 | 89.7 |
| N(2,4-$Br_2$−$C_6H_4$)$_3^{\bullet+}$ | 1.14 | pyridine | 12.5 | 98.3 |
| N(2,4-$Br_2$−$C_6H_4$)$_3^{\bullet+}$ | 1.14 | 2,6-$Me_2$−pyridine | 14.1 | 100.5 |
| reductant | $E_{1/2}$[a,b] | acid | p$K_a$[c] | $\Delta G_{H\bullet}$[d] |
| $Cp_2Fe$ | 0 | pyridinium | 12.5 | 71.5 |
| $(C_5Me_5)_2Fe$ | −0.48 | pyridinium | 12.5 | 61.0 |
| $Cp_2Fe$ | 0 | acetic acid | 22.3 | 85.5 |
| $Cp_2Co$[e] | −1.34[371] | acetic acid | 22.3 | 55.5[e] |

[a] Potentials are in V versus $Cp_2Fe^{+/0}$. [b] From ref 254 unless otherwise noted. [c] p$K_a$ of baseH$^+$ from ref 30. [d] Effective BDFE in kcal mol$^{-1}$ from eq 7. [e] For illustrative purposes; the stability of this combination is not known.

combination of an oxidant and a base. The required free energy can be obtained with a strong oxidant plus a weak base, or a weak oxidant plus a strong base. While this area has not received the same detailed study as traditional H-atom transfer reactions, we believe that it is a very important and versatile approach to PCET and will prove to be widely used in biology and valuable in the development of new chemical processes.

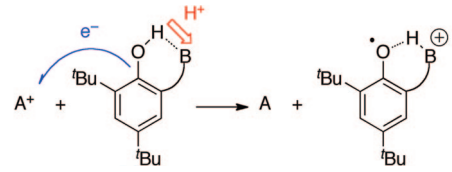
There are a huge number of possibilities for oxidant/base combinations (H$^\bullet$ acceptors) and reductant/acid combinations (H$^\bullet$ donors). This is because there are many one-electron redox reagents and a huge number of possible acids/bases. A few examples are listed in Table 20, with an emphasis on H$^\bullet$ acceptors in MeCN, based on our experience (cf., ref 366). The same principles should apply to other solvents and to "H$^\bullet$ donors". Listings are available of stable, isolable one-electron oxidants and reductants and their potentials in MeCN,[254] as well as tabulations of organic acids and bases and their p$K_a$ values.[28,30,89] There are, however, practical limitations at both the extremes of strong H$^\bullet$ acceptors (high BDFEs) and strong H$^\bullet$ donors (low BDFEs). In general, bases are electron-rich and can be oxidized, and in our experience this limits the combinations that are available at high BDFE. Similarly, strong reductants are electron rich and are often protonated by acids, and acids are often easily reduced to $H_2$. Some of the challenges are illustrated by the Schrock/Yandulov nitrogen reduction system, which uses decamethylchromocene as the very strong reductant ($E°$ for $CrCp^*_2$ = −1.47 V in THF vs $Cp_2Fe^{+/0}$ [Cp* = $C_5Me_5$]) and [2,6-lutidinium]BAr′$_4$ [Ar′ = 3,5-$(CF_3)_2C_6H_3$] as the acid.[245b] As Schrock wrote:

> "Heptane was chosen as the solvent to minimize the solubility of [2,6-lutidinium]BAr′$_4$ and thereby minimize direct reduction of protons by $CrCp^*_2$ in solution. Slow addition of the reducing agent in heptane to an Mo complex and [2,6-lutidinium]BAr′$_4$ in heptane (over a period of 6 h with a syringe pump) was chosen to minimize exposure of protons to $CrCp^*_2$ at a high concentration."[245b]

Waidmann has explored combinations of triarylaminium oxidants and substituted pyridine bases as strong H$^\bullet$ acceptors in $CH_2Cl_2$.[366] One of the key observations in these studies is that trace reducing impurities in the pyridine base can lead to decay of the aminium oxidant. Even with careful purification of the base, some oxidant−base combinations may not be compatible. For example, the N(4-Br−$C_6H_4$)$_3^{\bullet+}$ ($E_{1/2}$ = 0.67 V versus $Cp_2Fe^{+/0}$ in MeCN[254]) is stable in the presence of pyridine (p$K_a$ = 12.5[30]) at 298 K but decays in the presence of 4-$NH_2$−pyridine (p$K_a$ = 17.6[30]). [For the reader not accustomed to this electrochemical scale, $Cp_2Fe^{+/0}$ in MeCN is roughly +0.63 V vs aqueous NHE.[33]] By using different combinations of oxidant and base, effective BDFEs ranging from 76 to 100 kcal mol$^{-1}$ can be achieved (Table 20). Roughly the same BDFE can often be achieved with different combinations of oxidants and bases, which allows flexibility in selecting oxidant/base combinations based on the requirements or limitations of a given PCET system and which can be a valuable mechanistic test.

The discussion above has emphasized the *thermodynamics* of oxidant/base and reductant/acid combinations of reagents and that they are equivalent to the thermochemistry of single PCET reagents. However, equivalent BDFEs does not necessarily mean that the *kinetic behavior* will be the same for single PCET reagents vs combinations, or even that similar pathways—stepwise versus concerted—will be followed. A few studies have shown that two separate reagents can accomplish concerted transfer of H$^+$ and e$^-$, termed separated CPET (or multisite EPT). In perhaps the first clear example, Linschitz and co-workers oxidized phenols hydrogen bonded to pyridines, using photogenerated triplet $C_{60}$ as the oxidant (eq 23).[367] They showed that proton transfer to the pyridine is concerted with electron transfer to the oxidant. Hammarström and co-workers and Nocera and co-workers have studied reactions in which a tethered tyrosine is oxidized by a photoexcited transition metal complex (Ru or Re), with proton transfer to an intramolecular carboxylate or to the aqueous solvent or buffer.[10,14,368] Both separated CPET and stepwise proton transfer then electron transfer mechanisms have been observed. Rhile, Markle, and co-workers have examined oxidations of phenols with an attached base, in which outer-sphere electron transfer to an oxidant A$^+$ is concerted with intramolecular proton transfer (eq 24).[369] Hammarström and co-workers and Savéant and co-workers have examined similar systems.[368b,e,f,370] Costentin has thoroughly and clearly reviewed electrochemical CPET reactions, in which electron transfer to/from an electrode is concerted with proton transfer.[3]

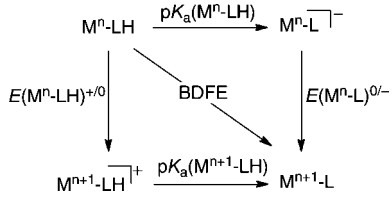
$$\mathrm{PhOH\cdots py} + {}^3\mathrm{C_{60}}^* \rightarrow \mathrm{PhO^\bullet\cdots Hpy^+} + \mathrm{C_{60}^-} \quad (23)$$




(24)

The examples in the previous paragraph show that combinations of oxidant and base, or reductant and acid, can in some circumstances accomplish concerted transfer of an electron and a proton. Thus, considering these combinations as having an "effective BDFE" is reasonable. More studies are needed to examine the generality and utility of these combination PCET reagents. In addition, as illustrated in the next section, the distinction between a single PCET reagent and two separate reagents is not always so clear.

**Scheme 12. Thermochemical Cycle for Transition Metal PCET Systems**




## 5.10. Selected Transition Metal Systems

The PCET chemistry of a wide range of transition metal systems has been investigated over the last few decades. No individual system has received the scrutiny of many of the classic organic systems discussed above, such as phenol, but there are examples for most of the transition metals that readily undergo one-electron redox change. A comprehensive account of all known transition metal PCET systems is beyond the scope of this review, which just presents selected examples.

Transition metal-containing systems can mediate a range of PCET reactions. Most of these systems undergo redox change at the metal coupled to protonation or deprotonation at a ligand. A classic example is the interconversion of a metal hydroxide complex with a one-electron oxidized metal−oxo compound (eq 25). This could be viewed as analogous to the oxidation of a phenol to a phenoxyl radical, in which the aromatic ring is oxidized by 1e$^-$. HAT reactions involving metal hydride complexes, which are well-known, are somewhat different because both the redox and acid/base chemistry occur at the metal center. In some ways, HAT from metal hydrides is similar to that of C−H bonds.

**Table 21. PCET Thermochemistry of Selected Transition Metal Systems[a]**

| compound (ML−H) | solvent | $E(M^n-L)^{0/-}$ | $E(M^n-LH)^{+/0}$ | $pK_a(M^{n+1}LH)$ | $pK_a(M^n-LH)$ | BDFE |
|---|---|---|---|---|---|---|
| $Fe^{II}(H_2O)_6^{2+}$ | $H_2O$ | [0.39] | 0.77[372] | 3[372] | 9.5[372] | 79.5 |
| $(H_2O)_5CrOOH^{2+}$ | $H_2O$ | | | | | 81.4[379 b] |
| $(H_2O)_5CrOH^{2+}$ | $H_2O$ | | | | | ≥91.6[380 b] |
| $(Me_6cyclam)Rh(H_2O)(OOH)^{2+}$ [b] | $H_2O$ | | | | | 80.0[381 b] |
| $(Me_6cyclam)Rh(HO)(OOH)^{2+}$ [b] | $H_2O$ | | | | | 79.5[381 b] |
| $(Me_6cyclam)Co(H_2O)(OOH)^{2+}$ [b] | $H_2O$ | | | | | 81.9[381 b] |
| $([14]aneN_4)Co(HO)(OOH)^{2+}$ [b] | $H_2O$ | | | | | 80.9[381 b] |
| $[(bpy)_2pyRu^{II}OH_2]^{2+}$ | $H_2O$ | 0.46[390] | 1.02[390] | 0.85[390] | 10.6[390] | 82.3 |
| $[[(bpy)_2pyRu^{III}OH]^{2+}$ | $H_2O$ | <0.48[383] | >1.6[383] | <0[383] | >13[383] | 84.8 |
| *trans*-$[Ru^V(tmc)(O)(O-H)]^{2+}$ [c] | $H_2O$ | 0.56[404] | [>0.67] | <1[404] | 2.8[404] | 74.3 |
| *trans*-$[Ru^{IV}(tmc)(O)(HO-H)]^{2+}$ [c] | $H_2O$ | 0.80[404] | | | 4.7[404] | 82.5 |
| $MnO_3(OH)^-$ | $H_2O$ | | 0.564[409] | 7.4[409] | | 80.7 |
| $[Mn_2(OH)_2(phen)_4]^{3+}$ | MeCN | −0.03[415] | | | 11.5[415] | 70.0 |
| $[Mn_2(O)(OH)(phen)_4]^{3+}$ | MeCN | −0.01[415] | | | 14.6[415] | 74.7 |
| $(salpn)_2(Mn_2(O)(OH))$[d] | MeCN | *−0.89*[410] | −0.21[410] | 24.5[410] | 13.4[410] | 68.4 |
| $(L^A)_2(Mn_2(O)(OH))$[e] | MeCN | *−0.63*[410] | 0.01[410] | 20.5[410] | 10.8[410] | 69.9,[e] 68.5[e] |
| $(L^B)_2(Mn_2(O)(OH))$[e] | MeCN | *−0.12*[410] | 0.47[410] | 13.3[410] | 5.0[410] | 72.6,[e] 70.4[e] |
| $(L^C)_2Mn_2OH_2$ [f] | —[e] | −0.52[411] | −0.09[411] | 10[411] | 19[411] | —[f] |
| $(L^C)_2Mn_2OH_2^+$ [f] | —[e] | 0.32[411] | *>0.97*[411] | <0[411] | 10[411] | —[f] |
| $[(L^D)Mn^{II}OH]^{2-}$ [g] | DMSO | <−2[392] | −1.51[391] | 28.3[391] | [>37] | 75.1 |
| $[(L^D)Mn^{III}OH^-$ [g] | DMSO | −1.0[391] | [−0.2] | ~15[392] | 28.3[391] | 86.8 |
| $[(L^D)Fe^{II}OH]^{2-}$ [g] | DMSO | | −1.79[391] | 25.0[391] | | 64.1 |
| $[(L^D)Fe^{II}OH]^-$ [g] | DMSO | *0.34*[391] | | | 25.0[391] | 113 |
| $(Py5)Fe^{II}(MeOH)^{2+}$ [h] | MeOH | *0.12*[394] | *0.32*[394] | [7.6] | 9.1[394] | 83.1 |
| $(Py5)Fe^{II}(OH_2)^{2+}$ [h] | DMSO | −0.095[395] | | | 8.1[395] | 63.8 |
| $(Py5)Mn^{II}(OH_2)^{2+}$ [h] | MeCN | 0.186[393] | 0.636[393] | [5.4] | 13[393] | 77.0 |
| $(bpy)_2V^V(O)(OH)^+$ | MeCN | | | | | 70.6[24] |
| $Ni^{II}$(cyclamN−H) | $H_2O$ | | 0.984[420] | 7.1[420] | | 89.1 |
| $TpOs^{III}(NH_2Ph)Cl_2$[i] | MeCN | −1.05[424] | 0.48[424] | [−3][424] | 22.5[424] | 61.5 |
| $Fe^{II}H_2bim$ [j] | MeCN | ~ −0.8[84] | −0.31[84] | 17.5[84] | ~26[84] | 71.7 (BDE = 67.0)[k] |
| $Fe^{II}H_2bip$[j] | MeCN | | −0.55[428] | 17.5[428] | | 66.2 (BDE = 62.0)[k] |
| $Co^{II}H_2bim$[j] | MeCN | | −0.53[429] | 20.3[429] | | 70.5 (BDE = 63.0)[k] |
| $(acac)_2Ru^{II}$(pyImH)[j] | MeCN | −1.00[430] | −0.64[430] | 16.0[430] | [22.1][430] | 62.1 (BDE = 68.1)[k] |
| $(hfacac)_2Ru^{II}$(pyImH)[j] | MeCN | −0.07[430] | 0.29[430] | [13.2][430] | 19.3[430] | 79.7 |
| $(TPP)Fe^{II}(MeImH)_2$[j] | MeCN | [−0.95][181] | −0.585[181] | 20.8[181] | 26.9[181] | 69.9 |
| $Ru^{II}CO_2H$[l] | MeCN | 0.047[27] | | | 18.5[27] | 81.3 |
| $Ru^{II}PhCO_2H$[l] | MeCN | 0.17[432] | | | 20.5[432] | 86.9 |
| $CpCr(CO)_3H$ | MeCN | −0.688[437] | *0.668*[438] | [−9.5] | 13.3[439] | 57.3 (BDE = 61.5)[m] |
| $CpMo(CO)_3H$ | MeCN | *−0.501*[437] | *0.800*[438] | [−8.0] | 13.9[439] | 62.4 |
| $CpW(CO)_3H$ | MeCN | *−0.491*[437] | *0.758*[438] | [−5.0] | 16.1[439] | 65.6 |
| $Mn(CO)_5H$ | MeCN | *−0.555*[437] | | | 15.1[440] | 62.8 |
| $Re(CO_5)H$ | MeCN | *−0.690*[437] | | | 21.1[440] | 67.9 |
| $CpFe(CO)_2H$ | MeCN | *−1.352*[437] | | | 19.4[440] | 50.3 |
| $CpRu(CO)_2H$ | MeCN | *−1.057*[437] | | | 20.2[440] | 58.2 |

[a] BDFE and BDE are in kcal mol$^{-1}$. Potentials are in V vs NHE for aqueous values and vs $Cp_2Fe^{+/0}$ in nonaqueous solvents. *Italicized* values are irreversible potentials, $E_{p,a}$ or $E_{p,c}$, measured by cyclic voltammetry. [b] These values differ from those originally reported because they have been reevaluated using the revised $E°(H^+/H^•)$ given in Table 19. $Me_6$cyclam = *meso*-hexamethylcyclam; $[14]aneN_4$ = 1,4,8,11-tetraazacyclotetradecane. [c] tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane. [d] salpn = 1,3-bis(salicylideneamino)propane. [e] $L^A$ = 1,3-bis(3,5-dichlorosalicylideneamino)propane and $L^B$ = 1,3-bis(3,5-dinitrosalicylideneamino)propane. Slightly different bond strengths are calculated from consecutive sides of a square scheme using the reported data. [f] $L^C$ = 2-hydroxy-1,3-bis(salicylideneamino)propane. Determined under various conditions in MeCN or mixed MeCN/water. See ref 411 for full details and additional examples. BDFEs cannot be calculated from these data because $C_G$ is not known in mixed solvent systems. [g] $L^D$ = tris[(*N′-tert*-butylureaylato)-*N*-ethyl)]aminato. [h] Py5 = 2,6-bis(bis(2-pyridyl)methoxymethane)pyridine. [i] Tp = hydrotris(1-pyrazolyl)borate. [j] Complex drawn in Figure 12. [k] BDE determined from variable-temperature equilibration methods and/or by calorimetry.[40] [l] Complex drawn in Scheme 14. [m] From solution calorimetry in toluene solvent, ref 441.

$$L_xM^{n+}(OH) \rightarrow L_xM^{(n+1)+}(O) + H^+ + e^- \text{ (or } H^\bullet) \quad (25)$$

The thermochemistry of transition metal PCET reagents is typically determined by p$K_a$ and $E°$ measurements (Scheme 12), and sometimes determined by equilibration with other PCET reagents. In the same manner as done previously, these free energy measurements yield BDFE values using eqs 7, 15, or 16, as listed in Table 21. Unlike the data for organic reagents, data are typically available for a given transition metal system only in one solvent, because of experimental limitations. BDFEs cannot be adjusted as previously because the Abraham model is untested and difficult to apply for metal complexes. Table 21 also does not include data for BDEs unless they have been directly measured via calorimetry or van't Hoff analysis. This is because, as discussed in section 3.1, ground-state entropy changes in transition metal PCET systems can be substantial. Thus, use of BDFEs is especially important in these cases.

### 5.10.1. Metal−Oxo and Hydroxo Complexes

The aqueous redox chemistry of transition metal ions has long been known to be critically dependent on the solution pH, and to involve aquo, hydroxo, and oxo species. Pourbaix first assembled a compendium of diagrams summarizing the aqueous behavior of each metal in 1945.[67] There are two excellent books on the properties of aqueous metal ions.[372] The chemical reactivity of transition metal−oxo complexes in particular have been of special interest to chemists and biochemists for many years.[373] Compounds such as $KMnO_4$, $OsO_4$, and $RuO_4$ are important reagents for organic oxidations,[374] and many of their reactions are proton coupled. Metal−oxo intermediates are similarly implicated in a range of biological oxidations, in particular the oxo−iron(IV) (ferryl) intermediates found in the catalytic cycles of peroxidases, cytochromes P450, and many other heme and nonheme iron enzymes.[375] The dissolution/precipitation of many oxide/hydroxide minerals in the environment can also be a PCET process.[376] For these reasons and others, there may be more interest in PCET reactions of the metal−oxo/hydroxo/aquo complexes than any other class of compounds.

For the simple aquo ions of metal cations, and for oxyanions of both main group and transition metal elements, most redox processes are proton-coupled.[67] A simple example is the oxidation of aqueous ferrous ion, $[Fe(H_2O)_6]^{2+}$, in mildly acidic solutions to give—at least in principle—the ferric hydroxo ion $[Fe(OH)(H_2O)_5]^{2+}$. This transformation is loss of H$^\bullet$ and has a BDFE of 79.5 kcal mol$^{-1}$ based on the well-known $Fe(H_2O)_6^{3+/2+}$ aqueous redox potential (0.77 V) and the p$K_a$ of aqueous $Fe^{III}$.[372] In practice, such reactions are challenging to study because of the hydrolysis of the cations—the $[Fe(OH)(H_2O)_5]^{2+}$ product under most conditions loses additional protons and precipitates a hydrous oxide/hydroxide. Using transient methods, Pestovsky and Bakac have studied aqueous PCET reactions of simple metal−oxo aquo ions, for example, showing that oxidation of organics by $Fe^{IV}O^{2+}$ occurs by either HAT or hydride transfer.[377] The chromium(III) superoxo complex $(H_2O)_5CrOO^{2+}$ was found to undergo various PCET reactions, and starting from Anson's $1H^+/1e^-$ electrochemical data,[378] a bond strength for $(H_2O)_5CrOO-H^{2+}$ (BDFE = 81.4 kcal mol$^{-1}$) was determined.[379] Bakac and co-workers have also discussed the BDFEs in $(H_2O)_5CrO-H^{2+}$, $(Me_6cyclam)(H_2O)Rh(OO-H)^{2+}$, $(Me_6cyclam)(H_2O)Co(OO-H)^{2+}$, and (1,4,8,11-tetraazacyclotetradecane)$(H_2O)Co(OO-H)^{2+}$, ($Me_6$cyclam = *meso*-hexamethylcyclam).[380,381] The BDFEs given for these species in Table 21 are slightly different than those in Bakac's original reports because of reevaluation of the value for $E°(H^+/H^\bullet)_{aq}$ [$C_G(H_2O)$] as noted in sections 3.1 and 5.8.3.

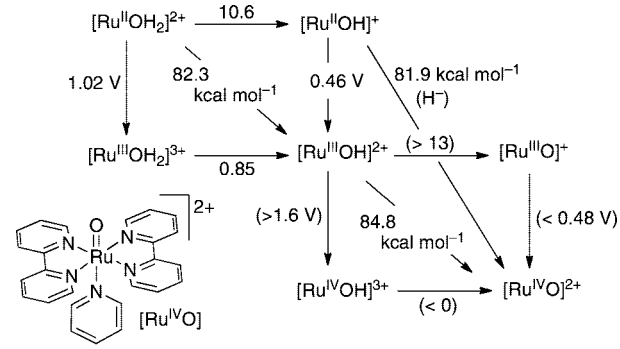


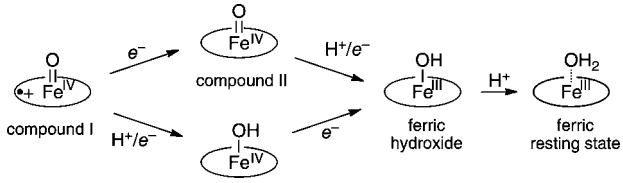

**Figure 10.** Double square scheme showing the PCET thermochemistry of $[cis\text{-}(bpy)_2(py)RuOH_x]^{n+}$ from ref(s) 383 and 390. Numbers above horizontal arrows give p$K_a$ values; numbers beside vertical arrows give electrochemical potentials vs NHE in water; numbers bisecting diagonal lines are BDFEs in kcal mol$^{-1}$ except for the long diagonal at right, which is a hydride affinity, determined following ref 385a. Values in (parentheses) are limits derived from experimental results in ref 383.

Probably the best-studied metal PCET system, and one of the earliest studied in detail, is the ruthenium polypyridyl complex $[cis\text{-}(bpy)_2(py)Ru^{IV}O]^{2+}$ (abbreviated $[Ru^{IV}O]$), developed by Moyer and Meyer (bpy = 2,2′-bipyridine, py = pyridine).[382] An extensive 2007 *Chemical Reviews* article is focused on this and other closely related complexes.[1a] Various reactions have been investigated including ET,[383] PCET,[384] C−H bond oxidations by HAT[385] and by hydride abstraction,[386] HAT from O−H bonds,[387] and others.[388] Related compounds are of much current interest as catalysts for the oxidation of water to $O_2$.[68,389] The thermochemical landscape of this system has been thoroughly worked out by Meyer and co-workers[383,390] and is summarized in Figure 10 and Table 21. $[Ru^{IV}O]$ has a very strong preference to accept $H^+$ and $e^-$ together; no well-defined p$K_a$ for its protonation or $E°$ for its nonproton-coupled reduction could be determined.[383] The limits on these values are included in Figure 10 in parentheses. The relatively large bond strengths in the $[Ru^{IV}O]$ system allow it to oxidize a number of strong C−H bonds via H-atom abstraction.

The PCET properties of a number of other transition metal oxo complexes have been examined. Borovik and co-workers have prepared unusual nonheme manganese and iron hydroxo/oxo systems stabilized by a hydrogen-bonding ligand and have reported a number of O−H bond strengths.[391,392] Stack and co-workers have determined O−H bond strengths for $H_2O$-ligated or MeOH-ligated iron and manganese complexes $(Py5)M(ROH)^{2+}$ as models for lipoxygenase enzymes that use a nonheme iron(III) hydroxide to oxidize fatty acids by a HAT mechanism [Py5 = 2,6-bis(bis(2-pyridyl)methoxymethane)pyridine].[393−395]

Oxidized iron−heme active sites are perhaps the most important and most studied PCET reagents. The so-called "compound I" and "compound II" intermediates are the reactive species in the catalytic cycles of cytochromes P450, peroxidases, and other enzymes that accomplish a wide range of important transformations.[396] Compound I species are two redox levels above the iron(III) resting state and are usually described as iron(IV)−oxo complexes with an oxidized ligand, usually a porphyrin radical cation. Compound II

**Scheme 13. PCET Reactions of High-Valent Heme Species**




species are one-electron oxidized and were traditionally viewed as iron(IV)−oxo compounds. However, Green and co-workers have recently described a number of lines of evidence that some compound II's are basic ($pK_a > 8.2$) and are actually iron(IV)−hydroxo species.[397,398] In these cases, the conversion of compound I to compound II is an unusual PCET process, in which the proton is transferred to the oxo group and the electron is transferred to the porphyrin radical cation (Scheme 13). On the basis of the apparent $pK_a$ values for compound II in myoglobin, horseradish peroxidase, cytochrome *c* peroxidase, and catalase, it was concluded that only thiolate-ligated compound IIs have substantial basicity. As should be clear to readers of this review, the basicity of compound II is a key component of the free energy of PCET or HAT to compound I. Thus, the ability of cytochrome P450 enzymes to abstract H• from strong C−H bonds is intimately tied to the basicity of compound II, as well as its redox potential. Behan and Green have also estimated, using eq 7 above, the minimum redox potentials and $pK_a$ values necessary for ferryl-containing systems to achieve a BDE of 99 kcal mol$^{-1}$ (so that HAT from cyclohexane would be isothermal).[398]

Small-molecule metal−oxo porphyrin species have been widely studied, both as models for heme proteins and as reactive intermediates in catalytic oxidation processes. These systems are very oxidizing, reacting via ET, PCET, oxygen atom transfer, and other pathways, which makes direct determination of redox and acid/base properties challenging. Groves and co-workers have reported aqueous $pK_a$ values for manganese(V)−oxo−hydroxo complexes with water-soluble porphyrins, 7.5 for the *tetra*-(*N*-methyl-2-pyridyl)porphyrin complex and 8.6 for the isomeric *N*-methyl-4-pyridyl (4TMPy) derivative.[399] They have also estimated, using rate constants for HAT reactions and the Brønsted−Evans−Polanyi relationship, O−H bond dissociation enthalpies of ∼100 kcal mol$^{-1}$ for [(5,10,15,20-tetra(*N*-methyl-4′-pyridylporphyrin))Fe$^{IV}$OH]$^{5+}$, ∼92 kcal mol$^{-1}$ for [(5,10,15,20-tetra(mesityl)porphyrin)Fe$^{IV}$OH]$^{+}$, and ∼86 kcal mol$^{-1}$ for [(5,10,15,20-tetra(pentafluorophenyl)]porphyrin)Fe$^{IV}$OH]$^{+}$.[400] Shaik and co-workers have computed an O−H BDE of ∼86 kcal mol$^{-1}$ for a gas-phase Fe$^{IV}$OH complex of a simplified protoporphyrin IX model.[396a,401] Lansky and Goldberg's porphyrinoid Mn$^{V}$O(corrolazine) complex has a relatively low redox potential in MeCN ($E_{1/2}$(Mn$^{V/IV}$) = −0.43 V vs $Cp_2Fe^{+/0}$) yet is able to abstract H• from fairly strong phenolic O−H bonds.[402] On the basis of these results and eq 7, they concluded that the reduced Mn$^{IV}$O species must be quite basic.

Related ruthenium compounds with porphyrin, salen, or tetramine macrocycles have also been studied in detail, as has been reviewed elsewhere.[403] For instance, Lau and co-workers have studied in detail oxidation reactions of *trans*-[Ru$^{VI}$(tmc)(O)$_2$]$^{2+}$, *trans*-[Ru$^{IV}$(tmc)(O)(solv)]$^{2+}$, and *trans*-[Ru$^{II}$(tmc)(H$_2$O)$_2$]$^{2+}$, where tmc is the macrocyclic tertiary amine ligand 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane.[404] A full Pourbaix diagram was developed from

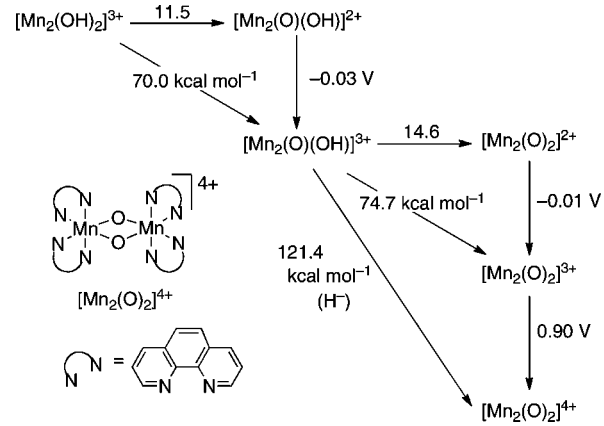



**Figure 11.** PCET thermochemistry of the [(phen)$_4$Mn$_2$(O)$_2$]$^{3+}$ system in MeCN, from ref 415. The phen ligands are omitted from the formulas for brevity. Numbers above horizontal arrows give $pK_a$ values; numbers beside vertical arrows give electrochemical potentials vs $Cp_2Fe^{+/0}$; numbers bisecting diagonal lines are BDFEs in kcal mol$^{-1}$ except for the long diagonal at left which is a hydride affinity.

aqueous electrochemical data, which indicates BDFEs of 74.3 kcal mol$^{-1}$ for Ru$^{V}$(O)(O−H) and 82.5 kcal mol$^{-1}$ for Ru$^{IV}$(O)(HO−H).[405] Consistent with these values, this and related complexes abstract H• from alkylaromatic compounds.[406] Lau and co-workers have also shown that Lewis acids can greatly enhance the ability of oxo reagents to abstract H• from C−H bonds, due to the stabilization of the reduced oxidant by the Lewis acid and therefore the larger O−H BDFE in the presence of the acid.[407]

The first studies of metal-mediated HAT in our laboratories involved chromyl chloride ($CrO_2Cl_2$) and permanganate.[211,408,409] The known aqueous $E°(MnO_4^{2-/-}) = 0.564$ V and $pK_a(HMnO_4^-) = 7.4$ give, using eq 7, BDFE($O_3MnO-H^-$) = 80.7 kcal mol$^{-1}$ (which was reported originally as a BDE of 80 ± 3 kcal mol$^{-1}$). The ability of $CrO_2Cl_2$ and $MnO_4^-$ to abstract H• from hydrocarbons was rationalized on the basis of this bond strength, which is high for isolable, stable species. More recently, H-transfer reactions of *cis*-vanadium dioxo complexes, (bpy)$_2$V$^{V}$(O)$_2^+$, have been examined,[24] and a VO−H BDFE of 70.6 kcal mol$^{-1}$ was obtained by equilibration with 2,6-di-*tert*-butyl-4-methoxyphenol. This system has unusually large barriers to HAT, which are due to the substantial inner-sphere reorganization that occurs between (bpy)$_2$V$^{V}$(O)$_2^+$ and (bpy)$_2$V$^{IV}$(O)(OH)$^+$.[24]

Bridging oxo and hydroxo ligands can also be involved in PCET reactions. Pecoraro, Baldwin, and Caudle,[410,411] and independently Brudvig, Crabtree, Thorp, and co-workers,[412] showed that dimeric $\mu$-oxo manganese compounds such as [(phen)$_2$Mn$^{IV}$($\mu$-O)$_2$Mn$^{III}$(phen)$_2$]$^{3+}$ ([Mn$^{IV}$Mn$^{III}_2$(O)$_2$]$^{3+}$, phen = 1,10-phenanthroline) are reduced with addition of protons to make [Mn$^{III}_2$(O)(OH)]$^{3+}$ and [Mn$^{III}$Mn$^{II}$(OH)$_2$]$^{3+}$. Pecoraro and co-workers derived BDE values and showed that these hydroxide complexes could donate H• to a phenoxyl radical, and thus suggested that these are potential models for the manganese cluster in photosystem II (the oxygen-evolving cluster), which is oxidized by the nearby tyrosine Z radical. A more recent report has described transfer of H• from a $\mu$-hydroxide to 2,4,6-$^t$Bu$_3$PhO•.[413] It was later shown that [Mn$^{IV}$Mn$^{III}_2$(O)$_2$]$^{3+}$ can abstract H• from alkylaromatic hydrocarbons with weak C−H bonds, consistent with the thermochemistry summarized in Figure 11.[414] The more highly oxidized dimer, [Mn$^{IV}_2$(O)$_2$]$^{4+}$, has a much higher 1e$^-$

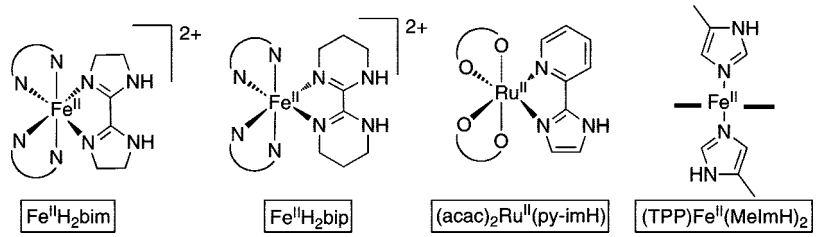



**Figure 12.** Examples of transition metal PCET systems with three bonds between the redox site and acid/base site. The ancillary ligands in $Fe^{II}H_2$bim and $Fe^{II}H_2$bip are the same as the ligand shown in full. The ancillary O−O ligands are acac (2,4-pentanedionato). The black bar in (TPP)$Fe^{II}$(MeImH)$_2$ represents *meso*-tetraphenylporphyrin.

redox potential and oxidizes aromatic hydrocarbons either by ET or by hydride abstraction.[415] H• abstraction by $[Mn^{IV}{}_2(O)_2]^{4+}$ is not observed because the one-electron reduced product $[Mn^{IV}Mn^{III}{}_2(O)_2]^{3+}$ is not basic, and therefore the thermodynamics are not favorable to form "$[Mn_2(O)(OH)]^{4+}$".[416] More recently, a number of laboratories have shown that dimeric $Cu^{III}$−$\mu$-oxo complexes abstract H• from C−H and O−H bonds, as has been reviewed and discussed elsewhere.[417] Unfortunately, this system has not proven amenable to detailed thermodynamic measurements, despite considerable effort.[417]

### 5.10.2. Metal Complexes with N−H Bonds

Metal−imido, −amide, and −amine complexes, MNR, $MNR_2$ and $MNR_3$, are isoelectronic with metal−oxo, −hydroxo, and −aquo species. These appear to undergo analogous PCET processes, although far fewer systems have been examined. The nitrogen derivatives have an additional substituent and are therefore more sterically encumbered than their oxygen relatives. Che,[418] Holland,[419] and others have shown that metal−imido species can abstract H• from C−H bonds, analogous to the oxo complexes above, but little thermochemical data are available. In principle, oxidizing metal amide complexes $MNR_2$ could be good H• acceptors because of the basicity of the amide ligand. For instance, De Santis et al. have reported $E°$ and p$K_a$ data for $Ni^{II}$(cyclam), which indicate BDFE = 89.1 kcal mol$^{-1}$ to give the $Ni^{III}$ with a deprotonated cyclam ligand.[420] However, the amide ligand itself is often susceptible to oxidation, losing hydrogen from the α-carbon to form imines or nitriles.[421] Che and co-workers have used the oxidation-protected 2,3-diamino-2,3-dimethylbutane ligand ($H_2NCMe_2CMe_2NH_2$) to prepare oxidizing $Ru^{IV}$ amides (and reported their Pourbaix diagrams).[422]

Anilido ligands, $NHAr^-$, cannot be oxidized by loss of α-hydrogens (but they can be susceptible to nucleophilic attack in oxidizing compounds[423]). The $Os^{IV}$ anilido complex TpOs(NHPh)$Cl_2$ (Tp = hydrotris(1-pyrazolyl)borate, $HBpz_3$) converts to the $Os^{III}$−aniline derivative TpOs($NH_2$Ph)$Cl_2$ on addition of one electron and one proton.[424] In the thermochemical square scheme in MeCN, there is a remarkably large shift of the p$K_a$ of the aniline ligand from −3 when bound to $Os^{IV}$ to 22.5 on $Os^{III}$. The redox potential shifts from strongly oxidizing for the protonated forms, $E_{1/2}$(TpOs($NH_2$Ph)$Cl_2^{+/0}$) = +0.48 V vs $Cp_2Fe^{+/0}$, to quite reducing for the anilide, $E$(TpOs(NHPh)$Cl_2^{0/-}$) = −1.05 V. The 1.53 shift in potential is, in free energy terms, exactly the same as a 25-unit shift in p$K_a$, as it has to be by Hess' law because these are all part of the same square scheme (Scheme 12). This large shift is reminiscent of the [*cis*-(bpy)$_2$(py)$Ru^{IV}$O]$^{2+}$ system (Figure 10) and probably has the same origin, that the oxidized form has a metal−ligand $\pi$-bond that is disrupted upon reduction. In the osmium system, the rate constants for degenerate ET, PT, and HAT self-exchange were all obtained.[424]

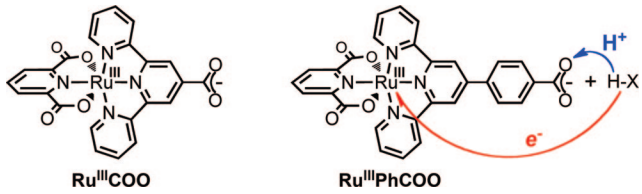
There are a number of metal−imidazole and related PCET systems where protonation/deprotonation occurs at the nitrogen not bound to the redox-active metal center. In such systems, there is a formal separation between the redox and the acid/base sites (see also section 6): there are 3 chemical bonds and ∼4 Å separation between the metal center and the acidic/basic nitrogen (Figure 12). Even with this separation, the redox and acid/base chemistry is still coupled. In general, protonation/deprotonation of metal−imidazole complexes results in a change of 0.3−0.5 V in reduction potential (Table 21 and ref 425). Even though this "thermochemical communication" is substantially less than in compounds where the proton is bound to an atom directly bonded to the metal, as discussed previously, imidazole complexes are still able to mediate concerted H-transfer reactions.

Of these systems, perhaps the most well explored are the iron(II)tris(2,2′-biimidazoline)$^{2+}$ ($Fe^{II}H_2$bip) and iron(II)-tris(2,2′-(tetrahydro)pyrimidine)$^{2+}$ ($Fe^{II}H_2$bip).[84,426−428] The $Fe^{II}$($H_2$bim) and $Fe^{II}$($H_2$bip) systems have similar acid/base properties in MeCN, with p$K_a$ = 17.5. The systems have slightly different redox potentials in MeCN, $E_{1/2}$($Fe^{III/II}$($H_2$bim)) = −0.31 V[84] and $E_{1/2}$($Fe^{III/II}$($H_2$bip)) = −0.55 V[428] (both vs $Fc^{+/0}$). Application of eq 7 gives BDFE($Fe^{II}H_2$bim) = 71.7 kcal mol$^{-1}$ and BDFE($Fe^{II}H_2$bip) = 66.2 kcal mol$^{-1}$. The $Fe^{II}H_2$bip and $Fe^{III}H_2$bip compounds are both mixtures of high-spin and low-spin forms at ambient temperatures in MeCN, which indirectly affects their hydrogen atom self-exchange rate.[427] The related cobalt−$H_2$bim complexes have similar thermochemistry, with a BDFE of 70.5 kcal mol$^{-1}$.[429] In this system, $Co^{II}H_2$bim is high spin while $Co^{II}H_2$bim is low spin, and HAT reactions that interconvert these two are very slow.[428,429] These iron and cobalt $H_2$bim and $H_2$bip systems all have large ground-state entropy changes ($\Delta S°$) associated with their 1e$^-$/1H$^+$ redox couples, so the initial analyses of these systems using BDEs has been revised.[39,40]

Related ruthenium systems have been developed using a bidentate 2-(2′-pyridyl)imidazole ligand (py-imH) and with either acac (2,4-pentanedionato) or 1,1,1,5,5,5-hexafluoro-acac (hfacac) as supporting ligands.[430] In both sets of compounds, deprotonation of the imidazole reduces the redox potential by 0.36 V (and, equivalently, oxidation from $Ru^{II}$ to $Ru^{III}$ makes the imidazole proton more acidic by 6.1 p$K_a$ units). The BDFEs in (acac)$_2$$Ru^{II}$(py-imH) and in $TpOs^{III}$($NH_2$Ph)$Cl_2$, 62.1 and 61.5 kcal mol$^{-1,}$ respectively, are unusually low for N−H bonds. HAT reactions of (acac)$_2$$Ru^{II}$(py-imH) show large H/D kinetic isotope effects and involve substantial hydrogen tunneling.[75]

Replacing acac with hfacac increases the BDFE by a remarkable 17.6 kcal mol$^{-1}$.[430] This is principally the result

**Scheme 14. Ruthenium Complexes with Large Separations between Basic and Redox Sites**




of differences in the reduction potentials; the p$K_a$ of the imidazole ligand is not strongly affected. This illustrates that the effect of ligands and substituents on BDFEs is not always straightforward. Electron-withdrawing groups, for instance, will make a complex more oxidizing but also more acidic, and these two effects are in opposite directions in terms of the BDFE. This is perhaps most clearly illustrated for substituted toluenes, where substituents strongly affect $E°$ and p$K_a$ values but the benzylic C−H bond strengths are much more constant.[346] In phenols, however, electron-donating substituents lower the redox potential more than they raise the p$K_a$, and therefore, these substituents lower the BDFE (Table 4). This is probably because the "hole" created upon oxidation of phenols resides mostly on the aromatic ring, rather than on the phenolic oxygen. Similarly, replacing $-CH_3$ for $-CF_3$ in the acac ligands of $(acac)_2Ru^{II}$(py-imH) has a much larger effect on the ruthenium center than on the distant imidazole ligand.[430]

The PCET chemistry of metal−imidazole compounds has been extended to models for biologically important bis(histidine) ligated hemes. Starting from the initial studies of Quinn, Nappa, and Valentine on *meso*-tetraphenylporphyrin−iron complexes with 4-methylimidazole, $(TPP)Fe^{III}(MeImH)_2^+$,[431] we have generated all of the compounds in the $Fe^{II/III}$ imidazole/imidazolate square scheme.[181] The thermochemistry and concerted H-transfer reactivity is similar to the $Fe^{II}H_2$bip, $Fe^{II}H_2$bim, and $(acac)_2Ru^{II}$py-imH systems discussed previously.

### 5.10.3. Separating the Redox and Protonation Sites

In the metal−oxo systems above, the oxo group that accepts the proton is only one bond away from the metal center that formally accepts the proton. In the imidazole compounds, the two sites are three bonds and ca. 4 Å removed. It is interesting to ask how far the two sites can be separated in a PCET reagent. From one perspective, this is related to the issues raised in the discussion of PCET by separate proton and electron donors in section 5.9. These concerns are probably very relevant to biological PCET, where proton acceptors may be able to be placed somewhat distant from redox cofactors.

Ruthenium systems developed by Manner and Mayer, shown in Scheme 14, are perhaps the clearest examples of a proton−electron accepting reagent with a long and fixed separation between the redox and acid/base sites. The complex with a trpy-carboxylate ligand, $Ru^{III}COO$, has a 6.9 Å separation between the ruthenium and the carboxylate oxygen atoms,[27] and in the trpy-benzoate analogue $Ru^{III}$PhCOO, the distance is ca. 11 Å (trpy = 2,2′;6′,2″-terpyridine).[432] As this distance gets larger, there is less communication between the redox and acid/base sites, as indicated by the thermochemical measurements. For $Ru^{III}CO_2H$, the redox potential decreases by only 0.13 V upon deprotonation, and for $RuPhCO_2H$, the change is only 0.02 V and the p$K_a$ of the carboxylate is almost the same as that for benzoic acid in MeCN. However, even though the two sites behave essentially independently, $Ru^{III}$PhCOO is still able to undergo concerted H• transfer from TEMPOH (see below).

### 5.10.4. Selected Metal Hydrides

Metal hydride complexes can transfer $e^-$, $H^+$, H•, or $H^-$ to substrates, and therefore, they can be considered to be PCET reagents. Metal hydrides are key intermediates in various homogeneous catalytic processes involved in the production of petrochemicals to fine chemicals as well as laboratory-scale reactions. Their thermochemistry has been investigated by a number of groups, especially by those of Parker,[44] Tilset,[43,44] Norton,[433] Bullock,[434] DuBois,[5,435] and Hoff.[436] The cited references provide excellent reviews of these data; in Table 21, we include only a few examples that illustrate some general features of metal hydride systems. In general, metal hydrides have M−H bond strengths that are somewhat weaker than the X−H bond strengths summarized previously. Furthermore, $H^+$ and $e^-$ transfers of many metal hydrides are highly coupled, meaning that there is a large change in p$K_a$ with reduction/oxidation of the metal and that the redox potential drops dramatically upon deprotonation. For example, the oxidation/reduction of $CpCr(CO)_3H$ changes the p$K_a$ by >20 orders of magnitude. These very large changes in acidity with redox state are reminiscent of the chemistry of C−H bonds.

## 6. Mechanistic Implications

The thermochemistry of individual PCET reagents provides a foundation for understanding *cross-reactions* between two potential PCET reagents. The following sections address how the individual $E°$, p$K_a$, and BDFE values are informative about the mechanism of a reaction, whether it occurs by PT, ET, HAT, or otherwise (e.g., hydride transfer). The previous discussion indicated that, in general, reagents that exhibit a large change in p$K_a$ upon redox change (equivalently, a large change in $E°$ upon protonation state change) preferentially undergo concerted rather than stepwise transfer of $H^+$ and $e^-$. In two examples emphasized previously, TEMPOH and toluene, the p$K_a$ values in MeCN change >40 orders of magnitude upon oxidation/reduction, and these reagents in most cases react by HAT.

The following sections outline situations where concerted H• transfer or stepwise $H^+/e^-$ transfers are more likely based on thermochemical arguments. One example is also discussed in which thermochemical arguments do not give a clear indication of mechanism. We emphasize here that it is best to use the solution bond dissociation free energies to understand solution hydrogen atom transfer reactions, despite the century-old use of gas-phase bond enthalpies for this purpose. For all-organic PCET reactions, this is usually a minor concern, as the entropic change is usually small; however, this is not the case for some metal-mediated PCET reactions.[39,40]

## 6.1. Using Thermochemical Data to Understand PCET Mechanisms

In any net one-electron/one-proton transfer reaction, there are three simple mechanisms, as shown in Scheme 1 at the start of this review: proton transfer (PT) followed by electron transfer (ET), ET followed by PT, and concerted transfer of

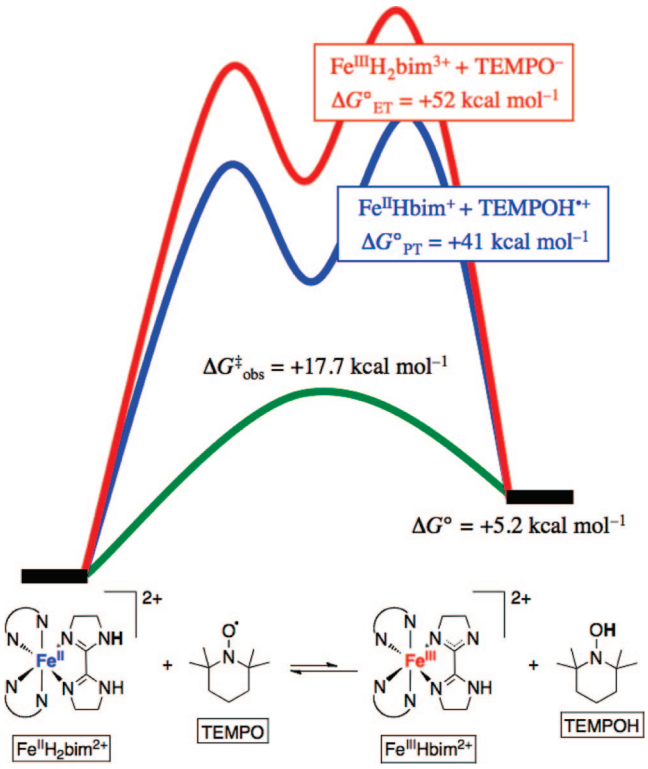



**Figure 13.** Potential energy surface showing free energy changes for different mechanisms of H-transfer for the reaction of $Fe^{II}H_2bim$ + TEMPO. Not drawn to scale.

the two particles (CPET or HAT). The thermochemical data in the previous tables can be used to calculate the ground-state free energy changes, $\Delta G°$, for each of these mechanisms, following eqs 26−28. The activation energies $\Delta G^{‡}$ must be at least as high as these free energy changes, so the $\Delta G°$ values are a conservative lower limit to $\Delta G^{‡}$. It should be noted that electron transfer theories use a slightly different free energy barrier, $\Delta G^{*}$, because a different pre-exponential factor is used.[442] Since this prefactor is smaller than the Eyring $kT/h$, the ET $\Delta G^{*}$ is always higher than the Eyring $\Delta G^{‡}$, and $\Delta G°$ is still a good conservative lower limit.

For X−H + Y,

$$\Delta G°(\mathrm{PT}) = -RT\ln(K_{eq}) = -(1.37\ \mathrm{kcal\ mol^{-1}}) \times [pK_a(YH^+) - pK_a(XH)] \quad (26)$$

$$\Delta G°(\mathrm{ET}) = -FE° = -(23.06\ \mathrm{kcal\ mol^{-1}\ V^{-1}}) \times [E°(XH^{+/0}) - E°(Y^{0/-})] \quad (27)$$

$$\Delta G°(\mathrm{CPET}) = [\mathrm{BDFE(X{-}H)} - \mathrm{BDFE(Y{-}H)}] \quad (28)$$

The reaction of $Fe^{II}H_2bim^{2+}$ + TEMPO will serve to illustrate this approach (Figure 13). The analysis uses the thermochemical data in MeCN for TEMPOH (Table 3) and $Fe^{II}H_2bim$ (Table 21). Initial PT from $Fe^{II}H_2bim^{2+}$ to TEMPO to yield $Fe^{II}Hbim^+$ + $TEMPOH^{•+}$ has $\Delta G° = +41$ kcal $mol^{-1}$ from the relevant $pK_a$ values. Similarly, $\Delta G°$ for initial ET to give $Fe^{III}H_2bim^{3+}$ + $TEMPO^-$, from the redox potentials, is +52 kcal $mol^{-1}$. The observed Eyring barrier ($\Delta G^{‡}$) is much lower, only 17.7 kcal $mol^{-1}$, so the reaction cannot be going through either of the stepwise pathways. Thus, the reaction of $Fe^{II}H_2bim$ + TEMPO most likely proceeds via concerted proton−electron transfer (CPET). This same treatment can be applied to any H-transfer reaction, provided the relevant reduction potentials and $pK_a$ values are known.

It should be noted that Figure 13 is a simplification of the actual multidimensional free energy surface for a PCET reaction. The stepwise intermediates are in different regions of the multidimensional space, particularly when the solvent coordinates are included. This has been discussed by Hammes-Schiffer and Soudackov[443] and Truhlar and co-workers[444] and is mentioned in other contributions to this special issue.

Many studies have used this thermochemical approach to show that the transfer of an electron and a proton must occur in the same kinetic step. This section is meant to be illustrative, not comprehensive. A particularly elegant example is the comproportionation of related ruthenium oxo and -aquo complexes to make the hydroxo derivative (eq 29), which has an H/D kinetic isotope effect of 16.1.[7,18,445] The aquo complex has an aqueous $pK_a$ of 10.3 and the oxo species is not protonated even in strong acid (Figure 10 above), so initial proton transfer is too endoergic to account for the observed rate. In this case, the large kinetic isotope effect and its linear dependence on the mole fraction of deuterium provide strong additional evidence against a mechanism of initial electron transfer and for a CPET pathway. The pseudo self-exchange reaction between the aquo complex and a related hydroxo complex (eq 30) proceeds by a similar mechanism, except at high pH when the aquo complex is deprotonated and the reaction becomes a pure electron transfer.

$$[Ru(bpy)_2(py)(OH_2)]^{2+} + [Ru(bpy)_2(py)(O)]^{2+} \rightarrow 2[Ru(bpy)_2(py)(OH)]^{2+} \quad (29)$$

$$[Ru(bpy)_2(py)(OH_2)]^{2+} + [Ru(tpy)(bpy)(OH)]^{2+} \rightarrow [Ru(bpy)_2(py)(OH)]^{2+} + [Ru(tpy)(bpy)(OH_2)]^{2+} \quad (30)$$

Reducing PCET reactions to the three mechanistic alternatives of Figure 13, eqs 26−28, and Scheme 1 is also a simplification. First of all, many PCET reagents form hydrogen bonds to solvent, and Litwinienko and Ingold have shown that, for reagents such as phenols, this hydrogen bond must be broken prior to HAT.[11,12] Second, the reaction of two PCET reagents likely involves precursor and successor complexes, by analogy to electron transfer theory, which determine whether the reaction proceeds by ET, PT, or HAT/CPET. Such complexes may have hydrogen bonds and be energetically significant.[446] In addition, one can envision a stepwise path of initial ET, for instance, which forms a successor complex that undergoes PT prior to dissociation to the products. The energetics of this situation are more complicated to analyze than eqs 26−28 above, as described in ref 447. Finally, PCET reactions can be mechanistically more complex, for instance, being catalyzed by trace acid or base, or trace oxidant or reductant, as in the mechanism shown in eq 31.[424] Thermochemical analysis of a reaction such as eq 31 requires the $pK_a$ of the catalytic acid, as well as the properties of the HY and HX systems.

$$Y + XH \overset{H^+}{\rightleftharpoons} YH^+ + XH \xrightarrow{ET} YH + XH^+ \xrightarrow{H^+} YH + X \quad (31)$$

### 6.2. Characteristics and Examples of Concerted Versus Stepwise Pathways

In general, the concerted mechanism is favored when one or both of the reagents have strong "thermodynamic coupling" between the proton and the electron, as indicated by large changes in p$K_a$ upon oxidation/reduction and large changes in $E°$ upon protonation/deprotonation. In the $Fe^{II}H_2bim^{2+}$ + TEMPO case analyzed in Figure 13, in the ruthenium−oxo system in eq 29, and in the TEMPOH/TEMPO self-exchange reaction analyzed in Scheme 7, both reagents have large $\Delta pK_a$ and $\Delta E°$ values. It is not necessary, however, for both reagents to have this property. For instance, TEMPOH transfers H$^•$ in a concerted fashion to the ruthenium carboxylate complexes in Scheme 14, even though the Ru complexes have very little thermodynamic communication. The very strong preference for CPET by TEMPOH is sufficient to make the PT−ET and ET−PT paths very high in energy.[27,432]

On the other hand, stepwise mechanisms for net PCET occur when there is a good match between the p$K_a$ values of HX and $HY^+$, or between the $E°$ values of $HX^{+/0}$ and $Y^{0/-}$. If the two p$K_a$ values are similar, then initial proton transfer will be accessible. A particularly clear example of this comes from Litwinienko and Ingold's studies of acidic phenols + the DPPH radical (DPPH = 2,2-diphenyl-1-picryhydrazyl radical).[11,12] In MeCN, DMSO, and THF, there is a p$K_a$ mismatch and proton transfer is thermodynamically unfavorable, so a CPET mechanism is operative. In alcohol solvents, however, the mismatch is much smaller and the reaction proceeds by initial $H^+$ transfer. These thermodynamic effects are compounded in this case by the unusual kinetic facility of proton transfer in hydroxylic solvents. As this example illustrates, solvent can alter the $E°$/p$K_a$ properties of a compound, so that there is no one set of mechanistic "rules" for a given PCET reagent.

Eberson has described a particularly clear example of a stepwise ET/PT mechanism, in the oxidation of aromatic hydrocarbons by polyoxometallates containing $Co^{III}$ ions such as $Co^{III}W_{12}O_{40}^{5-}$.[448] (Jönsson has extended these studies to $Ni^{IV}$- and $Mn^{IV}$-containing oxidants.[449]) Although these reactions show primary H/D kinetic isotope effects, consistent with CPET, they actually occur via fast, pre-equilibrium electron transfer, followed by rate-limiting proton transfer (the origin of the isotope effect). The hallmark of this mechanism is that the reactions are inhibited by addition of the reduced $Co^{II}$ species, which shifts the pre-equilibrium toward the reactants.[448b] This is an excellent example of the limits of thermochemical analyses, as this ET−PT mechanism would have been eliminated without the careful kinetics studies, and without considering the unusual stabilization of the ET successor complex by the strong attraction between the aromatic cation radical and the polyanionic polyoxometallate.

In biology, perhaps the clearest example of a stepwise PCET reaction is the $2H^+/2e^-$ reduction of the quinone Q at the end of the ET cascade in the reaction centers of photosynthetic bacteria.[450] The first electron transfer ($Q + e^- \rightarrow Q^{•-}$) occurs via conformational gating, as indicated by the absence of a driving force dependence for this step.[451] The second reducing equivalent is added in a PCET process, $Q^{•-} + H^+ + e^- \rightarrow QH^-$, which was indicated to occur by fast, pre-equilibrium proton transfer, followed by rate-limiting electron transfer, PT−ET.[450a] The cycle is completed by the addition of one proton, not coupled to electron transfer ($QH^- + H^+ \rightarrow QH_2$).

Finally, this section would be remiss without mentioning electrochemical PCET processes, which have been examined in detail by the groups of Savéant, Costentin, Robert, Finklea, Evans, and others.[3,9,15,142,154b,452] Often, the electrochemical reactions of organic molecules proceed by electrochemical−chemical (EC) mechanisms, akin to a ET−PT mechanism (and often by more complex paths such as ECE, etc.). However, some electrochemical processes have recently been shown to occur by concerted transfer of $e^-$ and $H^+$, as summarized in an excellent recent review in this journal.[3]

## 7. Conclusions

The primary goals of this review are (1) to assemble thermochemical data—reduction potentials, p$K_a$ values, and bond dissociation free energies and enthalpies—from disparate sources and (2) to illustrate the utility of these data in understanding proton-coupled redox chemistry. We hope to have illustrated the value and power of thermochemical cycles ("square schemes") and made them accessible to readers. For example, the square schemes for tyrosine and tryptophan indicate why biochemical oxidations of tyrosine residues form tyrosyl radicals directly, while those of tryptophan residues typically proceed via indole radical cations. The square schemes are particularly valuable in analyzing mechanistic pathways for H-transfers. A detailed knowledge of all of the microscopic steps (ET, PT, and H$^•$ transfer) is a key part of understanding a PCET process. We hope that this review will have value for workers developing and understanding proton-coupled redox phenomena. This area has grown tremendously in scope and depth in the past 25 years, and there is still much to be learned about PCET in chemistry and biology and much to be done in using PCET processes in chemical synthesis and chemical energy transduction.

## 8. Acknowledgments

We are grateful to the many co-workers and colleagues who have measured values and contributed in other ways to the field of PCET. In particular, Dr. Christopher R. Waidmann undertook studies of separated CPET reagents with support from the National Science Foundation funded Center for Enabling New Technologies through Catalysis and Prof. David Stanbury provided valuable comments on the manuscript, as did Ms. Sophia Tran, Dr. Adam Tenderholt, Dr. Mauricio Cattaneo, Dr. Lisa S. Park-Gehrke, and Dr. Michael P. Lanci. Prof. Andreja Bakac directed us to an important value. We gratefully acknowledge the financial support of the U.S. National Institutes of Health (grant GM-50422 supporting J.J.W. and (in part) J.M.M.) and the Center for Molecular Electrocatalysis, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences (supporting T.A.T. and (in part) J.M.M.), and the U.S. National Science Foundation Center for Enabling New Technologies through Catalysis (in part supporting J.M.M.).

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CR100085K