CHAPTER 1

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

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1.1 Introduction

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

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

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

$$\mathrm{X{-}H} + \mathrm{Y} \xrightarrow{k_{\mathrm{XH/Y}}} \mathrm{X} + \mathrm{Y{-}H} \tag{1.1}$$

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

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

1.2 An Introduction to Marcus Theory

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

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

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

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

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

$$\mathrm{X} + \mathrm{X}^- \xrightarrow{k_{\mathrm{XX}}} \mathrm{X}^- + \mathrm{X} \tag{1.5}$$

$$k_{\mathrm{XY}} = \sqrt{k_{\mathrm{XX}} k_{\mathrm{YY}} K_{\mathrm{XY}} f} \tag{1.6}$$

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

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

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

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

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

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

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

$$\mathrm{XH} + \mathrm{X} \rightarrow \mathrm{X} + \mathrm{XH} \tag{1.9}$$

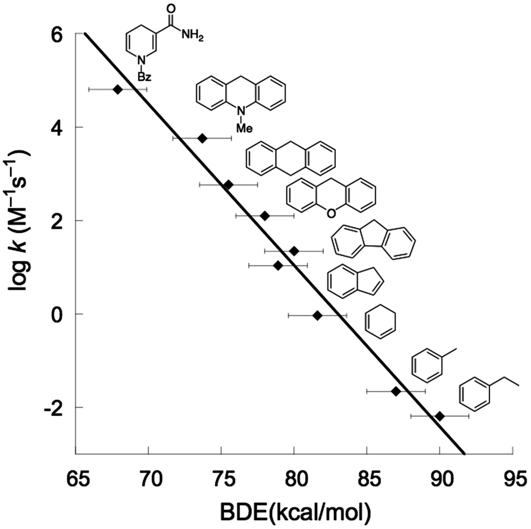


Figure 1.1 Plot of statistically corrected rate constants *versus* BDE for H-abstraction from C–H bonds by $[Ru(O)(bpy)_2py]^{2+}$.[29]

1.3 Predicting Organic Hydrogen Atom Transfer Rate Constants

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

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

1.3.1 Obtaining Self-Exchange Rate Constants and Equilibrium Constants

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

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

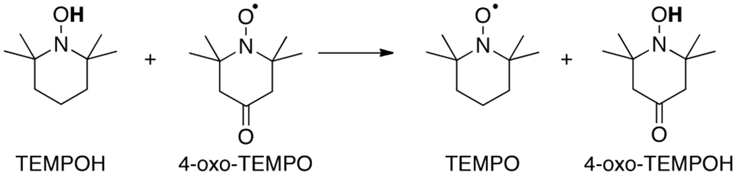
One powerful method to determine BDFEs uses a solution thermochemical cycle with the reduction potential of XH and the pK_a of XH^+, or with $E^{\circ}(X^-)$ and pK_a(XH). The BDFE in kcal mol^{-1} is given by $23.1E^{\circ} + 1.37\text{p}K_a + C_G$.[39–42] Bordwell and others have used this approach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

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

Self-exchange rate constants, $k_{XH/X}$ and $k_{YH/Y}$, are best measured directly when this is possible. NMR line broadening is a powerful technique for degenerate exchange reactions of stable species if the rate constant is *ca.* 10^3–10^6 M^{-1} s^{-1};[44] faster reactions can be monitored by EPR methods.[45] In the ^{1}H NMR experiments, typically one reactant is diamagnetic and has a sharp spectrum while the other is paramagnetic. In the slow-exchange limit, addition of the paramagnetic species to the diamagnetic causes broadening of the spectrum but not shifting, and the amount of broadening is directly related to the rate constant. We have used this method to measure a number of $k_{XH/X}$ values for transition metal reagents.[29b,46–49]

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

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



(1.11)

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

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

1.3.2 Tests of the Cross Relation for Organic HAT Reactions

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

Table 1.1 Properties of reagents in selected solvents: solution bond dissociation free energies (BDFEs) and self-exchange rate constants ($k_{XH/X}$) in selected solvents.^{a}

Compound (α_2^H)^b	*Solvent* (β_2^H)^b	*BDFE*^{a}	$k_{XH/X}{}^a$
$^t\mathrm{Bu_3PhOH}$ (0.2)^c	MeCN (0.44)	77.8	2.0×10^1
BHT (0.2)^{c,d}	MeCN (0.44)	77.5	2.0×10^1
2,6-$^t\mathrm{Bu_2PhOH}$ (0.2)^c	Styrene (0.18)	78.5	6.0×10^1
$^t\mathrm{Bu_2(MeO)PhOH}$ (0.2)^{c,e}	MeCN (0.44)	74.9	2.0×10^1
Phenol (0.60)	MeCN (0.44)	87.8	3.2×10^5
Hydroquinone (0.53)	MeCN (0.44)	78	$1.6 \times 10^{5\ f}$
Tyrosine (0.60)	Water (0.38)	87.8	6.4×10^4
1-Naphthol (0.61)	Isopentane (0)	79.7	9×10^5
2-Naphthol (0.61)	Isopentane(0)	83.0	$\leq 9 \times 10^5$
TEMPOH (0.39)	MeCN (0.44)	66.5	4.7
$\mathrm{Et_2NOH}$ (0.29)	MeCN (0.44)	72.0	2.0×10^1
$^t\mathrm{Bu_2NOH}$ (0.29)	MeCN (0.44)	64.5	2.0×10^1
^{t}BuOOH (0.44)	Hexane (0)	80.4	5.0×10^2
L-Ascorbate (0.3^g)	Water (0.38)	73.6	8×10^5
$i\mathrm{AscH}^-$ (0.3 ^{g})^h	MeCN (0.44)	66.4	5×10^5
α-Tocopherol (0.4)	Styrene (0.18)	74.0	1.5×10^5
Trolox C (0.4)^i	Water (0.38)	78.5	3×10^5
^{t}BuOH (0.32)	DTBP (0.35)^g	104.4	3×10^4
DHA (0)^j	MeCN (0.44)	75	$5 \times 10^{-11\ k,l}$
Xanthene (0)	MeCN (0.44)	73	$1 \times 10^{-10\ k,l}$
Fluorene (0)	MeCN (0.44)	77	$1 \times 10^{-10\ k,l}$
Toluene (0)	DTBP (0.35)^g	86.8	$8 \times 10^{-5\ k}$
$[\mathrm{Fe(H_2bip)_3}]^{2+}$	MeCN (0.44)	66.2	1.8×10^3
$[\mathrm{Fe(H_2bim)_3}]^{2+}$	MeCN (0.44)	71.7	9.7×10^2
$[(^t\mathrm{Bu_2bpy})_2\mathrm{V(O)(OH)}]^+$	MeCN (0.44)	70.6	6.5×10^3
$\mathrm{(acac)_2Ru(pyimH)}$	MeCN (0.44)	62.1	3.2×10^5
$\mathrm{TpOs(NH_2Ph)Cl_2}$	MeCN (0.44)	61.5	1.5×10^{-3}
$[\mathrm{(bpy)_2(py)RuOH}]^{2+}$	Water (0.38)	84.8	–
$[\mathrm{(bpy)_2(py)RuOH}]^{2+}$	MeCN (0.44)	83	7.6×10^4
$[\mathrm{(phen)_4Mn_2(O)(OH)}]^{3+n}$	MeCN (0.44)	74.7	$4 \times 10^{3\ l}$
$[\mathrm{(phen)_4Mn_2(OH)_2}]^{3+}$	MeCN (0.44)	70.0	$3 \times 10^{5\ l}$

[a] BDFE in kcal mol^{-1} and $k_{XH/X}$ in M^{-1} s^{-1} at 298 K. A more complete list, with full derivations for BDFEs, self-exchange rate constants and accompanying references, is given in reference 14. BDFEs are reported to one decimal place in most cases to eliminate ambiguity due to rounding. Values with only two significant figures have errors greater than ± 1 kcal mol^{-1}.[14] Self-exchange rate constants are given to one decimal place unless KSE[14] or cross relation[51] approximations introduce relatively large errors. Abbreviations for ligands of transition metal complexes are given in ref. 54.

[b] α_2^H(solute) from reference 35 and β_2^H(solvent) from reference 36. For saturated alkyl compounds $\alpha_2^H = \beta_2^H = 0$. α_2^H and β_2^H are not known for transition metal complexes.

[c] α_2^H and $k_{XH/X}$ for the 2,6-di-t-butyl-4-R substituted phenols are approximated as equal due to their structural similarity.

[d] BHT = 2,6-di-*tert*-butyl-4-methyl-phenol.

[e] $^t\mathrm{Bu_2OMePhOH}$ = 2,6-di-*tert*-butyl-4-methoxy-phenol.

[f] Taken as $\frac{1}{2}k_{XH/X}$(PhOH) to account for statistical factor of 2, see ref. 55.

[g] Reference 14.

[h] $i\mathrm{AscH}^-$ = 5,6-*O*-isopropylidene ascorbate.

[i] Trolox C = (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid.

[j] DHA = 9,10-dihydroanthracene.

[k] $k_{XH/X}$ are not expected to vary with solvent since α_2^H(C–H) ~ 0.

[l] Estimated using the Marcus cross relation; see references 51 and 91.

Table 1.2 Summary of observed and calculated (eqn (1.8)) organic HAT rate constants.

Entry	*Reaction*	*Solvent* $(\beta_2^H)^b$	$K_{XH/Y}$ ^{c}	k_{obs} ^{a}	k_{calc} ^{a}	k_{rel}	*Ref.*
1*	$^t\mathrm{Bu_3PhO^{\bullet}}$ + TEMPOH	MeCN (0.44)	5×10^7	1.25×10^4	2.9×10^4	2.3	14
2*	$^t\mathrm{Bu_3PhO^{\bullet}}$ + TEMPOH	DMSO (0.78)	5×10^7	2.7×10^3	7.2×10^3	2.6	14
3*	$^t\mathrm{Bu_3PhO^{\bullet}}$ + TEMPOH	C_6H_6 (0.14)	3.5×10^8	9.5×10^4	2.2×10^5	4.2	14
4*	$^t\mathrm{Bu_3PhO^{\bullet}}$ + TEMPOH	CCl_4 (0.05)	3.5×10^8	9.5×10^4	2.2×10^5	6.4	14
5*	$^t\mathrm{Bu_2MeOPhO^{\bullet}}$ + TEMPOH	MeCN (0.44)	3×10^5	2.67×10^3	3.5×10^3	1.3	14
6*	$^t\mathrm{Bu_2MeOPhO^{\bullet}}$ + TEMPOH	DMSO (0.78)	3.5×10^4	6.2×10^2	8.3×10^2	1.4	14
7*	$^t\mathrm{Bu_2MeOPhO^{\bullet}}$ + TEMPOH	C_6H_6 (0.14)	2.5×10^6	1.85×10^4	2.7×10^4	3.1	14
8*	$^t\mathrm{Bu_3PhO^{\bullet}}$ + $i\mathrm{AscH^-}$	MeCN (0.44)	2.3×10^8	3.4×10^6	1.3×10^7	3.8	56
9*	$^t\mathrm{Bu_2MeOPhO^{\bullet}}$ + $i\mathrm{AscH^-}$	MeCN (0.44)	1.5×10^6	5.3×10^5	1.9×10^6	3.7	56
10	$\mathrm{ROO^{\bullet}}$ + $^t\mathrm{Bu_2MeOPhOH}^d$	styrene (0.18)	3.8×10^6	1.1×10^5	4.1×10^4	3.0	57
11	$\mathrm{ROO^{\bullet}}$ + BHT^d	styrene (0.18)	4×10^3	1.4×10^4	5.6×10^3	2.8	57
12	$\mathrm{ROO^{\bullet}}$ + 2,6-$^t\mathrm{Bu_2PhOH}^d$	styrene (0.18)	2×10^2	3.1×10^3	1.4×10^3	2.5	57
13	$\mathrm{ROO^{\bullet}}$ + TocOH^e	styrene (0.18)	4.6×10^5	3.2×10^6	1.8×10^6	2.1	57
14*	$^t\mathrm{BuOO^{\bullet}}$ + $^t\mathrm{Bu_2MeOPhOH}$	alkane^e (0)	2.4×10^5	1.1×10^5	8.8×10^4	1.3	57
15*	$^t\mathrm{BuOO^{\bullet}}$ + BHT	alkane^e (0)	2.5×10^3	2.4×10^4	1.2×10^4	2.0	57
16	$^t\mathrm{BuOO^{\bullet}}$ + TocOH	alkane^e (0)	4×10^5	2.6×10^6	3.8×10^6	1.5	57
17	α-$\mathrm{Toc^{\bullet}}$ + $^t\mathrm{BuOOH}$	ethanol (0.44)	1.7×10^{-6}	4.1×10^{-1}	3.8×10^{-1}	1.2	58
18	$^t\mathrm{Bu_3PhO^{\bullet}}$ + tetralin-OOH	PhCl (0.11)	3.9×10^{-4}	3.4×10^{-1}	2×10^0	7.4	59
19	$^t\mathrm{Bu_3PhO^{\bullet}}$ + PhOH	hexane (0)	3.1×10^{-7}	5.7×10^0	1.9×10^1	3.0	72
20	$^t\mathrm{BuOO^{\bullet}}$ + 1-naphthol	isopentane (0)	1.2×10^1	1.5×10^5	5.3×10^5	2.0	60
21	$^t\mathrm{BuOO^{\bullet}}$ + 2-naphthol	isopentane (0)	1.3×10^{-2}	3.1×10^4	1.7×10^4	1.8	61
22	$^t\mathrm{BuOO^{\bullet}}$ + PhOH	heptane (0)	5.5×10^{-4}	3×10^3	2.8×10^3	1.1	62
23*	$^t\mathrm{BuO^{\bullet}}$ + PhOH	DTBP:C_6H_6 ^{f}	3×10^{12}	3.3×10^8	5.9×10^9	16	63
24*	$\mathrm{PhO^{\bullet}}$ + TocOH	2:1 DTBP:MeCN	9×10^9	3.2×10^8	1.2×10^9	3.3	64
25*	$\mathrm{PhO^{\bullet}}$ + TocOH	3:1 DTBP:C_6H_6	9×10^9	1.1×10^9	1.2×10^9	1.0	64
26	$\mathrm{PhO^{\bullet}}$ + Trolox C	water (0.38)	1×10^8	4.1×10^8	9.7×10^8	2.4	65
27	$^t\mathrm{Bu_3PhO^{\bullet}}$ + PhOH	PhCl (0.09)	1.6×10^{-7}	$<8 \times 10^0$ ^{g}	6.6×10^0	1.3	66
28	Trolox C radical + $\mathrm{AscH^-}$	water (0.38)	4.7×10^3	1.4×10^7 ^{h}	2.5×10^7	1.8	67
29				8.3×10^6 ^{h}		3.0	65
30	tyrosyl radical + $\mathrm{AscH^-}$	water (0.38)	4×10^{10}	4.4×10^8	7.0×10^9	16	68

Table 1.2 *(Continued)*

Entry	*Reaction*	*Solvent* $(\beta_2^H)^b$	$K_{XH/Y}$ ^{c}	k_{obs} ^{a}	k_{calc} ^{a}	k_{rel}	*Ref.*
31	tyrosyl radical + Trolox C	water (0.38)	9.3×10^6	3.1×10^8	4.5×10^8	1.5	68
32	$PhO^{\bullet}$ + DHA	PhCl (0.09)	2.3×10^8	$<1.1 \times 10^2$ ^{g}	2.1×10^2	1.7	66
33*	$^t Bu_3PhO^{\bullet}$ + DHA	MeCN (0.44)	3.0×10^1	1.8×10^{-3}	3.3×10^{-4}	3.1	14
34*	$^t BuO^{\bullet}$ + DHA	DTBP:C_6H_6	9×10^{21}	9.5×10^6	7.9×10^5	15	63
35*	$^t BuO^{\bullet}$ + toluene	DTBP:C_6H_6	3×10^{12}	2.3×10^5	3.4×10^5	2.5	63
36	$^t BuOO^{\bullet}$ + toluene	toluene (0.14)	2.6×10^{-4}	1×10^{-2}	1.5×10^{-3}	9.4	62

[*] Indicates that both $k_{XH/X}$ and $k_{YH/Y}$ are known in the given solvent.
[a] k in M^{-1} s^{-1} at 298 K. k_{rel} is defined as k_{obs}/k_{calc} or k_{calc}/k_{obs}, whichever is greater than 1.
[b] β_2^H values from ref. 36.
[c] $K_{XH/Y}$ in organic solvents corrected using the Abraham model, except for *. $K_{XH/Y}$ in water from thermochemical cycles.
[d] $ROO^{\bullet}$ = peroxylpolystyryl.
[e] Alkane = decane or cyclohexane.
[f] DTBP = $^t BuOO^t Bu$.
[g] Rate constant measured at 333 K.
[h] Independent determinations of the rate constant for Trolox radical + $AscH^-$ give slightly different values.

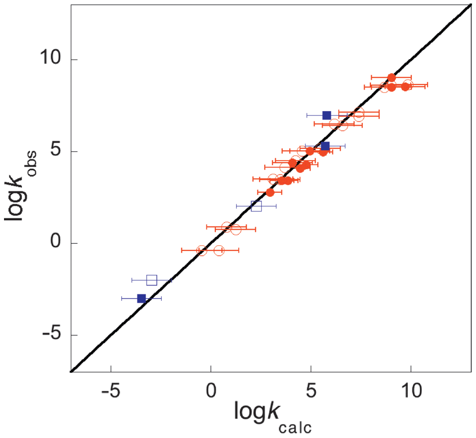


Figure 1.2 Comparison between HAT rate constants measured experimentally (k_{obs}) *vs.* those determined from the Marcus cross relation (eqn (1.8), k_{calc}) for reactions where $k_{XH/Y}$, $k_{XH/X}$ and $k_{YH/Y}$ have been measured in the same solvent. The line indicates perfect agreement. The closed symbols are reactions where all of the inputs for the cross relation are known (marked with * in Table 1.2). The reactions (Table 1.2 with *) involve oxyl radicals + O–H bonds (red ● or ○) or C–H bonds (blue ■ or □).

The agreement between the experimental HAT rate constants and those predicted using the Marcus cross relation (eqn (1.8)) is remarkably close, as shown in Figure 1.2. The diagonal line in the Figure represents perfect agreement. The average deviation is a factor of 4.4, and for 14 of the 17 reactions the cross rate constants ($k_{XH/Y}$) are predicted to within a factor of 4. These reactions span 10^{12} in $k_{XH/Y}$, 10^{18} in $K_{XH/Y}$, and 10^{18} in self-exchange rates. The implications of this remarkable result are discussed below.

1.3.3 Solvent Effects on HAT Rate and Equilibrium Constants

In some instances self-exchange rate constants are not available in the solvent of interest. A solvent correction is necessary in these cases because, as shown by Ingold and Litwinienko, rate constants for $H^\bullet$ abstraction from O–H or N–H bonds in organic molecules can vary by more than 10^2 between strongly and weakly H-bond accepting solvents.[33,69] This is because HAT does not occur with substrates that are hydrogen bonded to solvent, X–H···solvent; the hydrogen bond to solvent must be cleaved prior to reaction. The Ingold kinetic solvent effect model (KSE) quantitatively accounts for this effect, using the empirical Abraham α_2^H and β_2^H parameters to estimate the strength of the X–H···solvent hydrogen bond.[34–36] The model (eqn (1.13)) gives the HAT rate constant in solvent S (k^S) in terms of the rate constant for the same reaction in a non-hydrogen bonding solvent, such as an alkane (k^0). Table 1.3 shows how the self-exchange rate constants (and BDFEs, see below) vary with solvent

Table 1.3 Self exchange rate constants and bond dissociation free energies (BDFEs) for ^{t}Bu$_3$PhO($^\bullet$/H) in different solvents.[a]

Solvent	$k_{XH/X}$	*BDFE*
Hexane	140 ± 25	76.0
CCl_4	130 ± 20	76.7
Benzene	95 ± 14	76.9
MeCN	20 ± 3	77.8
DMSO	8 ± 2	79.2

[a] $k_{XH/X}$ in M^{-1} s^{-1} and BDFE in kcal mol^{-1}. See reference 14.

for 2,4,6-tri-*tert*-butylphenol. This model can also be used to convert rate constants between two solvents without knowing k^0.

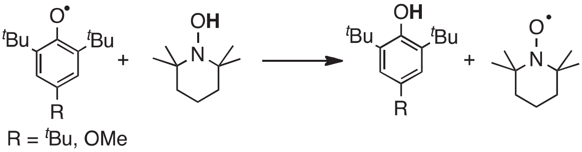
$$\log(k^S) = \log(k^0) - 8.3\alpha_2{}^H(XH)\beta_2{}^H(S) \tag{1.13}$$

The free energy of an HAT reaction also varies with the solvent. $\Delta G^\circ{}_{HAT}$ for $X + H–Y$ is the difference in the BDFEs for X–H and Y–H. The variation of these BDFEs with solvent can be estimated using the same Abraham parameters. As described in more detail elsewhere,[14,39] BDFE(X–H) in solvent *S* is related to the gas-phase BDFE(X–H) by $\Delta G^\circ{}_{solvation}(H^\bullet)$ and the difference in the free energies of solution of XH and X , which is primarily due to differences in hydrogen bonding.[70] In polar aprotic solvents that act primarily as hydrogen bond acceptors, the difference in solvation is essentially the strength of the XH $\cdots$ solvent hydrogen bond, which is given by Abraham parameters (eqn (1.14)). In protic solvents, H-bonding between the radical and solvent ($X^\bullet \cdots H–S$) also needs to be included. This model gives BDFEs that are in good agreement with values from other methods, such as thermochemical square schemes.[14,39]

$$\begin{aligned}\Delta G^\circ{}_{solv}(HX) - \Delta G^\circ{}_{solv}(X^\bullet) &\cong \Delta G^\circ{}_{H\text{-bond}} \\ &= -10.02\alpha_2{}^H(XH)\beta_2{}^H(S) - 1.492\end{aligned} \tag{1.14}$$

1.3.4 A Test Case: Reactions of Bulky Phenoxyl Radicals with TEMPOH

As a means to test the combined cross relation/KSE/Abraham model, we examined the reactions of bulky phenoxyl radicals with the hydroxylamine TEMPOH, using cross and self-exchange rate constants in CCl_4, C_6H_6, MeCN and DMSO.[14] The cross reaction is shown in equation 1.15. Self-exchange rate constants for TEMPO($^\bullet$/H) were determined using the pseudo-self exchange reaction of TEMPOH and the stable radical 4-oxo-TEMPO (eqn (1.11)).[14,52,53]



(1.15)

$k_{XH/X}$ values for ^{t}Bu$_3$PhO($^\bullet$/H) in these solvents were similarly determined from the pseudo-self exchange reaction of isolated ^{t}Bu$_3$PhO$^\bullet$[71] with 2,6-di-*tert*-butyl-4-methyl-phenol (BHT, ^{t}Bu$_2$MePhOH), as described elsewhere.[72] Starting with the $k_{XH/X}$ in the least polar solvent, the ^{t}Bu$_3$PhO($^\bullet$/H) and TEMPO($^\bullet$/H) self-exchange rate constants in the various other solvents were calculated using eqn (1.13). The predicted rate constants are within error of the measured values for all but one of the reactions; the calculated value for ^{t}Bu$_3$PhO($^\bullet$/H) in DMSO deviates by a factor of two, slightly outside the error limits.[14] Thus, as expected,[33] the KSE model holds for these self-exchange reactions.

Using $k_{XH/X}$, $k_{YH/Y}$, and $K_{XH/Y}$ measured in the same solvent, the Marcus cross relation predicts cross rate constants that are all in very good agreement, within a factor of 6.5, of the measured values. To test the combined cross relation/KSE model, cross rate constants in polar solvents have also been calculated using rate constants from less polar media adjusted using the KSE model, as described above. These calculated cross reaction rate constants are again in very good agreement with those directly measured, within a factor of 4.5. This agreement is not surprising since the self-exchange rate constants predicted by the KSE model are close to the measured values. This exercise validates the interchangeable use of KSE-adjusted or directly measured self-exchange rate constants in the cross relation. In the next section, we use this conclusion to test the cross relation with a larger dataset.

1.3.5 Tests of the Cross Relation using KSE-Corrected Self-Exchange Rate Constants

Bringing together the issues described above gives a combined cross relation/kinetic solvent effect (KSE) model. Self-exchange rate constants $k_{XH/X}$ and equilibrium constants $K_{XH/Y}$ measured in different solvents can be used, correcting them to the solvent of interest using the KSE model (eqn (1.13)) or eqn (1.14). These solvent-corrected values are inserted into the cross relation (eqn (1.8) and (1.7)) to give a predicted cross rate constant. This model has been tested for 19 organic reactions in addition to the 17 where all of the inputs were measured in the same solvent (Section 1.3.2, above). These are listed in Table 1.2.

Very good agreement is found between the measured rate constants and those predicted by the cross relation/KSE model, as illustrated in Figure 1.2. The average deviation between k_{calc} and k_{obs} for the collective data set is 3.8. Thirty of the 36 predicted $k_{XH/Y}$ are within a factor of 5 of the experimentally observed rate constants. One notable feature is that the model allows for calculation of rate constants in protic media, such as aqueous reactions of biologically interesting molecules such as ascorbate, even though we know of no reports of HAT self-exchange rate constants in such solvents.

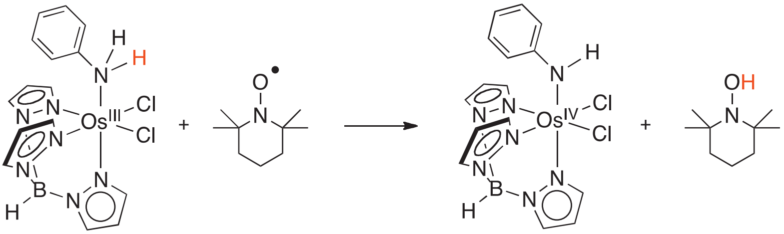
The accuracy of the cross relation/KSE model for a highly diverse set of HAT reactions is remarkable. The agreement even as good as, or better than, is found for application of the cross relation to electron transfer.[73] In all other cases that we are aware of, rate/driving-force relationships of this kind only hold within a set of similar reactions, such as hydride transfers among NADH-analogues.[22] The reactions in Table 1.2 are not similar: they involve O–H and/or C–H bonds, and are done in solvents from alkanes to water. As shown in the next section, the cross relation holds fairly well for HAT reactions of transition metal complexes as well, further increasing the diversity of the reaction set. Various implications of the success of the cross relation/KSE model – and its limitations – will be discussed in Section 1.5 below. We emphasize here that the close agreement validates the conceptual model. HAT occurs from non-hydrogen bonded X–H substrates and its rate is well determined by the combination of the free energy of reaction and the intrinsic barriers, which can be independently determined from self-exchange reactions.

1.4 Predicting HAT Rate Constants for Transition Metal Complexes

Transition metal compounds, complexes, heterogeneous catalysts, and enzyme active sites are involved in a wide variety of important HAT reactions. Among the earliest indications of this mechanism were for organic oxidations by permanganate and chromium(VI) compounds, dating back many decades.[74] However, the generality of this reaction chemistry has only come to light more recently, perhaps starting with the discovery of HAT reactivity of the ferryl (Fe=O) centers in cytochromes P450.[75] HAT is now recognized as probably the most important mechanism for the oxidation of C–H and O–H bonds by transition metal centers. Examples include the use of permanganate and other oxometal reagents in organic syntheses,[76] selective alkane oxidations over oxide surfaces,[77] and many enzymatic processes including aliphatic C–H hydroxylation by methane monooxygenase and other non-heme iron enzymes,[78] fatty acid oxidation by the iron-hydroxide in lipoxygenase,[79] and ascorbate recycling by cytochrome b_{561}.[80] Thus, there is a great deal of interest in understanding the factors that influence the HAT reactivity of transition metal complexes.

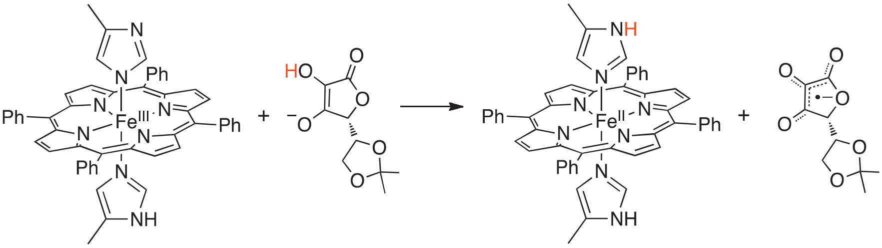
The HAT reactions of transition metal complexes described here all involve redox change at the metal coupled to proton transfer to/from a ligand (eqn (1.16)). One example is shown in equation (1.17), in which oxidation of an Os(III) center is coupled to deprotonation of an aniline to an anilide ligand. There is also an extensive literature of HAT reactions of metal-hydride species, L_nM–H, which in some ways more closely resemble organic HAT reactions.[81,82]

$$L_nM^{z+}(X:) + H{-}Y \rightarrow L_nM^{(z-1)+}(XH) + Y \qquad (1.16)$$



(1.17)

In equation 1.16, there are various ligands X:/XH that can accept/donate the proton. These include the oxo group in the ferryl active sites in heme and non-heme oxygenase enzymes, the hydroxide at the active site in lipoxygenase, the aniline in equation (1.17), and an imidazolate, as in equation (1.18). As these examples illustrate, some metal-mediated HAT reactions involve a formal separation of the e^- and H^+ that make up the transferred $H^\bullet$. In the case of metal-imidazole complexes the proton and electron are 3 bonds or ∼4 Å separated. Despite this separation, we refer to all of these reactions as HAT. Recent interest into the intimate details of HAT reactions has led to new thinking and new definitions.[10–13] Still, we prefer the simplest definition of HAT, as reactions where H^+ and e^- are transferred from one donor to one acceptor in a single kinetic step (eqn (1.1)). The definitions and abbreviations of the organic ligands used in the transition metal HAT systems described below are given in ref. 54.



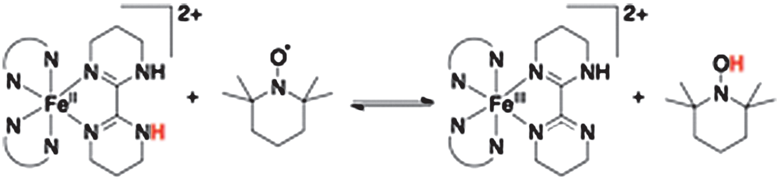
(1.18)

Our initial interest in applying the cross relation to HAT grew out of the limitations of the Bell–Evans–Polanyi (BEP) equation discussed above. This equation holds within a set of similar reactions, but with the expansion of HAT reactions to include transition metal reactions it was not clear what made reagents "similar." It was not evident why different classes of reactions fall on different correlation lines (defined by the parameters α and β, see above). For example, it has long been known that, at the same driving force, $H^\bullet$ abstraction from O–H bonds is substantially faster than from C–H bonds. Transition metal reagents show the same kinetic pattern, O–H faster than C–H.[5] Clearly, even for the simplest HAT reactions, there is more at play than simply driving force and/or bond strengths. Additional factors are important for transition metal systems, as was revealed when the rates for roughly isoergic HAT reactions of isostructural cobalt- and iron-(tris(bi-imidazoline) complexes differed by many orders of magnitude (see below).[15,47,83]

We have found that the Marcus theory/cross relation approach provides a valuable conceptual framework to address these issues, as well as being a predictive tool. The following sections present a few examples of transition metal HAT systems that have been studied in detail. These build on our first tests of the applicability of the cross relation, presented in 2004, which were mostly reactions of bipyrimidine- and biimidazoline-ligated iron coordination complexes (the top entries in Table 1.3).[15] We then summarize all of the systems that have been analyzed, including updates of the original examples. These and following sections discuss the overall applicability of the cross relation to transition metal HAT reactions and some of the challenges associated with this analysis.

1.4.1 Applying the Cross Relation as a Function of Temperature; the Importance of Using Free Energies

The reaction of iron(II) tris-bi(tetrahydro)pyrimidine ($Fe^{II}H_2bip$) with TEMPO (eqn (1.19)) is a typical transition metal mediated HAT reaction. It is also a very unusual HAT reaction in that it occurs *faster* at lower temperatures ($\Delta H^{\ddagger} = -2.7 \pm 0.4$ kcal mol^{-1}).[53]



(1.19)

To better understand this unusual effect, all of the inputs of the cross relation were measured between 277 and 328K, allowing application of the cross relation as a function of temperature. These values are illustrated in the combined van't Hoff/Eyring plot in Figure 1.3. There is excellent agreement between the measured cross rate constants (blue dots) and the rate constants calculated with the cross relation, indicated by the red line. *The cross relation quantitatively predicts the negative temperature dependence of the rate constant*. The cross relation also provides an understanding of this unusual effect, *i.e.* that it results from the strong temperature dependence of the equilibrium constant. The reaction proceeds faster at low temperatures because it is significantly more downhill at lower temperatures.

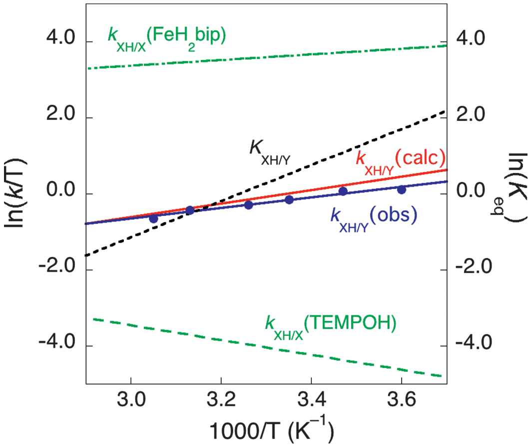


Figure 1.3 Combined Eyring and van't Hoff plot for reaction (19): self-exchange rate constants $k_{\mathrm{XH/X}}(\mathrm{FeH_2bip})$ and $k_{\mathrm{XH/X}}(\mathrm{TEMPOH})$ (left axis); $K_{\mathrm{HX/Y}}$ (right axis), and the rate constants measured ($k_{\mathrm{XH/Y}}$(obs), blue ●) and calculated from the cross relation ($k_{\mathrm{XH/Y}}$(calc) red line) (left axis).[84]

The large temperature dependence of the equilibrium constant for reaction (1.19) was surprising because of the large magnitude of the ground-state entropy change: $\Delta S^\circ = -30 \pm 2\ \mathrm{cal\ K^{-1}\ mol^{-1}}$.[41,42] HAT reactions typically have $|\Delta S^\circ| \sim 0$ because there is no change in charge for a HAT reaction, and usually little change in size. Detailed studies of this and related reactions indicate that this is primarily a change in vibrational entropy (related to the large entropy changes in high-spin/low-spin equilibria).[41,42] The excellent agreement in Figure 1.3 requires that the analysis use the free energy of reaction; if the enthalpy were used the calculated rate constants would deviate by a factor of $\sim 10^3$. These results show that solution HAT reactions, and PCET in general, are best understood using free energies, such as bond dissociation free energies (BDFEs), rather than enthalpies and BDEs as is done in Bell–Evans–Polanyi correlations. In fact, in 1938 Evans and Polanyi derived their equation in terms of free energies, then restated it in terms of enthalpy explicitly assuming that entropic effects were small.[24] Thus, the common use of enthalpies and BDEs has an implicit assumption that $\Delta S^\circ \cong 0$ and $\Delta H^\circ \cong \Delta G^\circ$, an assumption that is probably valid for the large majority of *organic* HAT reactions.[41,42] However, it is more appropriate to use free energies, as is done in the Marcus model, and to identify the Bell–Evans–Polanyi correlation as a linear free energy relationship (LFER) that is a limiting case of the Marcus equation.

1.4.2 Applying the Cross Relation to Oxidations by $[\mathrm{Ru^{IV}(O)(bpy)_2(py)}]^{2+}$

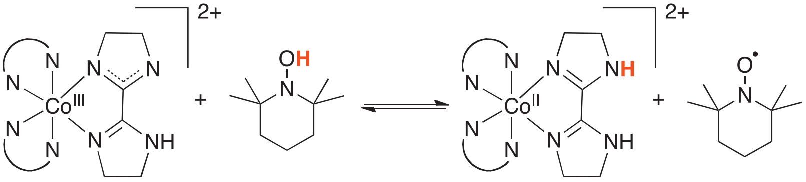
$[\mathrm{Ru^{IV}(O)(bpy)_2(py)}]^{2+}$ oxidizes a wide range of organic compounds, as extensively developed by Meyer and coworkers.[3] Our re-examination of the oxidation of alkylaromatic compounds in MeCN showed that these reactions proceed by initial HAT.[29] The ruthenium oxo/hydroxo self-exchange rate constant of 7.6×10^4 M^{-1} s^{-1} was estimated from ^1H NMR line broadening measurements, which were challenging because of the concurrent disproportionation of the hydroxide complex $Ru^{III}(OH)(bpy)_2(py)^{2+}$. The BDFE for $Ru^{III}(OH)(bpy)_2(py)^{2+} \rightarrow Ru^{IV}(O)(bpy)_2(py)^{2+} + H^{\bullet}$ is known in water,[29,84] but not in acetonitrile. The Abraham model can be used to adjust BDFEs between solvents, as noted above, but this can only be done approximately for transition metal species since the relevant $\alpha_2{}^H$ and $\beta_2{}^H$ parameters are not known. With the assumptions that $\alpha_2{}^H$(RuO–H) is the same as for H_2O or ROH (0.35) and that $\beta_2{}^H$(Ru=O) is similar to that for a ketone (0.5), the $[Ru^{III}(O–H)(bpy)_2(py)]^{2+}$ BDE in MeCN is 82.5 ± 1.5 kcal mol^{-1}. The relatively large error bar reflects the uncertainty in the assumptions. Using this value, and the known organic $k_{XH/X}$ rate constants (Table 1.1), the cross relation provides reasonably good predictions. For $[Ru^{IV}(O)(bpy)_2(py)]^{2+}$ + toluene, for example, the calculated value of 6.0×10^{-2} M^{-1} s^{-1} is within a factor of 9 of that measured, 6.4×10^{-3} M^{-1} s^{-1}. This system illustrates, however, that it is more difficult to account for kinetic solvent effects in metal-mediated HAT reactions than for organic reagents, and that this is one of the issues that limit the accuracy of the cross relation analysis in these cases.

1.4.3 Precursor and Successor Complexes for HAT

The Marcus theory model is derived for unimolecular electron transfer. It is applied to bimolecular reactions by assuming that the reactants weakly associate in a ‘precursor complex’ within which ET occurs to give the successor complex.[16–18] The cross relation analyses above have implicitly adopted this same model, but HAT precursor complexes are quite different then ET ones. This is because proton transfer occurs only over very short distances, so HAT precursor complexes have distinct conformations, rather than the weakly interacting encounter complexes of ET. In this way, HAT resembles proton transfer and inner-sphere electron transfer.[85,86] Including the equilibria for precursor and successor complex formation expands equation (1.1) into equation (1.20).

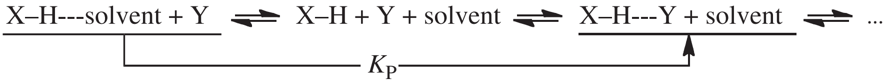
$$\text{X–H} + \text{Y} \underset{}{\overset{K_p}{\rightleftharpoons}} \text{X–H---Y} \overset{K_{HAT}}{\rightleftharpoons} \text{X---H–Y} \overset{K_{S-1}}{\rightleftharpoons} \text{X} + \text{H–Y} \qquad (1.20)$$

One case where the importance of HAT precursor and successor complexes is clear is the reaction of $[Co(Hbim)(H_2bim)_2]^{2+}$ (abbreviated to Co(Hbim)) with TEMPOH (eqn (1.21)).[87] Reaction (1.22) shows kinetic saturation behavior in the forward direction, indicating pre-equilibrium formation of a Co(Hbim)$\cdots$TEMPOH precursor complex with $K_P = 61.3 \pm 0.8$ M^{-1} ($\Delta G_P{}^{\circ} = -2.44 \pm 0.05$ kcal mol^{-1}). In the reverse direction, saturation was not observed but kinetic models indicate $\Delta G_S{}^{\circ} = 0.24 \pm 0.83$ kcal mol^{-1}. Taking these values into account, the unimolecular HAT step in reaction (1.21) has $\Delta G_{21}{}^{\circ}(\text{HAT}) = -0.3 \pm 0.8$ kcal mol^{-1}, while the net reaction has $\Delta G^{\circ}{}_{21} = -3.0 \pm 0.4$ kcal mol^{-1}. This difference of -2.7 ± 1.0 kcal mol^{-1} corresponds to a difference of an order of magnitude in the rate constant predicted by the cross relation.



(1.21)

A more complete description of HAT reactions would also include the presence of hydrogen-bonded solvent molecules, which (as described in Section 1.3 above) must dissociate prior to formation of the precursor complex (eqn (1.22); formation of the successor complex is similar). A detailed model including these equilibria is presented in reference 14 and its Supporting Information.



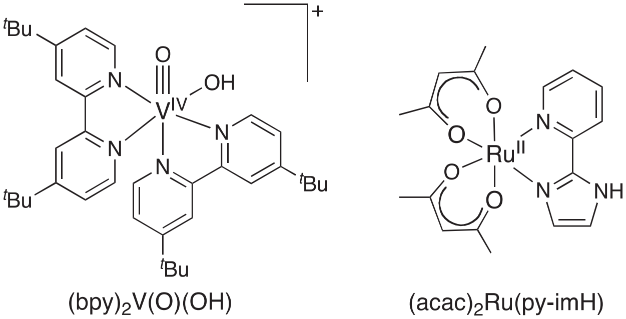
(1.22)

For the organic reactions discussed above, the magnitude of the equilibria can be fairly well predicted using Abraham's hydrogen bonding model, although some parameters have to be estimated, such as the hydrogen bonding basicities ($\beta_2{}^{H}$) of the organic radicals. Fortunately, the effects of these equilibria prior to the HAT step are typically small. The effects are larger for reactions in protic solvents, and for reactions where the reactants and products have very different hydrogen-bonding properties, such as reactions of oxyl radicals with C–H bonds ($RO^{\bullet} + R'H \rightarrow ROH + R'^{\bullet}$).[14] Even in these cases, including H-bond equilibria in the analysis usually causes shifts that are within the uncertainty of the calculated cross rate constant (typically *ca.* an order of magnitude), so this can be neglected in most analyses of organic reactions. The situation is less clear for HAT reactions of transition metal complexes because the H-bonding properties of $L_nM^{z+}(X:)$ can be very different than those of $Y^{\bullet}$ (eqn (1.16)) and the Abraham parameters are not available. As shown by the cobalt example above, this effect can be significant.

1.4.4 Applying the Cross Relation for Transition Metal HAT

Since the 2004 report applying the cross relation to transition metal HAT reactions, we have examined number of new systems, including $(acac)_2Ru(py\text{-}imH)$,[48] $(bpy)_2V(O)(OH)$,[51] and $TpOs(NH_2Ph)Cl_2$ complexes[49] (Scheme 1.1 and eqn (1.17); ligand abbreviations given in ref. 54). As discussed above, we have discovered that entropic effects can be quite important and free energies of reaction should be used.[42] We also now understand the importance of solvent effects on both self-exchange and equilibrium constants (Section 1.3.3 above). For instance, the newly measured $k({}^tBu_3PhO^\bullet/H)$ self-exchange rate in MeCN[14] is more than a factor of 10 smaller than the previously reported value in CCl_4 that was used in our original analysis.

For all of these reasons, it is appropriate to update and extend the tests of the cross relation for transition metal HAT reactions. The results are given in Table 1.4 and shown in Figure 1.4. The analyses use the BDFEs in Table 1.1 to calculate the $K_{XH/Y}$ values (instead of the originally used BDEs),[15] except for the cases for which the equilibrium constant could be measured directly (entries 1, 8, 9, and 16 in Table 1.4). While there is somewhat more scatter than for the organic reactions, there is generally good agreement between the observed and calculated cross rate constants. Only four of the 29 calculated rate constants deviate from the fit line by more than two orders of magnitude. These include the reactions of $TpOs^{III}(NH_2Ph)Cl_2$ with aminoxyl radicals, and reactions of $V^V(O)_2(bpy)_2{}^+$ or $Ru^{IV}(O)(bpy)_2(py)^{2+}$ with xanthene, which are discussed below. Excluding these cases, the average deviation is 15 and about half of the values are predicted to better than a factor of ten. The overall agreement to within 1–2 orders of magnitude is remarkable for a very disparate set of metal complexes, including first, second and third row transition metal ions, with oxo, imidazole and aniline ligands, and with various spin states.



Scheme 1.1 Additional transition metal systems for investigations of HAT reactions.

Table 1.4 Summary of observed and calculated (eqn (1.7)) rate constants for transition metal PCET reactions.[a]

Entry	*Reaction*	K_{XY}	k_{obs}[a]	k_{calc}[a]	k_{rel}[b]	*Ref.*
1	$Fe^{III}Hbim^{2+} + TEMPOH$	5.0×10^{3}	3.1×10^{3}	3.9×10^{3}	1.2	15,41
2	$Fe^{III}Hbim^{2+} + Et_2NOH$	6.3×10^{-1}	1.1×10^{1}	5.6×10^{1}	9.2	15
3	$Fe^{III}Hbim^{2+} + H_2Q$	2.5×10^{-5}	2.8×10^{1}	4.0×10^{1}	1.4	15
4	$Fe^{II}H_2bim^{2+} + {}^{t}Bu_3PhO^{\bullet}$	1.7×10^{4}	6.8×10^{5}	1.4×10^{4}	50	15
5	$Fe^{II}H_2bim^{2+} + PhCH_2$	1.1×10^{11}	3.0×10^{3}	2.0×10^{4}	6.6	15
6	$Fe^{II}Hbim^{2+} + xanthene$	1.1×10^{-1}	1.5×10^{-3}	7.8×10^{-5}	14	88
7	$Fe^{III}Hbip^{2+} + TEMPOH$	5.9×10^{-1}	2.6×10^{2}	7.2×10^{1}	3.7	15,41
8	$Fe^{II}H_2bip^{2+} + TEMPO$	1.7×10^{0}	1.5×10^{2}	1.2×10^{2}	1.2	15,41
9	$Fe^{II}H_2bip^{2+} + {}^{t}Bu_2NO^{\bullet}$	5.7×10^{-2}	6.3×10^{0}	7.6×10^{1}	6.5	15
10	$Fe^{II}H_2bip^{2+} + {}^{t}Bu_3PhO^{\bullet}$	2.0×10^{8}	1×10^{7}	8.7×10^{5}	11.6	15
11	$Ru^{II}(acac)_2(pyimH) + TEMPO$	1.8×10^{3}	1.4×10^{3}	4.3×10^{4}	31	48
12	$TpOs^{III}(NH_2Ph)Cl_2 + TEMPO$	4.6×10^{3}	4×10^{-2}	4.8×10^{0}	120	49
13	$TpOs^{III}(NH_2Ph)Cl_2 + {}^{t}Bu_2NO$	1.9×10^{3}	2×10^{-2}	3.3×10^{0}	300	49
14	$V^{V}(O)_2(bpy)_2{}^{+} + TEMPOH$	1.0×10^{3}	1×10^{-1}	5.0×10^{0}	50	51
15	$V^{V}(O)_2(bpy)_2{}^{+} + xanthene$	1.7×10^{-2}	3.8×10^{-5}	5.8×10^{-7}	370	51
16	$V^{V}(O)_2(bpy)_2{}^{+} + {}^{t}Bu_2OMePhOH$	1.4×10^{-3}	1.4×10^{-3}	1.2×10^{-2}	8.6	51
17	$V^{V}(O)_2(bpy)_2{}^{+} + DHA$[c]	2.5×10^{-4}	2×10^{-7}	1.3×10^{-8}	25	51
18	$V^{V}(O)_2(bpy)_2{}^{+} + H_2Q$[d]	3.7×10^{-6}	1×10^{-2}	4.0×10^{-2}	4.0	51
19	$Ru^{IV}(O)(bpy)_2py^{2+} + DHA$[c]	1×10^{5}	1.6×10^{1}	5.4×10^{-1}	30	29b
20	$Ru^{IV}(O)(bpy)_2py^{2+} + xanthene$	1×10^{7}	5.8×10^{2}	5.6×10^{0}	100	29b
21	$Ru^{IV}(O)(bpy)_2py^{2+} + toluene$	8×10^{-4}	6.4×10^{-3}	6.0×10^{-2}	9	29b
22	$Ru^{IV}(O)(bpy)_2py^{2+} + fluorene$	1×10^{4}	5.5×10^{0}	1.8×10^{-1}	30	29b
23	$Mn_2O_2(phen)_4{}^{3+} + xanthene$	1.7×10^{1}	6.7×10^{-3} [e]	2.6×10^{-3}	2.6	89
24	$Mn_2O_2(phen)_4{}^{3+} + fluorene$	2.0×10^{-2}	6.2×10^{-4} [f]	8.6×10^{-5}	7.2	89
25	$Mn_2(O)(OH)(phen)_4{}^{3+} + xanthene$	5.9×10^{-3}	6.4×10^{-3} [e]	4.0×10^{-4}	16	89
26	$Mn_2(O)(OH)(phen)_4{}^{3+} + fluorene$	6.9×10^{-6}	4.3×10^{-4} [f]	1.1×10^{-5}	40	89

[a] k in $M^{-1}\ s^{-1}$ in MeCN solvent at 298 K, unless otherwise noted. Ligand abbreviations are given in ref. 54.
[b] k_{rel} is defined as k_{obs}/k_{calc} or k_{calc}/k_{obs}, whichever is greater than 1.
[c] DHA = 9,10-dihydroanthracene.
[d] H_2Q = 1,4-hydroquinone.
[e] Rate constant measured at 292 K.
[f] Rate constant measured at 333 K.

1.4.5 Transition Metal Systems that Deviate from the Cross Relation

A number of reactions of transition metal complexes show significant deviations from the predictions of the cross relation, as noted above. The reaction of $TpOs^{III}(NH_2Ph)Cl_2$ with TEMPO (eqn (1.17)) may deviate because of uncertainties in the $TpOs^{III}(NH_2Ph)Cl_2$ self-exchange rate constant. HAT self-exchange in this system is substantially slower than related electron and proton transfer self-exchanges, and as a result measurements of HAT reactions are plagued by catalysis by trace acid or base.[49] The $TpOs^{III}(NH_2Ph)Cl_2$ system may also deviate due to significant steric crowding. The cross relation implicitly assumes that the transition state for the cross reaction resembles the self-exchange transition states, but if one of the reagents is sterically encumbered its

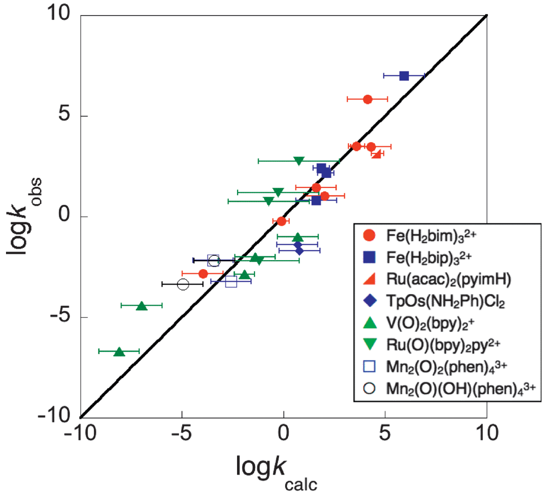


Figure 1.4 Comparison between HAT rate constants measured experimentally (k_{obs}) *vs.* those determined from the cross relation (eqn (1.8), k_{calc}). The line indicates perfect agreement. The errors bars are one log unit, except for $Ru^{IV}(O)(bpy)_2(py)^{2+}$ oxidations, which are 2 log units, reflecting the uncertainty in its bond strength in MeCN solvent (see text). The correlation coefficient (R^2) for all data is 0.82.

self-exchange process may be inhibited in a way that is not reflected in the cross reaction (in essence, an effect of the precursor complex). However, this should lead to calculated cross rate constants that are too small, while the calculated k for the $TpOs^{III}(NH_2Ph)Cl_2$ reactions are too large.

The reaction of $(acac)_2Ru(py\text{-}imH)$ with TEMPO shows a significant deviation, considering that the estimated errors are small because all of the inputs for cross relation analysis have been directly measured, including $K_{XH/Y}$.[48] This reaction shows substantial tunneling, with a hydrogen/deuterium kinetic isotope effect (KIE) of 23 ± 3 at 298 K. Interestingly, the Ru self-exchange reaction has a KIE close to 1,[48] but the TEMPO self-exchange reaction has a large KIE and tunneling is again implicated.[52] The Marcus cross relation is essentially a classical theory that does not include nuclear tunneling, so good agreement with experiment is not necessarily expected when tunneling contributes substantially to HAT rates. (This could also be the case for $TpOs^{III}(NH_2Ph)Cl_2$, but an isotope effect could not be obtained.[49]) Hydrogen tunneling has been shown to be integral to many biological processes.[90]

The origin of the deviation from the cross relation for the reactions of $[V^V(O)_2(bpy)_2]^+$ or $[Ru^{IV}(O)(bpy)_2(py)]^{2+}$ with xanthene is not known. Three other HAT reactions of xanthene do not show this large deviation (Table 1.4), so the deviations are not likely to be due to an erroneous xanthene self-exchange rate constant [taken as that of 9,10-dihydroanthracene[91] (DHA, Table 1.1)]. Tunneling could be important in reactions of $Ru^{IV}(O)(bpy)_2(py)^{2+}$, as the reaction with DHA has $k_H/k_D \geq 35$.[29b] Interestingly, the cross relation appears to hold for the reaction of $Ru^{IV}(O)(bpy)_2(py)^{2+}$ with DHA (Table 1.4), but not for that with xanthene.

These examples highlight that while the cross relation works for many cases, it is a simplified treatment and does not account for a number of other factors that influence transition metal HAT rates. It cannot, for instance, predict when tunneling will be important. Still, the general success of the cross relation, as shown in Figure 1.4, indicates that it captures the largest contributors to HAT reactivity: the free energy of reaction and the intrinsic barrier as measured by self-exchange rate constants. For example, the reactions of $V^{V}(O)_2(bpy)_2{}^{+}$, while they may not all quantitatively follow the cross relation, are all very slow because of a large intrinsic barrier.[51] The $V^{V}(O)_2(bpy)_2{}^{+}/V^{IV}(O)(OH)(bpy)_2{}^{+}$ self-exchange rate constant is a million times slower than that of $Ru^{IV}(O)(bpy)_2(py)^{2+}/Ru^{IV}(OH)(bpy)_2(py)^{2+}$, and this is clearly reflected in the cross reaction rates. The origin of this striking difference in intrinsic barriers has been traced to a larger inner-sphere reorganization energy in the vanadium system, due in large part to the sizable changes in the lengths of the strong vanadium–oxygen bonds.[51] Thus, the qualitative Marcus picture of inner-sphere reorganization energies, developed for electron transfer, also holds for HAT. In addition to the intuition that carries over from electron transfer, PCET and HAT also bring the additional issues associated with the proton transfer component. These are presumably responsible for the dramatically lower reactivity of C–H *vs.* O–H bonds,[5] but a consensus on the origin of this difference has not yet been reached.[92]

1.5 Conclusions: Implications and Limitations of the Cross Relation for Hydrogen Atom Transfer Reactions

A kinetic model has been developed for hydrogen atom transfer (HAT) reactions using the Marcus cross relation. The model has been used to predict rate constants for 62 HAT reactions, including both purely organic reactions and reactions involving transition metal complexes. The reactions involve cleavage and formation of C–H, O–H, and N–H bonds, and occur in solvents ranging from alkanes to water. The systems examined include biologically important HAT reactions involving tocopherol, ascorbate, hydroperoxides, transition metal-oxo compounds, and non-heme iron complexes. The hydrogen abstractors can be organic radicals in which the X–H bond forms at the site of high unpaired spin density, or transition metal complexes in which there are no unpaired spins. The transition metal reactions involve redox change at the metal coupled to protonation/deprotonation of a ligand, for instance interconversion of $L_nV^{V}{=}O$ with $L_nV^{IV}{-}OH$. The 62 reactions include data that have been measured by different groups, using different physical techniques, over 50 years. They span more than 10^{17} in rate constant, 10^{28} in equilibrium constant, and 10^{18} in the self-exchange rate constants of the reactants.

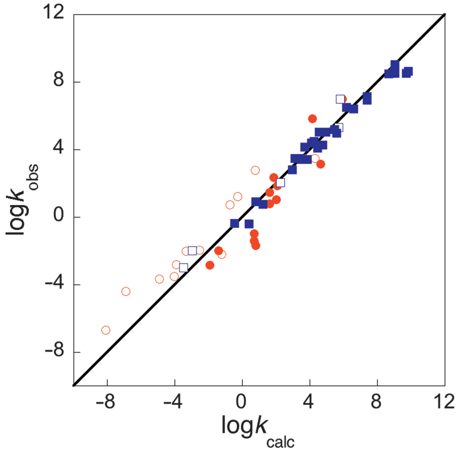


Figure 1.5 Comparison of 63 organic-only and transition metal HAT rate constants measured experimentally (k_{obs}) *vs.* those determined from the cross relation (eqn (1.8), k_{calc}). The line indicates perfect agreement. The reactions (Tables 1.2 and 1.4) involve oxyl radicals + O–H bonds (blue ■), oxyl radicals + C–H bonds (blue ☐), transition metal complexes + O–H bonds (red ●) and transition metal complexes + C–H bonds (red ○). Error bars are omitted for clarity (see Figures 1.2 and 1.4). The correlation coefficient (R^2) for all data is 0.94.

Over this wide variety of reactions, the cross relation predicts the rate constants very well, as shown in the combined plot showing all 62 reactions in Figure 1.5. The correlation coefficient is 0.94 for all data, and rate constants for 46 of the 62 reactions are predicted to within a factor of 9 of the observed rate constant. Only four of the predicted rate constants deviate by more than a factor of 10^2.

The success of this model is notable for a number of reasons. In particular, it is remarkable that the model holds so well for such a wide variety of reactions and reactants. Linear free energy relationships (LFERs) relating rate constants with driving force (*e.g.*, Brønsted relationships) are a very useful part of reaction chemistry, but they are essentially always limited to a set of closely related compounds and reactions. LFERs such as $\Delta G^{\ddagger} = \alpha\Delta G^{\circ} + \beta$ have parameters (α,β) that are defined only by this relationship. In contrast, the values that enter into the cross relation, $K_{XH/Y}$, $k_{XH/X}$ and $k_{YH/Y}$, and the parameters for the KSE model (${\alpha_2}^H$ and ${\beta_2}^H$), are all independently measured and have independent meaning. *There are no adjustable or fitted parameters in this model.*

This general agreement with the cross relation appears to hold only for HAT and for outer-sphere electron transfer.[22,41] The other examples of application of the cross relation, to H^+ transfer, H^- transfer, and S_N2 reactions, only hold within a limited subset of similar reactions.[21–23] The critical feature here appears to be the broad applicability of the additivity postulate for HAT, that the intrinsic barrier for a reaction is well estimated by the average of the intrinsic barriers to the self-exchange reactions (eqn (1.4)). This postulate is intuitively reasonable for outer-sphere electron transfer reactions, in which no bonds are made or broken and in which precursor complexes are loosely associated, but it is very surprising that it holds so well for HAT. As pointed out by Sutin in the context of electron transfer,[17] the success of the cross relation is in part a result of its inherent averaging. Still, the cross reactions do not always resemble the average of the self reactions. In $RO^{\bullet}$ abstractions from C–H bonds, for example, the $RO^{\bullet}\cdots H{-}R$ transition state does not have a significant hydrogen bond, but in most cases the $RO^{\bullet} + H{-}OR$ self-exchange transition state does.

A class of HAT reactions for which the additivity postulate appears not to hold are those with strong "polar effects." In some HAT reactions, as pointed out by Tedder, "…the rate of atom transfer is very dependent on the degree of polarity in the transition state."[93] For instance, Rong *et al*. showed that alkyl radicals abstract $H^{\bullet}$ faster from thiols than from silanes or stannanes, while the kinetic preference is reversed for perfluoroalkyl radicals.[94] The more electron rich $R^{\bullet}$ radical preferentially abstracts the electron deficient $RS^{\delta-}{-}H^{\delta+}$ while the electron deficient $R_F^{\bullet}$ radical reacts faster with $R_3Sn^{\delta+}{-}H^{\delta-}$. Such an inversion of reactivity cannot be accounted for by a cross relation treatment, because from the additivity postulate the reactivity of a reagent is not dependent on its partner.

The success of the cross relation for HAT supports the conclusion that these reactions need to be analyzed using free energies. We advocate revising the traditional Bell–Evans–Polanyi (BEP) relation to use ΔG° rather than ΔH°. This will require a change from bond dissociation enthalpies (BDEs) to bond dissociation free energies (BDFEs), which we have tabulated in a recent review.[39] The use of free energies is also consistent with the Ingold kinetic solvent effect (KSE) model and Abraham hydrogen bonding parameters, as these are also based on ΔG°'s.

The agreement with the cross reaction is slightly better for the organic reactions than for those reactions involving transition metal complexes. This is in part because corrections could be made for solvent effects when necessary in the organic case. Ingold's kinetic solvent effect (KSE) analysis and Abraham's hydrogen bonding parameters allow solvent effects to be accounted for when the inputs of the cross relation ($k_{XH/X}$, $k_{YH/Y}$, $K_{XH/Y}$) are not all measured in the same solvents. This combined model is shown to be very successful at predicting HAT rate constants. For transition metal complexes, however, the Abraham parameters are not available and therefore solvent hydrogen bonding effects and precursor complex formation are more difficult to account for.

The Marcus cross relation (and the KSE model) are also valuable as indicators of mechanism. Good agreement between experiment and theory is a strong indication that all of the kinetic components, $k_{XH/Y}$, $k_{XH/X}$, and $k_{YH/Y}$ are for processes that occur by concerted HAT mechanisms. Of course, $K_{XH/Y}$ must refer to the thermodynamics of the overall $H^{\bullet}$ transfer as well. Similar arguments have been made for the application of the cross relation to ET, and Ingold *et al*. have made this point about the KSE model.[33] For instance, one set of reactions where the KSE model fails was shown to follow a mechanism of sequential proton transfer then electron transfer (PT/ET), rather than HAT. We do not believe, however, that disagreement with the cross relation necessarily means that a non-HAT mechanism is being followed. The reactions in Tables 1.2 and 1.4 for which k_{calc} differs substantially from k_{obs} are still indicated to be HAT, from thermochemical arguments. The observed deviations from the cross relation are likely due to other factors, such as the effects of precursor/successor complexes, hydrogen tunneling, steric effects or non-adiabatic effects.

It should be emphasized that the cross relation is conceptually a very simplified model. It ignores many of the lessons taught by sophisticated treatments of HAT and PCET, such as Hammes–Schiffer's multistate continuum theory.[13] This theory has been applied to many interesting systems, for instance explaining the unusual temperature dependence of a quinol oxidation[95] and the extremely large KIEs in lipoxygenase.[96] The theory uses a non-adiabatic Marcus theory-type approach, treating both the electron transfer and the proton transfer in a quantum mechanical fashion. It therefore includes both electronic and vibrational couplings, summed over vibrational levels and integrated over a range of proton donor–acceptor distances. The cross relation, as applied here, ignores or simplifies all of these factors. We reiterate that the cross relation is viewed as being successful when its prediction within an order of magnitude or two of the observed rate constant. This cross relation analysis is not appropriate to study finer issues of HAT reactions, such as isotope effects.

Most importantly, the success of this Marcus-based model indicates that it captures the primary determinants of the rate of an HAT reaction: the driving force $K_{\mathrm{XH/Y}}$ ($\Delta G^{\circ}{}_{\mathrm{XH/Y}}$), the intrinsic barrier λ, which can be determined from self-exchange rates, and solvent–solute hydrogen bonding. To a first approximation, the electronic structure of the reactants are only important as they influence ΔG° and λ. Notably, there is no evidence for the spin or 'radical character' of the oxidant having a significant influence on the facility of HAT reactions, despite the common intuition to the contrary. As emphasized elsewhere,[15c] measured or estimated self-exchange rate constants are not higher for species with more spin density on the atom that accepts the proton. Diamagnetic compounds such as permanganate and CrO_2Cl_2 are reactive H-atom abstractors despite being diamagnetic.[5,25]

The conceptual picture for HAT developed here places the essentially kinetic information in the intrinsic barriers (self-exchange rate constants). Our understanding of these HAT intrinsic barriers is still limited, but some patterns are emerging. C–H bonds are intrinsically much less reactive than O–H bonds, as shown by the values of $k_{\mathrm{XH/X}}$ in Table 1.1. For transition metal reagents, there is evidence that the factors that contribute to electron transfer inner-sphere reorganization energies will also contribute to HAT intrinsic barriers. In the vanadium–oxo system, for instance, large changes in bond lengths of the high frequency V–O bonds are the primary origin of the very slow self-exchange rate constant.[51] Thus the cross relation + KSE model, while a simplification, is a conceptual and predictive tool that can be used to understand a wide range of solution HAT reactions.

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