

Predicting organic hydrogen atom transfer rate constants using the Marcus cross relation

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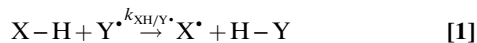
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Chemical reactions that involve net hydrogen atom transfer (HAT) are ubiquitous in chemistry and biology, from the action of antioxidants to industrial and metalloenzyme catalysis. This report develops and validates a procedure to predict rate constants for HAT reactions of oxyl radicals (RO[•]) in various media. Our procedure uses the Marcus cross relation (CR) and includes adjustments for solvent hydrogen-bonding effects on both the kinetics and thermodynamics of the reactions. Kinetic solvent effects (KSEs) are included by using Ingold's model, and thermodynamic solvent effects are accounted for by using an empirical model developed by Abraham. These adjustments are shown to be critical to the success of our combined model, referred to as the CR/KSE model. As an initial test of the CR/KSE model we measured self-exchange and cross rate constants in different solvents for reactions of the 2,4,6-tri-*tert*-butylphenoxy radical and the hydroxylamine 2,2'-6,6'-tetramethylpiperidin-1-ol. Excellent agreement is observed between the calculated and directly determined cross rate constants. We then extend the model to over 30 known HAT reactions of oxyl radicals with OH or CH bonds, including biologically relevant reactions of ascorbate, peroxy radicals, and α -tocopherol. The CR/KSE model shows remarkable predictive power, predicting rate constants to within a factor of 5 for almost all of the surveyed HAT reactions.

free radicals | Marcus theory | proton-coupled electron transfer | reactive oxygen species | oxyl radicals

Hydrogen atom transfer (HAT) reactions (Eq. 1) have been a cornerstone of organic and biological chemistry for over a century (1, 2). These reactions are key steps in many important processes, from energy conversion to the chemistry of reactive oxygen species and antioxidants (3). Thus, developing a detailed understanding of the factors that dictate HAT reactivity has long been a goal.



A large number of HAT rate constants have been measured in many laboratories with various techniques (4, 5). Rates of HAT reactions have traditionally been understood by using the Bell-Evans-Polanyi (BEP) relation, which relates the activation energy to the enthalpic driving force (6). Whereas the BEP relation holds well within sets of similar reactions, a comprehensive theoretical understanding of HAT is still emerging (3).

Our group has been exploring the use of the Marcus cross relation (CR) Eq. 2 (7), a corollary of the Marcus theory of electron transfer, as the basis for a general model for HAT rates (8–12). This use of the CR grew out of recognizing HAT as one class of a larger set of reactions in which one electron and one proton are transferred ($\text{H}^{\bullet} \equiv \text{H}^+ + e^-$), termed proton-coupled electron transfer. In this paper, we use “HAT” to refer to any reaction in which H[•] is transferred from a donor to an acceptor in a single kinetic step (Eq. 1), although other definitions have been used (13).

$$k_{\text{XH/Y}^{\bullet}} = \sqrt{k_{\text{XH/X}^{\bullet}} \cdot k_{\text{YH/Y}^{\bullet}} \cdot K_{\text{XH/Y}^{\bullet}} \cdot f} \quad [2]$$

The CR, with respect to HAT reactions, relates the cross rate constant ($k_{\text{XH/Y}^{\bullet}}$, Eq. 1) to the two degenerate self-exchange rate constants ($k_{\text{XH/X}^{\bullet}}$ and $k_{\text{YH/Y}^{\bullet}}$), the equilibrium constant ($K_{\text{XH/Y}^{\bullet}} = k_{\text{XH/Y}^{\bullet}}/k_{\text{YH/X}^{\bullet}}$), and the frequency factor (f). The variable f is defined as $\ln(f) = [\ln(K_{\text{XH/Y}^{\bullet}})]/4 \ln(k_{\text{XH/X}^{\bullet}} \cdot k_{\text{YH/Y}^{\bullet}} \cdot Z^{-2})$, with the collision frequency Z typically taken as $10^{11} \text{ M}^{-1} \text{ s}^{-1}$ (7). For transition metal complexes, Eq. 2 has been found to predict HAT cross-reaction rate constants within 1–2 orders of magnitude (10). Marcus theory has also been successfully applied to proton transfers (14), hydride transfers (15), and methyl transfers ($\text{S}_{\text{N}}2$ reactions) (6, 16), although only within sets of very closely related reactions.

Here we develop a predictive model of HAT rate constants by using the CR explicitly and accounting for both kinetic and thermodynamic solvent effects. The rates of many HAT reactions, particularly those involving O–H bonds, are highly solvent-dependent. Litwinienko and Ingold have described a quantitative kinetic solvent effect (KSE) model for HAT rate constants, on the basis of the strength of the substrate–solvent hydrogen bond (17), which is estimated by using Abraham's empirical model (18–20). The composite CR/KSE model presented here combines the Marcus CR, Ingold's KSE model, and Abraham's H-bonding parameters. The calculated rate constants are compared with directly measured values for a broad range of HAT reactions, including several biologically relevant reactions of vitamin E, vitamin C, peroxy radicals, and phenoxy radicals.

Results

Approach. The Marcus CR in its simplest form (Eq. 2) predicts HAT rate constants $k_{\text{XH/Y}^{\bullet}}$ by using three inputs: the equilibrium constant $K_{\text{XH/Y}^{\bullet}}$ and the two degenerate self-exchange rate constants $k_{\text{XH/X}^{\bullet}}$ and $k_{\text{YH/Y}^{\bullet}}$. *Solvent Effects on Equilibrium and Rate Constants* provides an overview of how these parameters are obtained, including how adjustments are applied to obtain them in the same solvent. *A Test Case: Reactions of Bulky Phenoxy Radicals with TEMPOH* describes measurements of one small set of reactions as a detailed test of the model. Finally, *Broader Application of the CR/KSE Model* extends this approach to a wide range of HAT reactions. The properties of all of the reactants used in this study are summarized in Table 1; the derivations and citations for these values are given in *SI Text*.

Solvent Effects on Equilibrium and Rate Constants. $K_{\text{XH/Y}^{\bullet}}$, bond dissociation free energies (BDFEs), and solvent effects. Ideally $\Delta G_{\text{XH/Y}^{\bullet}}^{\circ}$ ($= -RT \ln K_{\text{XH/Y}^{\bullet}}$) is determined by direct equilibrium measurements in the solvent of interest, which is typically possible only when $|\Delta G_{\text{XH/Y}^{\bullet}}^{\circ}|$ is small. A more general procedure gives $\Delta G_{\text{XH/Y}^{\bullet}}^{\circ}$ as the difference in the BDFEs of the reactants and products (XH and YH) in the same solvent. Solution-phase

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BDFEs (Eq. 3) can be calculated from the commonly tabulated gas phase bond dissociation enthalpies (BDEs) by using a two-step procedure. First, BDEs are converted to gas phase BDFEs (Eq. 4) by using $S^\circ(\text{H}^\bullet) = 27.42 \text{ cal K}^{-1} \text{ mol}^{-1}$ and the common assumption that $S^\circ(\text{XH}) \sim S^\circ(\text{X}^\bullet)$ for organic compounds (21–23). Converting these to solution BDFEs ($\text{BDFE}_{\text{solv}}$) requires $\Delta G_{\text{solv}}^\circ(\text{H}^\bullet)$ in a given solvent (24) and the difference in the free energy of solvation of XH and X^\bullet (Eq. 5).

$$\text{XH}_{\text{solv}} = \text{X}_{\text{solv}}^\bullet + \text{H}_{\text{solv}}^\bullet \quad [3]$$

$$\text{BDFE}_{\text{g}} = \text{BDE}_{\text{g}} - \text{TS}^\circ(\text{H}^\bullet) \quad [4]$$

$$\begin{aligned} \text{BDFE}_{\text{solv}} = & \text{BDFE}_{\text{g}} + \Delta G_{\text{solv}}^\circ(\text{H}^\bullet) \\ & + [\Delta G_{\text{solv}}^\circ(\text{X}^\bullet) - \Delta G_{\text{solv}}^\circ(\text{XH})] \end{aligned} \quad [5]$$

For the hydroxyl/oxy radical substrates examined here, the solvation difference $\Delta G_{\text{solv}}^\circ(\text{X}^\bullet) - \Delta G_{\text{solv}}^\circ(\text{XH})$ is dominated by the differences in hydrogen bonding between the OH/O \bullet groups and the solvent. Other contributions to solvation essentially cancel because XH and X^\bullet have the same charge and are similar in size (25, 26). Abraham et al. have developed an empirical relation to estimate the free energy of formation of 1:1 complexes $\text{X} - \text{H} \cdots \text{Y}$ in CCl_4 solvent (18), by using H-bonding acidity (α_2^{H}) and basicity parameters (β_2^{H} , Eq. 6). We use Eq. 6, following Ingold (17), as a measure of the free energy of solvent-solute hydrogen bonds. The constants α_2^{H} and β_2^{H} are obtained from ref. 19 and 20, respectively, unless otherwise noted. In aprotic solvents, the $[\Delta G_{\text{solv}}^\circ(\text{X}^\bullet) - \Delta G_{\text{solv}}^\circ(\text{XH})]$ term in Eq. 5 is therefore taken as the energy of the XH-solvent hydrogen bond. In protic solvents, solvent H bonding to X^\bullet is included as well. This model gives solution BDFEs of good accuracy, either from gas phase values or by converting BDFEs between solvents (*SI Text*).

$$\Delta G_{\text{solv}}^\circ = -10.02\alpha_2^{\text{H}}\beta_2^{\text{H}} - 1.492 \quad [6]$$

Table 1. Properties of reagents: solution BDFEs and self-exchange rate constants ($k_{\text{XH}/\text{X}^\bullet}$) in selected solvents*

Compound (α_2^{H}) [†]	Solvent (β_2^{H}) [†]	BDFE	$k_{\text{XH}/\text{X}^\bullet}$
2, 4, 6- ^t Bu ₃ PhOH (0.22) [‡]	MeCN (0.44)	77.8	20
2, 6- ^t Bu ₂ -4-OMePhOH (0.22) [‡]	MeCN (0.44)	74.9	20
TEMPOH (0.39)	MeCN (0.44)	66.5	4.7
Phenol (0.60)	DTBP [§] (0.35)	87.8	3.2×10^5
1-naphthol (0.61)	Isopentane (0)	79.7	$\leq 9 \times 10^5$
2-naphthol (0.61)	Isopentane (0)	83.0	9×10^5
Tyrosine (0.60)	H ₂ O (0.38)	88.0	1.8×10^6
^t BuOOH (0.44)	Isopentane (0)	80.4	500
L-ascorbate (0.27)	MeCN (0.44)	67.8	5×10^5
L-ascorbate (0.27)	H ₂ O (0.38)	73.6	8×10^5
α -tocopherol (0.38)	MeCN (0.44)	75.1	2.2×10^4
Trolox C (0.38)	H ₂ O (0.38)	78.5	3.5×10^5
^t BuOH (0.32)	DTBP (0.35)	104	3×10^4
9,10-dihydroanthracene	DMSO (0.78)	75	5×10^{-11}
Toluene	toluene (0.14)	86.4	8×10^{-5}

*BDFE in kcal mol⁻¹ and $k_{\text{XH}/\text{X}^\bullet}$ in M⁻¹ s⁻¹ at 298 K. Full derivation of BDFEs, self-exchange rate constants and accompanying references are in *SI Text*.

[†] α_2^{H} (solute) from ref. 19 and β_2^{H} (solvent) from ref. 20.

[‡] $k_{\text{XH}/\text{X}^\bullet}$ for the 2, 6-di-*t*-butyl-4-R substituted phenols are approximated as equal because of their structural similarity.

[§]DTBP = ^tBuOO^tBu.

^{||}Trolox C = (\pm)-6-hydroxy-2, 5, 7, 8-tetramethylchromane-2-carboxylic acid.

^{||} $k_{\text{XH}/\text{X}^\bullet}$ are not expected to vary with solvent because $\alpha_2^{\text{H}}(\text{C-H}) \sim 0$.

Solution BDFEs can also be derived from redox potentials (E°) and pK_a values [(21, 27); see *SI Text*]. BDFEs relevant to this study are summarized in Table 1 (and *SI Text*).

Self-exchange rate constants. $k_{\text{XH}/\text{X}^\bullet}$ or $k_{\text{YH}/\text{Y}^\bullet}$ are best measured directly, e.g., by NMR line broadening (12, 28), or they can be extracted from “pseudo-self-exchange” reactions between two very similar reagents, as described below. When these values are not available in the solvent of interest, we use Litwinienko and Ingold’s KSE model, which is necessary because HAT rate constants can vary by $>10^2$ between weakly and strongly H-bonding solvents (17). The KSE model gives the rate constant for H-atom abstraction from an O-H or N-H bond 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), and the Abraham H-bonding parameters α_2^{H} and β_2^{H} (Eq. 7). Eq. 7 can also be recast to convert k between two H-bonding solvents (*SI Text*). A key implication of the KSE model is that substrates are unreactive towards HAT when H-bonded to solvent (XH \cdots S). Whereas Eq. 7 does not explicitly include solvent effects on $K_{\text{XH}/\text{Y}^\bullet}$, such effects are included in the CR/KSE treatment developed here (see above).

$$\log(k^{\text{S}}) = \log(k^0) - 8.3\alpha_2^{\text{H}}(\text{XH})\beta_2^{\text{H}}(\text{solv}) \quad [7]$$

A Test Case: Reactions of Bulky Phenoxy Radicals with 2,2',6,6'-tetramethyl-piperidin-1-ol (TEMPOH).

Self-exchange and cross-reaction rate constants in various solvents have been measured for bulky phenols/phenoxy radicals and for the nitroxyl radical/hydroxyl amine TEMPO(\bullet /H) (TEMPO = 2, 2', 6, 6'-tetramethylpiperidine-1-oxyl radical) (Tables 2 and 3). These reactions all proceed via HAT mechanisms (concerted transfer of H⁺ and e⁻; see *SI Text*), and they therefore provide a detailed test of the CR/KSE model.

Self-exchange reactions. We have determined the $k_{\text{XH}/\text{X}^\bullet}$ for ^tBu₃PhO \bullet + ^tBu₃PhOH HAT self-exchange in dry CCl₄, C₆H₆, MeCN, and DMSO by studying the reaction of isolated ^tBu₃PhO \bullet (29) and 2,6-di-*tert*-butyl-4-methyl-phenol (BHT, Me^tBu₂PhOH). The disappearance of ^tBu₃PhO \bullet in the presence of excess BHT was monitored by UV-vis stopped-flow spectrophotometry (see *Materials and Methods*). As described in *SI Text*, this reaction proceeds by initial HAT from BHT to ^tBu₃PhO \bullet , which is an example of a pseudo-self-exchange reaction, X-H + X'. This is because X and X' are very similar and because it is essentially isoergic [$K_{\text{eq}} = 1.45 \pm 0.13$ in C₆H₆ (30)]. In such cases (9, 11, 31), $k_{\text{XH}/\text{X}^\bullet}$ is taken as the geometric

Table 2. Self-exchange rate constants for ^tBu₃PhO(\bullet /H) and for TEMPO(H) from measured pseudo-self-exchange reactions and from the KSE model (Eq. 7)

Self-exchange	Solvent	$k_{\text{XH}/\text{X}^\bullet}$ (M ⁻¹ s ⁻¹ at 298 K)	
		Measured*	Calculated [†]
^t Bu ₃ PhO(\bullet /H) [‡]	Hexane	140 ± 25	–
^t Bu ₃ PhO(\bullet /H)	CCl ₄	130 ± 20	110 ± 25
^t Bu ₃ PhO(\bullet /H)	Benzene	95 ± 14	74 ± 20
^t Bu ₃ PhO(\bullet /H)	MeCN	20 ± 3	19 ± 5
^t Bu ₃ PhO(\bullet /H)	DMSO	8 ± 2	4 ± 1
TEMPO(H) [‡]	CCl ₄	110 ± 20	–
TEMPO(H)	Benzene	60 ± 14	56 ± 25
TEMPO(H) [‡]	MeCN	4.7 ± 1.0	6 ± 4
TEMPO(H)	DMSO	0.60 ± 0.13	0.5 ± 0.4

* $k_{\text{XH}/\text{X}^\bullet}$ derived from pseudo-self-exchange reaction $k_{\text{XH}/\text{X}^\bullet}$ and $K_{\text{XH}/\text{X}^\bullet}$ by using Eq. 8; $K_{\text{XH}/\text{X}^\bullet}$ are from BDFEs given in *SI Text*.

[†]Calculated for the solvent given, by using Eq. 7 and the $k_{\text{XH}/\text{X}^\bullet}$ in hexane (for ^tBu₃PhO \bullet) or CCl₄ (for TEMPO).

[‡]Refs. 32 (^tBu₃PhOH), 31 (TEMPOH/CCl₄), and 11 (TEMPOH/MeCN).

Table 3. Rate constants for TEMPOH + 2, 6-^tBu₂-4-R-PhO[•] (R = ^tBu, OMe) [Eq. 9]: measured; predicted from the CR (Eq. 2); and predicted from the CR/KSE model

Reaction 9, R =	Solvent	k_9 ($10^3 \text{ M}^{-1} \text{ s}^{-1}$ at 298 K)		
		Measured	CR*	CR/KSE [†]
^t Bu	CCl ₄	98 ± 6	624	–
^t Bu	C ₆ H ₆	95 ± 6	400	340
^t Bu	MeCN	12.5 ± 0.5	29	55
^t Bu	DMSO	2.7 ± 0.2	7.0	4.4
OMe	C ₆ H ₆	18.5 ± 1.5	56	48
OMe	MeCN	2.7 ± 0.4	3.6	5.9
OMe	DMSO	0.62 ± 0.08	0.88	0.55

* k_9 calculated by using Eq. 2 with the $k_{\text{XH}/\text{X}^\bullet}$ in Table 2 for the relevant solvent and the K_9 values from the BDFEs/Abraham's model (SI Text).

[†] k_9 calculated by using Eq. 2 with the $k_{\text{XH}/\text{X}^\bullet}$ values from the last column in Table 2, derived by using the KSE model.

mean of the forward and reverse rate constants $k_{\text{XH}/\text{X}^\bullet}$ and $k_{\text{X}^\bullet/\text{XH}}$ (Eq. 8). Analyzing our rate constants in various solvents, as well as a value in hexane reported by Prokof'ev (32), gives the self-exchange rate constants in Table 2 (SI Text).

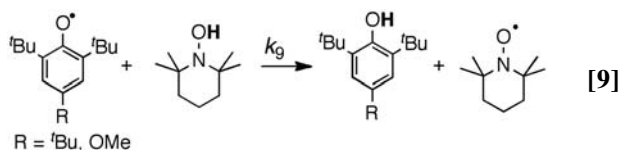
$$k_{\text{XH}/\text{X}^\bullet} = \sqrt{k_{\text{XH}/\text{X}^\bullet} \cdot k_{\text{X}^\bullet/\text{XH}}} = k_{\text{XH}/\text{X}^\bullet} \cdot (K_{\text{XH}/\text{X}^\bullet})^{-1/2} \quad [8]$$

Self-exchange rate constants for TEMPO([•]/H) have been determined from the pseudo-self-exchange reaction of TEMPOH with the stable radical 4-oxo-TEMPO and Eq. 8 ($K_{\text{XH}/\text{X}^\bullet} = 5.5$) in benzene and DMSO, complementing prior measurements in MeCN (11) and CCl₄ (31) (Table 2).

Testing the KSE model. The ^tBu₃PhO([•]/H) and TEMPO([•]/H) self-exchange rate constants provide a test of the KSE model for self-exchange reactions. The needed α_2^{H} (substrate) and β_2^{H} (solvent) values are from ref. 19 and 20, respectively, or from our measurement of $\alpha_2^{\text{H}}(\text{TEMPOH}) = 0.39 \pm 0.05$ (SI Text), using Abraham's ¹H NMR method (33, 34). To confirm this methodology, we also measured $\alpha_2^{\text{H}}(\text{BHT}) = 0.22 \pm 0.05$ and $\alpha_2^{\text{H}}(\text{Et}_2\text{NOH}) = 0.28 \pm 0.05$ by ¹H NMR, which are in excellent agreement with the literature values determined by IR spectroscopy (35, 36).

The KSE model (Eq. 7) has been used to predict TEMPO([•]/H) and ^tBu₃PhO([•]/H) self-exchange rate constants in other solvents by using the rate constant in the least polar solvent as the reference point (the last column of Table 2). The predicted rate constants are within error of the measured values for all but one of the reactions. [The calculated value for ^tBu₃PhO([•]/H) in DMSO deviates by a factor of 2, slightly outside the error limits.] The KSE model thus works well for self-exchange reactions, as expected (17).

Cross reactions and application of the CR. Phenoxy radicals ^tBu₂RPhO[•] (R = ^tBu, OMe) rapidly oxidize TEMPOH to give the corresponding phenol and TEMPO (Eq. 9). Rate constants were measured by UV-vis stopped-flow spectrophotometry under pseudo-first-order conditions of excess TEMPOH, monitoring the change from the blue phenoxy radical to the pale orange TEMPO. As predicted by the KSE model, the reactions are much slower in the more polar solvents (Table 3).



These cross rate constants provide a test of the CR (Eq. 2), by using the self-exchange rate constants presented above (Table 2)

and equilibrium constants from the BDFEs in Table 1 and from the Abraham model (SI Text). The frequency factor (f ; see above) has also been included in this analysis (SI Text). The cross rate constants computed from Eq. 2 are in good agreement with those that were directly measured, all within a factor of 6.5. As a test of the CR/KSE model, cross rate constants in polar solvents have also been calculated by using the KSE-derived self-exchange rates from Table 2. The calculated cross-reaction rate constants are again in agreement with those directly measured, within a factor of 4.5. This agreement is expected because the KSE model predicted self-exchange rate constants are close to the measured values. This exercise serves to validate the interchangeable use of KSE-adjusted or directly measured self-exchange rate constants in Eq. 2.

Broader Application of the CR/KSE Model. To examine the validity of the CR/KSE model over a wider range of reactions, we have culled data from the literature and measured a few more rate constants. In this section we present our new measurements first and then a variety of tests of the model.

Reactions of phenoxy radicals, ascorbate, and related species. ^tBu₃PhO[•] abstracts H[•] from α -tocopherol (TocOH) in MeCN as indicated by disappearance of the UV bands of ^tBu₃PhO[•] and growth of an optical signature characteristic of the α -tocopheroxy radical (TocO[•]) (37; SI Text). The measured rate constant $k_{\text{TocOH}/\text{tBu}_3\text{PhO}^\bullet} = 8,100 \pm 600 \text{ M}^{-1} \text{ s}^{-1}$ is close to that reported for TocOH + 2, 6-di-*tert*-butyl-4-phenyl-phenoxy (Ph^tBu₂PhO[•]) in ethanol, $k_{\text{TocOH}/\text{Ph}^t\text{Bu}_2\text{PhO}^\bullet} = 8,800 \pm 440 \text{ M}^{-1} \text{ s}^{-1}$ (38). These reactions have similar driving forces, because the BDFEs of ^tBu₃PhOH and Ph^tBu₂PhOH are the same, as measured in benzene (39). The TocOH self-exchange rate constant is best estimated from the CR by using $k_{\text{TocOH}/\text{tBu}_3\text{PhO}^\bullet}$, $\log K_{\text{TocOH}/\text{tBu}_3\text{PhO}^\bullet} = 2.21 \pm 0.18$ (30), and $k_{\text{XH}/\text{X}^\bullet}(\text{tBu}_3\text{PhO}^\bullet)$ from Table 2, yielding $k_{\text{XH}/\text{X}^\bullet}(\text{TocOH}) = 2.4 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ in MeCN (40).

A similar analysis can be done for the reported reaction of TEMPO with 5,6-isopropylidene ascorbate (*i*AscH⁻), an organic soluble ascorbate analog (41): The measured $k_{i\text{AscH}^-/\text{TEMPO}^\bullet} = 1,720 \pm 150 \text{ M}^{-1} \text{ s}^{-1}$ and $K_{i\text{AscH}^-/\text{TEMPO}^\bullet} = 1.2 \pm 0.2$ in MeCN yield $k_{\text{XH}/\text{X}^\bullet}(i\text{AscH}^-)_{\text{MeCN}} = (5.4 \pm 1.2) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. Application of the KSE model with $\alpha_2^{\text{H}}(i\text{AscH}^-) = 0.3$ then gives $k_{\text{XH}/\text{X}^\bullet}(\text{AscH}^-) = 3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ in water, assuming that ascorbate (AscH⁻) and *i*AscH⁻ have similar properties (SI Text).

^tBu₃PhO[•] oxidizes 9,10-dihydroanthracene (DHA), to give anthracene and ^tBu₃PhOH based on UV and ¹H NMR spectra. This reaction proceeds by rate limiting HAT, and the rate constant for that step at 298 K in MeCN has been determined (under pseudo-first-order conditions with excess DHA) to be $k_{\text{DHA}/\text{tBu}_3\text{PhO}^\bullet} = (1.1 \pm 0.1) \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ (SI Text). This reaction is much slower than H-atom abstractions from O-H bonds of comparable strength, as expected (8).

Tests of the CR where $k_{\text{XH}/\text{X}^\bullet}$ and $k_{\text{YH}/\text{Y}^\bullet}$ are known in the same solvent. By using the experimental results above and literature data (see Tables 1 and 4 and SI Text), there are 17 oxyl radical reactions for which the Marcus CR can be tested by using measured $k_{\text{XH}/\text{X}^\bullet}$ and $k_{\text{YH}/\text{Y}^\bullet}$ values measured in the same solvent. The $K_{\text{XH}/\text{Y}^\bullet}$ values are estimated from the BDFE values in Table 1 and Eq. 6 above. These 17 reactions, indicated in Table 4 by §, include RO[•] radicals abstracting hydrogen from both O-H and C-H bonds. These reactions span 10^{12} in cross rate constant ($k_{\text{XH}/\text{Y}^\bullet}$) and 10^{18} in equilibrium constant ($K_{\text{XH}/\text{Y}^\bullet}$). There is very good agreement between experimentally determined rate constants and those predicted by using Eq. 2, as indicated by the average deviation of a factor of 4.4 and as illustrated in Fig. 1 (42). For all but 3 of the 17 reactions, the deviation between k_{calc} and k_{obs} is less than a factor of 4.

Table 4. Summary of observed and calculated hydrogen transfer rate constants.

Entry	Reaction (XH + Y•)	Solvent (β_2^H)*	$K_{XH/Y\bullet}^\dagger$	k_{obs}^\ddagger	k_{calc}^\ddagger
1 ^s	TEMPOH + ^t Bu ₃ PhO• [¶]	MeCN (0.44)	5.0×10^7	1.25×10^4	2.9×10^4
2 ^s	TEMPOH + ^t Bu ₃ PhO• [¶]	DMSO (0.78)	4.7×10^7	2.7×10^3	7.0×10^3
3 ^s	TEMPOH + ^t Bu ₃ PhO• [¶]	C ₆ H ₆ (0.14)	2.4×10^8	9.5×10^4	4.0×10^5
4 ^s	TEMPOH + ^t Bu ₃ PhO• [¶]	CCl ₄ (0.05)	2.7×10^8	9.8×10^4	6.2×10^5
5 ^s	TEMPOH + ^t Bu ₂ MeOPhO• [¶]	MeCN (0.44)	3.2×10^5	2.67×10^3	3.6×10^3
6 ^s	TEMPOH + ^t Bu ₂ MeOPhO• [¶]	DMSO (0.78)	3.4×10^4	6.2×10^2	8.8×10^2
7 ^s	TEMPOH + ^t Bu ₂ MeOPhO• [¶]	C ₆ H ₆ (0.14)	1.8×10^6	1.85×10^4	5.6×10^4
8 ^s	<i>i</i> AscH ⁻ + ^t Bu ₃ PhO•	MeCN (0.44)	2.3×10^8	3.4×10^6	1.3×10^7
9 ^s	<i>i</i> AscH ⁻ + ^t Bu ₂ MeOPhO•	MeCN (0.44)	1.5×10^6	5.3×10^5	1.9×10^6
10	^t Bu ₂ MeOPhOH + ROO•	Styrene (0.18)	4.5×10^5	1.1×10^5	3.6×10^4
11	BHT + ROO•	Styrene (0.18)	4.7×10^3	1.4×10^4	5.0×10^3
12	2,6- ^t Bu ₂ PhOH + ROO•	Styrene (0.18)	2.3×10^2	3.1×10^3	1.3×10^3
13	TocOH + ROO•	Styrene (0.18)	4.8×10^5	3.2×10^6	1.5×10^6
14 ^s	^t Bu ₂ MeOPhOH + ROO•	Alkane** (0)	2.4×10^5	1.1×10^5	8.8×10^4
15 ^s	BHT + ^t BuOO•	Alkane** (0)	2.5×10^3	2.4×10^4	1.2×10^4
16	TocOH + ^t BuOO•	Alkane** (0)	4.0×10^5	2.6×10^6	3.8×10^6
17	^t BuOOH + TocO•	EtOH (0.44)	1.5×10^{-6}	4.1×10^{-1}	3.5×10^{-1}
18	tetralin hydroperoxide + ^t Bu ₃ PhO•	PhCl (0.11)	4.2×10^{-4}	3.4×10^{-1}	2.5
19	PhOH + ^t Bu ₃ PhO•	Hexane (0)	3.1×10^{-7}	5.7	17
20	1-NapOH + ^t BuOO•	Isopentane (0)	3.5	1.5×10^5	2.9×10^5
21	2-NapOH + ^t BuOO•	Isopentane (0)	1.4×10^{-2}	3.1×10^4	1.7×10^4
22	PhOH + ^t BuOO•	Heptane (0)	5.5×10^{-4}	3×10^3	2.9×10^3
23 ^s	PhOH + ^t BuO•	DTBP:C ₆ H ₆	1.6×10^{12}	3.3×10^8	5.1×10^9
24 ^s	TocOH + PhO•	2:1 DTBP:MeCN	2.6×10^9	3.2×10^8	1.1×10^9
25 ^s	TocOH + PhO•	3:1 DTBP:C ₆ H ₆	2.6×10^9	1.1×10^9	1.1×10^9
26	Trolox C + PhO•	Water (0.38)	1.0×10^8	4.1×10^8	9.7×10^8
27	PhOH + ^t Bu ₃ PhO•	PhCl (0.09)	1.8×10^{-7}	<8 ^{††}	6.1
28	AscH ⁻ + Trolox C radical	Water (0.38)	4.7×10^3	$1.4 \times 10^{7++}$	2.5×10^7
29	AscH ⁻ + Trolox C radical	Water (0.38)	4.7×10^3	$8.3 \times 10^{6++}$	2.5×10^7
30	AscH ⁻ + tyrosyl radical	Water (0.38)	4.0×10^{10}	4.4×10^8	7.0×10^9
31	Trolox C + tyrosyl radical	Water (0.38)	9.3×10^6	3.1×10^8	4.5×10^8
32	DHA + PhO•	PhCl (0.09)	1.9×10^8	< $1.1 \times 10^{2++}$	1.8×10^2
33 ^s	DHA + ^t Bu ₃ PhO• [¶]	MeCN (0.44)	1.2×10^2	1.1×10^{-3}	3.3×10^{-4}
34 ^s	DHA + ^t BuO•	DTBP:C ₆ H ₆	4.0×10^{21}	9.5×10^6	6.2×10^5
35 ^s	toluene + ^t BuO•	DTBP:C ₆ H ₆	8.9×10^{12}	2×10^5	5.0×10^5
36	toluene + ^t BuOO•	Toluene (0.14)	2.6×10^{-4}	1×10^{-2}	1.1×10^{-3}

* β_2^H values from ref. 20.

[†] $K_{XH/Y\bullet}$ in organic solvents from BDFEs and the Abraham model; $K_{XH/Y\bullet}$ in water from thermochemical cycles.

[‡] k in M⁻¹s⁻¹ at 298 K unless otherwise noted; full details and citations are given in *SI Text*.

[§]Indicates both $k_{XH/X\bullet}$ and $k_{YH/Y\bullet}$ are known in the given solvent.

[¶]This work.

^{||}ROO• = polyperoxystyryl.

**Alkane = decane or cyclohexane.

^{††}Rate constant at 333 K.

⁺⁺Independent determinations of the rate constant for Trolox radical + AscH⁻ give slightly different values (*SI Text*).

Tests of the CR/KSE model. For many HAT reactions, the relevant self-exchange rate constants are known, but not in the solvent of interest. In these cases, we use the KSE model (Eq. 7) to predict self-exchange rate constants in the solvent of the cross-reaction, which expands the set of applicable reactions to 36 (Table 4 and Fig. 2). Some of these HAT reactions are in protic media where, to our knowledge, there have been no reports of HAT self-exchange rate constants. Remarkably, for these 36 reactions the average deviation is 3.8, and the deviation between k_{calc} and k_{obs} is less than a factor of 5 for all but six of the reactions.

Discussion

Agreement Between Theory and Experiment. The CR/KSE approach developed here combines the Marcus CR (Eq. 2) and two other well-established empirical models. Ingold's KSE (Eq. 7) model is used to calculate self-exchange rate constants in one solvent when they have been measured in another, and Abraham's hydrogen-bonding model allows estimation of $K_{XH/Y\bullet}$ in different solvents. The combined CR/KSE model is a powerful predictor of organic HAT rate constants, on the basis of the close agreement between k_{calc} and k_{obs} (Table 4 and Fig. 2). By removing the need to have all of the inputs measured in the solvent of interest, the KSE model and Abraham's H-bonding model dramatically broaden

the scope of reactions that can be understood by using the CR. It should be noted, however, that the KSE model is not universally applicable, as noted by Ingold and coworkers (43), and that the Abraham model can be difficult to use in some cases because parameters are not available or because the parameters apply to an entire molecule rather than a particular XH fragment (33). Despite these caveats, the combined CR/KSE model works very well for the diverse set of organic HAT reactions discussed here.

The CR/KSE method is much more powerful than the traditional BEP relation. As noted above, the BEP relation is typically limited to reactions of a series of similar compounds under similar reaction conditions. In contrast, the set of HAT reactions examined here is extensive and diverse, including reactions of phenoxyl, nitroxyl, peroxy, and alkoxy radicals with phenols, hydroxylamines, ascorbate, and alkylaromatic compounds. The reaction solvents range from alkanes to water, covering polar, nonpolar, protic, and aprotic media. The reactions have equilibrium constants spanning more than 10^{20} , and the cross rate constants range from 10^{-3} to 10^9 M⁻¹s⁻¹. There are a wide distribution of oxyl radical reactions studied by different physical and spectroscopic techniques and by different research groups over the past 50 years. The broad success of the CR/KSE model

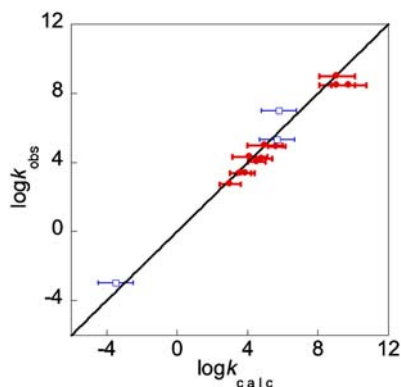


Fig. 1. Comparison between HAT rate constants measured experimentally (k_{obs}) vs. those determined from the Marcus CR (Eq. 2, k_{calc}) for reactions where $k_{\text{XH}/\text{Y}\cdot}$, $k_{\text{XH}/\text{X}\cdot}$, and $k_{\text{YH}/\text{Y}\cdot}$ have been measured in the same solvent (Table 4). The reactions involve oxyl radicals +O-H bonds (\bullet) or C-H bonds (\square).

is surprising because previous applications of the CR to atom and group transfer reactions (other than electron transfer) have been restricted to limited sets of structurally similar reagents under very similar reaction conditions (6, 14–16).

Implications and Limitations of the Model. The success of the CR/KSE model provides fundamental understanding of HAT reactions. First, it indicates that HAT reactions should be described by using free energies rather than the enthalpies commonly used in free-radical chemistry (including the BEP relation). All of the components of the CR/KSE model use free energies, and this is an essential feature of Marcus theory. Furthermore, recent work from our group on a specific transition metal HAT reaction shows directly that free energies are more appropriate than enthalpies (27).

It should be emphasized that the model developed here is not simply an extended linear free energy relation (44). Linear free energy relations, such as Hammett analyses and the Brønsted relation, are valuable but are typically limited to a set of closely related compounds or reactions, and the parameters are derived from the analysis (like Hammett ρ values). In the CR/KSE model, all of the parameters— $k_{\text{XH}/\text{X}\cdot}$, $k_{\text{YH}/\text{Y}\cdot}$, $K_{\text{XH}/\text{Y}\cdot}$, α_2^{H} , and β_2^{H} —are measured from independent experiments and have independent meaning. The rates of HAT cross reactions are directly related to the rates of the corresponding self-exchange reactions and the hydrogen-bonding properties of the reagents with the solvent.

For a particular reaction, the success of the CR/KSE treatment indicates that it proceeds by a HAT mechanism (concerted H⁺ transfer) because all of the inputs ($k_{\text{XH}/\text{X}\cdot}$, $k_{\text{YH}/\text{Y}\cdot}$, and $K_{\text{XH}/\text{Y}\cdot}$) are for HAT mechanisms. In addition, Ingold has emphasized that Eq. 7 does not hold for reactions that do not proceed by HAT, for instance, when the mechanism is sequential proton loss and then electron transfer (17). Thus, all of the reactions discussed here appear to follow a HAT mechanism, on the basis of the agreement between experiment and theory (as well as other evidence; cf. *SI Text*).

The success of the CR/KSE model is remarkable given that it ignores or simplifies various aspects of HAT reactions. The CR, and the Marcus theory of electron transfer (ET) from which it is derived, applies to unimolecular reactions of weakly bound precursor and successor complexes (7). In ET reactions, these complexes are typically weakly associated, and their energies are often estimated with a simple electrostatic calculation. In HAT, the electrostatic term is usually not needed because no net charge is transferred and because typically at least one of the reactants is neutral (as is the case for all of the reactions here). However, H-transfer occurs over very short distances (3) so HAT precursor complexes have distinct configurations, often with a hydrogen bond. A more complete analysis of HAT re-

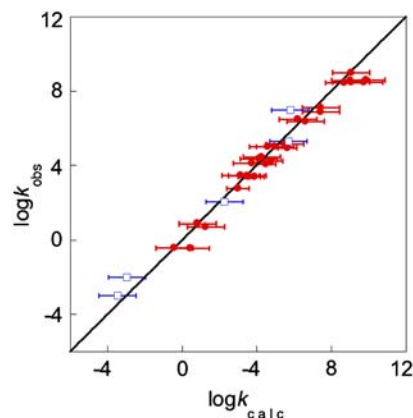


Fig. 2. Comparison between HAT rate constants measured experimentally (k_{obs}) vs. those from the CR/KSE model (k_{calc}). The line indicates perfect agreement. The reactions (Table 4) involve oxyl radicals +O-H bonds (\bullet) or C-H bonds (\square). The correlation coefficient (R^2) for all data is 0.97.

actions, including these precursor and successor complexes, and estimating their energies using the Abraham model, is given in *SI Text*. As described there, the more complex treatment may be preferred in special cases, when there is a large variation in α_2^{H} values and in protic solvents. Still, the CR/KSE model described here gives excellent agreement in most cases.

A more fundamental concern with the CR/KSE treatment is the use of the CR at all. It was derived for ET reactions of weakly interacting reagents, and there is little theoretical basis for its application to HAT reactions. Hydrogen tunneling, nonadiabatic effects, vibrational excited states, and donor-acceptor motions are all included in the current theoretical models of HAT (45) but are not in the Marcus treatment. The TEMPO(\cdot /H) self-exchange reaction proceeds predominantly by hydrogen tunneling (31), making the success of the CR for this reagent even more remarkable.

In our view, the striking success of the CR/KSE model in predicting rate constants is largely because it captures the most important aspects of a HAT reaction: the driving force ($K_{\text{XH}/\text{Y}\cdot}$); the intrinsic barriers ($k_{\text{XH}/\text{X}\cdot}$); and the interaction of the reactants with solvent. In terms of predicting a HAT rate constant to within a factor of 5, one can usually ignore other effects such as hydrogen tunneling, nonadiabatic behavior, and precursor complex formation. The success of the CR, in this and other applications, may partially be a result of its inherent averaging, as pointed out by Sutin (7).

Conclusions

A kinetic model has been developed for hydrogen atom transfer reactions by using the Marcus CR. We use Ingold's KSE analysis and Abraham's hydrogen-bonding parameters to account for solvent effects on the parameters for the CR ($k_{\text{XH}/\text{X}\cdot}$, $k_{\text{YH}/\text{Y}\cdot}$, and $K_{\text{XH}/\text{Y}\cdot}$). This combined CR/KSE model is shown to be very successful at predicting rate constants for oxyl radicals abstracting H⁺ from O-H bonds in phenols, hydroxyl amines, and ascorbate and from C-H bonds in alkylaromatic compounds. Of the 36 hydrogen atom transfer reactions that have been examined, the model predicts $k_{\text{XH}/\text{Y}\cdot}$ with an average deviation from the measured value of a factor of 3.8 and is within a factor of 5 for all but six cases. The reactions span 28 orders of magnitude in $K_{\text{XH}/\text{Y}\cdot}$ and 12 orders of magnitude in $k_{\text{XH}/\text{Y}\cdot}$ and occur in solvents ranging from alkanes to water. The success of this approach over a broad set of reactions and solvents indicates that the model captures the three primary determinants of the rate of a HAT reaction: the driving force $K_{\text{XH}/\text{Y}\cdot}$ ($\Delta G_{\text{XH}/\text{Y}\cdot}$); the intrinsic barriers (from self-exchange rate constants, $k_{\text{XH}/\text{X}\cdot}$ and $k_{\text{YH}/\text{Y}\cdot}$); and solvent-solute H bonding. Taken together, the data

show that the CR/KSE model is a conceptual and predictive tool that can be used to understand a wide range of organic HAT reactions in solution, including biologically important hydrogen atom transfer reactions involving tocopherol, ascorbate, and hydroperoxides.

Materials and Methods

Physical Techniques and Instrumentation. UV-vis stopped-flow measurements used an OLIS RSM-1000. ^1H NMR spectra were recorded on Bruker Avance spectrometers at 300 or 500 MHz. All reactions were performed anaerobically by using standard glovebox and high vacuum techniques.

Materials. Reagent grade solvents were purchased from Fischer Scientific, unless otherwise noted. Anhydrous MeCN (Honeywell Burdick and Jackson) was sparged with Ar. C_6H_6 and DMSO were dried by using a Seca solvent system. CCl_4 (99.9%; Aldrich) was used as received in a Sure/Seal bottle. Deuterated solvents were obtained from Cambridge Isotope Laboratories. CDCl_3 was stored over CaH_2 and freshly distilled before use. TEMPOH (27) and $^t\text{Bu}_3\text{PhO}^*$ (29) were prepared according to the literature. 4-oxo-TEMPO

was sublimed under static vacuum onto a -78°C cold finger. BHT and DHA were recrystallized 3 times from absolute EtOH and dried in vacuo.

Stopped-Flow Kinetic Experiments. In a typical procedure, solutions of $^t\text{Bu}_3\text{PhO}^*$ (1.1 mM) and BHT (5.5–78 mM) were prepared in anhydrous MeCN in an N_2 -filled glovebox and loaded into syringes. The two syringes were removed from the glovebox and placed immediately into the stopped-flow apparatus. The mixing chamber of the stopped-flow apparatus was flushed with reagents before collecting kinetic data. A minimum of five kinetic runs were collected at each concentration. The data were well fit over four half-lives in using an $\text{A} \rightarrow \text{B}$ kinetic model with SPECFIT software. Plots of the pseudo-first-order k_{obs} as a function of $[\text{BHT}]$ were linear with a zero intercept, the slope giving the bimolecular rate constant.

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