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Kinetic Effects of Hydrogen Bonds on Proton-Coupled Electron Transfer from Phenols

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Abstract: The kinetics and mechanism of proton-coupled electron transfer (PCET) from a series of phenols to a laser flash generated $[Ru(bpy)_3]^{3+}$ oxidant in aqueous solution was investigated. The reaction followed a concerted electron−proton transfer mechanism (CEP), both for the substituted phenols with an intramolecular hydrogen bond to a carboxylate group and for those where the proton was directly transferred to water. Without internal hydrogen bonds the concerted mechanism gave a characteristic pH-dependent rate for the phenol form that followed a Marcus free energy dependence, first reported for an intramolecular PCET in Sjödin, M. et al. *J. Am. Chem. Soc.* **2000**, *122*, 3932−3962 and now demonstrated also for a bimolecular oxidation of unsubstituted phenol. With internal hydrogen bonds instead, the rate was no longer pH-dependent, because the proton was transferred to the carboxylate base. The results suggest that while a concerted reaction has a relatively high reorganization energy (λ), this may be significantly reduced by the hydrogen bonds, allowing for a lower barrier reaction path. It is further suggested that this is a general mechanism by which proton-coupled electron transfer in radical enzymes and model complexes may be promoted by hydrogen bonding. This is different from, and possibly in addition to, the generally suggested effect of hydrogen bonds on PCET in enhancing the proton vibrational wave function overlap between the reactant and donor states. In addition we demonstrate how the mechanism for phenol oxidation changes from a stepwise electron transfer−proton transfer with a stronger oxidant to a CEP with a weaker oxidant, for the same series of phenols. The hydrogen bonded CEP reaction may thus allow for a low energy barrier path that can operate efficiently at low driving forces, which is ideal for PCET reactions in biological systems.

Introduction

The importance of proton-coupled electron transfer (PCET)[1] from amino acids in the function of many redox proteins is being increasingly recognized.[2,3] Because enzymes usually operate with small reaction free energies, a coupled deprotonation is often required to turn oxidation of a high-potential amino acid into an overall exergonic process. An important example is the water-oxidizing Photosystem II, where a tyrosine residue (Tyr_Z) interfaces the P_{680} chlorophylls and the water-oxidizing manganese cluster in a chain of PCET reactions.[3] The Tyr_Z transfers an electron to the oxidized chlorophyll pigment P_{680}^+, regenerating the chlorophylls, and the resulting tyrosine radical subsequently oxidizes the manganese cluster. The potential for tyrosine oxidation is high: $E^0 = 1.4-1.5$ V vs NHE[4] in water for the $TyrO^{\bullet}H^+$/TyrOH couple. The concomitant shift in pK_a from 10 to -2[4b] typically results in deprotonation, however, giving a lower proton-coupled $TyrO^{\bullet}$/TyrOH potential and an overall downhill reaction. The PCET from Tyr_Z is presumably facilitated by hydrogen bonding to a base that accepts the proton, most likely a histidine and possibly also aspartate or glutamate.[3] The electron is not transferred through the hydrogen bond in this system, but the electron and proton are transferred in different directions. The mechanism by which hydrogen bonds promote such bidirectional PCET is not clear. Mechanistic studies in synthetic model systems, and theoretical work, have given insight into different aspects of PCET.[5] These have in

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(1) We use the term PCET to denote all regimes of coupling, from sequential electron−proton transfer or vice versa to a concerted reaction. The latter is denoted CEP and is defined as a reaction with a single transition state for the transfer of both the electron and proton.

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(4) In ref 4a, $E°(TyrO^{\bullet}/TyrO^-) = 0.72$ V vs NHE was reported, and from ref 4b, a pK_a value for the tyrosine radical cation of ca. -2 can be estimated. Coupled with the assumption of the amino-group pK_a values being essentially equal for the radical and the parent, we predict $E°(TyrOH^{\bullet+}/TyrOH) \approx 1.44$ V. (a) Lind, J.; Shen, X.; Eriksen, T. E.; Merényi, G. *J. Am. Chem. Soc.* **1990**, *112*, 479. (b) Dixon, W. T.; Murphy, D. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 1221.

10.1021/ja063264f CCC: $33.50

general not included bidirectional PCET, however, or been concerned with different aspects other than explicit effects of hydrogen bonds.

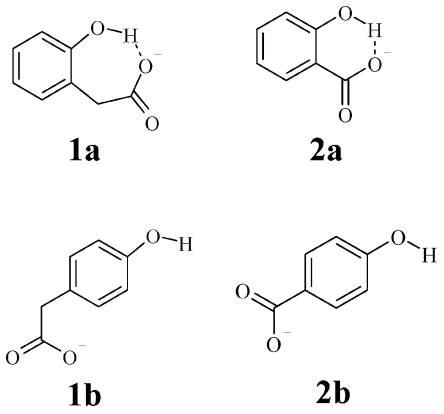
We have shown that the intramolecular PCET from tyrosine to Ru^{III} in a covalently linked $Ru(bpy)_3^{3+}$−tyrosine complex follows a concerted electron−proton transfer mechanism (CEP).[6,7] We defined "concerted" as a reaction with a single transition state for the transfer of both particles. Because of the kinetic similarities to Tyr_Z oxidation in Mn-depleted PSII, we suggested that also this reaction follows a CEP mechanism. For $Ru(bpy)_3^{3+}$−tyrosine, we found that the rate constant for oxidation of the phenolic form increased with pH at pH < 10, while oxidation of the phenolate form at pH > 10 was independent of pH. At a pH around the pK_a value, we observed biexponential kinetics, where the component representing a pure electron transfer (ET) oxidation of tyrosinate was 2 orders of magnitude larger than that for the PCET from tyrosine. Note that the pH-dependence for CEP from the phenol form could not be explained by a deprotonation followed by electron transfer (a stepwise PTET mechanism).[8] Instead, the pH-dependence for the CEP tyrosine oxidation rate could, unexpectedly, be described by a Marcus equation, derived for pure ET (eq 1).[9] We used the pH-dependence of the tyrosine potential, where $E^{\circ\prime}_{TyrO^\bullet/TyrOH}$ decreases by 59 meV per pH unit, to calculate the pH-dependence of the driving force for the overall reaction: $-\Delta G^{\circ\prime} = E^{\circ\prime}_{Ru^{3+/2+}} - E^{\circ\prime}_{TyrO^\bullet/TyrOH}$ (primed symbols denote standard states but with the proton activity at the given pH). This relation between $\Delta G^{\circ\prime}$ and pH we then used in a fit to eq 1 of the observed rate constant as a function of pH and temperature. In our analysis, we found that the reorganization energy was significantly larger for CEP from the phenol form ($\lambda = 1.4$ eV) than for a pure ET from the phenolate form ($\lambda = 0.9$ eV),[6,7,10] presumably due to the extra internal and solvent reorganization associated with the proton transfer.

$$k_{ET} = \frac{2\pi H_{rp}^{\ 2}}{\hbar\sqrt{4\pi\lambda k_B T}} \exp\left[-\frac{(\Delta G^\circ + \lambda)^2}{4\lambda k_B T}\right] \qquad (1)$$

For further modeling of enzymatic redox reactions, it is important to study the effect of hydrogen bonds on phenol oxidation. Recent model studies have typically concerned only structure and static properties,[11] while the dynamic and kinetic effects of hydrogen bonds have not been explored, with a few notable exceptions.[12]

In the present paper we examined the PCET kinetics for oxidation of phenols with and without internal hydrogen bonds, in aqueous solution. From our results we suggest that internal hydrogen bonds may promote PCET by reducing the reorganization energy for CEP. We also report that the oxidation kinetics for unsubstituted phenol in a bimolecular reaction is pH-dependent, just like in our previously reported intramolecular reaction,[6,7] in a way that cannot be described only by a simple pH-dependent ratio of the phenol and phenolate forms. Despite numerous reports on phenol oxidation kinetics, this behavior has, to the best of our knowledge, not been reported before for bimolecular reactions. Our data show that phenol oxidation in the present case follows a concerted PCET mechanism (CEP), which we suggest is far more common that generally believed.

Scheme 1. Structure of the Substituted Phenols in Their Carboxylate Forms



Results and Discussion

The different phenols were oxidized by laser flash−quench generated $[Ru(bpy)_3]^{3+}$ [13] (see Experimental Section for details). Each laser flash generated c.a. 5 μM $[Ru(bpy)_3]^{3+}$ that reacted with a large excess of phenol. The kinetics of the PCET from phenol to $[Ru(bpy)_3]^{3+}$ was followed by the transient absorption changes on a nanosecond−microsecond time scale. The hydrogen-bonded phenols **1a** and **2a**, and the corresponding reference compounds **1b** and **2b**, were examined, as well as the unsub-

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(8) In ref 7 we showed, for the intramolecular CEP reaction in the Ru−tyrosine complex, that the rate constant was insensitive to the concentration and identity of the buffer over the range examined (0−10 mM). Moreover, tyrosine deprotonation (pK_a = 10) by H_2O is too slow ($k \approx 10\ s^{-1}$) to explain the data and so is diffusion controlled deprotonation by OH^- ($k \approx 10^3\ s^{-1}$ at pH = 7). Finally, the rate of deprotonation by OH^- or base forms of the buffer would increase 10-fold for each pH unit, in contrast to the much weaker dependence observed.

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(10) As we noted in ref 6 the temperature-dependence of $\Delta G^{\circ\prime}$, which arises due to the reaction entropy involved with proton release to the bulk, was not considered in the evaluation of λ. This resulted in a larger (apparent) value, $\lambda = 2.0$ eV, as compared to the value later reported in ref 7, $\lambda = 1.4$ eV when the temperature-dependence of $\Delta G^{\circ\prime}$ had been estimated.

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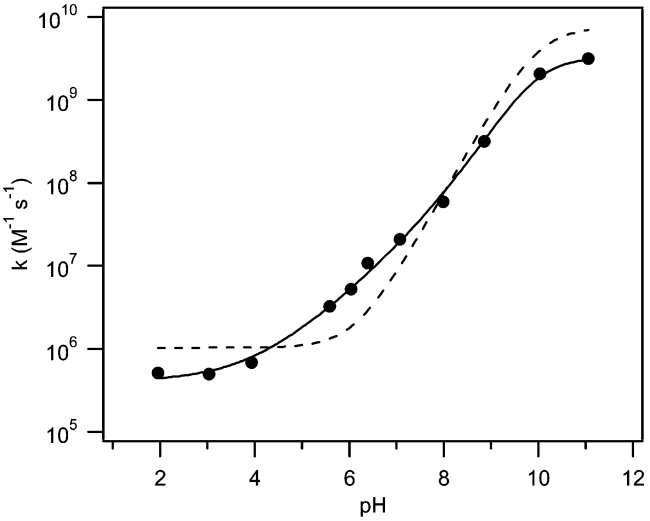

Figure 1. The pH-dependence of the rate constant for oxidation of the unsubstituted phenol. The dashed line is a fit to eq 2, while the solid line is a fit to eq 3.

stituted phenol (Scheme 1). As the latter has only one pH-titratable group and shows the least complicated behavior, we begin by discussing those results.

Oxidation of Phenol: Figure 1 shows the observed pH-dependence of the second-order rate constant for phenol oxidation by $[Ru(bpy)_3]^{3+}$. The pH-dependence of phenol oxidation rates, with chemical or electrochemical oxidation, is usually interpreted as a simple sum of two pH-independent rate constants: one for the phenol form (k_{phenol}) and a larger one for the phenolate form ($k_{phenolate}$), with relative contributions determined by the phenol acid−base titration:

$$k = \alpha\, k_{phenol} + (1 - \alpha)k_{phenolate} \qquad (2a)$$

$$\alpha = (1 + 10^{pH - pK_a})^{-1} \qquad (2b)$$

where the fraction of phenol and phenolate forms (α and $1 - \alpha$, respectively) is given by the Henderson−Hasselbalch equation. A fit of our data to this simple equation, with the phenol pK_a value fixed to 10.0 as independently determined, is shown as a dashed line in Figure 1. The fit to eq 2 is clearly not good, even though it was allowed to overestimate the rate constant for the phenolate form (the rate at pH $\gg$ 10).

Instead, we have to account for the intrinsic pH-dependence of the oxidation rate for the phenol form itself. For intramolecular oxidation of the phenol form in Ru(bpy)$_3$−tyrosine complexes, we found a pH-dependence following eq 1 (see above) which is a signature of a concerted PCET with proton release to the bulk. In the limited range of pH values (i.e., a limited range of $\Delta G^{\circ\prime}$ values) this pH-dependence can be described by an exponential term (see Experimental Section, eq 11): $k_{CEP} = k^{\circ}_{CEP}10^{\gamma pH}$, where the constant γ gives the steepness of the pH-dependence and is given by the fit as $\gamma = 0.5$. With this modification of eq 2 the fit to the data is much improved, but before showing that, we also need to account for the pH-dependence at very low pH, where the rate constant seems to reach a constant value of c.a. 4×10^5 M^{-1} s^{-1}. This can be explained by a switch to a stepwise mechanism in which electron transfer is followed by deprotonation (ETPT). We have recently shown that with a sufficiently strong oxidant and/or low enough pH, the ETPT mechanism may dominate over the concerted one.[14] The rate of ETPT is independent of pH, because the initial ET step is rate determining. The oxidation rate of the phenol form itself is given by a sum of the rates for the two mechanisms. Thus, we obtain the following expression for the observed oxidation of phenol:

$$k = \alpha(k_{ETPT} + k^{\circ}_{CEP}10^{\gamma pH}) + (1 - \alpha)k_{phenolate} \qquad (3)$$

where the fractions of phenol (α) and phenolate ($1 - \alpha$) are given by eq 2b. The fit of our data to eq 3, with α fixed according to p$K_a = 10.0$,[15] shows an excellent agreement (solid line in Figure 1). Thus, at very low pH values, oxidation proceeds predominantly via the ETPT from the phenol form, which generates the protonated phenoxy radical in an initial, rate-determining and pH-independent step. The rate is therefore almost constant at pH 2−4 in this particular case. At intermediate pH values, the pH-dependent CEP mechanism dominates instead. Finally, at even higher pH values the increasing fraction of the phenolate form becomes more important as this is an intrinsically more rapid electron donor. The observed pH-dependence is analogous to the one we reported previously on the covalently linked Ru(bpy)$_3$−tyrosine system, except that we of course do not observe biphasic kinetics around the pK_a value for the bimolecular reaction of Figure 1. This is because the rate of Ru^{III} reaction with a large excess of phenol is given by the sum of the contributions from the phenol and phenolate forms, while in the intramolecular reaction each Ru^{III} reacted with its linked partner that is in either the phenol or the phenolate form.

The pH-dependence of the oxidation rate for the phenol form is represented by the term $k^{\circ}_{CEP}10^{\gamma pH}$ in eq 3. This behavior has, to the best of our knowledge, not been reported before for bimolecular phenol oxidation, but is analogous to the behavior of our previously reported intramolecular tyrosine oxidation.[6,7] Frequently, this pH-dependence has been masked by the pH-dependence due to the increasing fraction of phenolate, and in a more limited range of pH values and with more data scatter, the difference between the behaviors of eqs 2 and 3 has not always been obvious.

We emphasize that the pH-dependence for the rate of phenol oxidation cannot be explained by an initial deprotonation to OH^- or base forms of the buffers, followed by electron transfer from the phenolate (PTET). First, the rate would have increased in proportion to the base concentration, i.e., by a factor of 10 per pH unit ($\gamma = 1.0$ in eq 3) in contrast to the much weaker dependence observed ($\gamma = 0.5$). Second, the experiments were repeated replacing the mixed phosphate/borate buffer with pure phosphate, borate, or MES buffer (MES = 2-[*N*-morpholine]-ethanesulfonic acid; p$K_a = 6.1$), in the range pH = 6.0−8.5 where the CEP reaction of the phenol form dominates the rate. The resulting rates showed no significant difference between the buffers. Most importantly, the rate showed the same monotonic increase with pH as in Figure 1 also above the pK_a of the relevant buffer species (6.1 for MES, 7.2 for $H_2PO_4^-$), although the concentration of the base form of the buffer is then constant. Third, PTET via OH^- or PO_4^{3-} would give diffusion-

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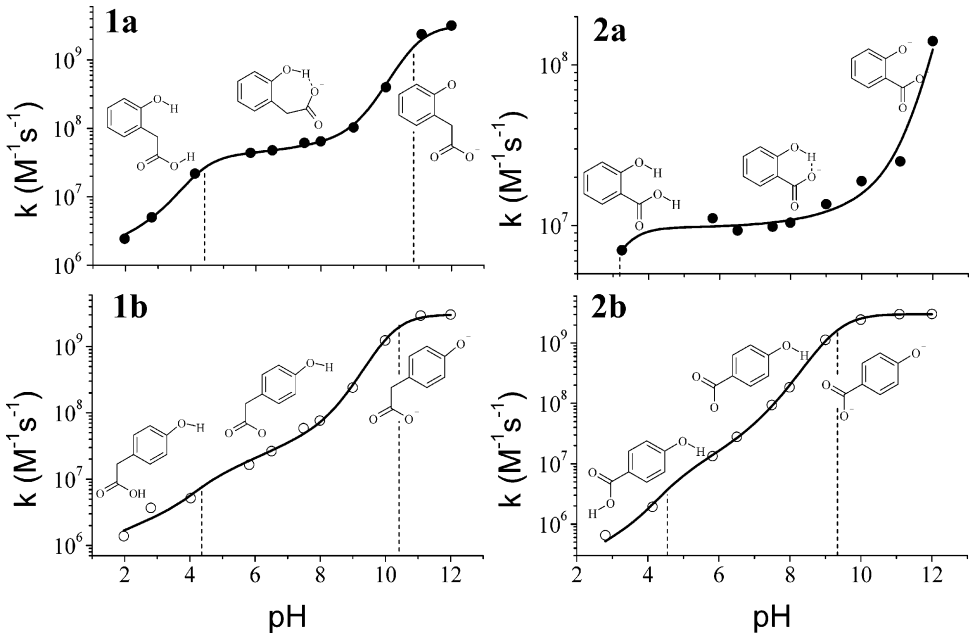

Figure 2. The pH-dependence of the rate constant for oxidation of the substituted phenols **1a**, **1b**, **2a**, and **2b**. The solid lines are fits to eq 3′ (lower panels) or 4 (upper panels). The dashed vertical lines indicate the pK_a values for the carboxylic and phenolic groups (the phenolic pK_a for **2a** is out of range).

Table 1. Thermodynamic and Kinetic Data for the Phenols Studied

compound	**1a**	**1b**	**2a**	**2b**	phenol
p$K_{aPhenOH}$	10.9[a]	10.3[a]	13.5[b]	9.3[b]	10.0[b]
pK_{aCOOH}	4.3[a]	4.3[a]	3.1[b]	4.5[b]	–
$E°_{PhenO•/PhenO^-}$[c] (V)	0.71	0.75	0.77	0.90	0.78
$E°_{PhenOH•^+/PhenOH}$[d] (V)	1.42	1.46	1.48	1.61	1.49
$k_{phenolate}$[e] (M^{-1} s^{-1})	3.6×10^9	3.2×10^9	3.0×10^9	3.0×10^9	3.5×10^9
k_{HB}[e] (M^{-1} s^{-1})	4.8×10^7	–	9.3×10^6	–	–

[a] Determined by pH titration. [b] From ref 15. [c] Determined by pulse radiolysis (see Experimental Section). [d] Calculated from the $E°_{PhenO•/PhenO^-}$ value and eq 8 (Experimental Section). [e] Rate constants from oxidation by $[Ru(bpy)_3]^{3+}$; see text.

limited pseudo-first-order rate constants below 1×10^4 s^{-1} at pH = 7, which is by far too slow to explain the observed values.

Oxidation of Substituted Phenols: The corresponding kinetic data for oxidation of the carboxylic-acid-substituted phenols by $[Ru(bpy)_3]^{3+}$ are shown in Figure 2, and the $E°$ and pK_a values are given in Table 1. Starting with data for the phenols without hydrogen bonds, **1b** and **2b**, these show a behavior much like that of the unsubstituted phenol, with a pH-dependent rate over the entire pH interval below the phenolic pK_a. The solid lines are fits to eq 3, which is a modification of eq 3 due to the titration of the carboxylic acid group. Deprotonation of this group makes the phenol negatively charged and gives a small increase in bimolecular oxidation rate with the positively charged $[Ru(bpy)_3]^{3+}$. Thus, the term $k°_{CEP}10^{\gamma pH}$ was replaced by $(f_{(a)}k°_{CEP(a)} + f_{(b)}k°_{CEP(b)})10^{\gamma pH}$, where $f_{(a)}$ and $f_{(b)}$ are the pH-dependent fractions of carboxylic acid and carboxylate forms, respectively.

$$k = \alpha\,(k_{ETPT} + (f_{(a)}k°_{CEP(a)} + f_{(b)}k°_{CEP(b)})10^{\gamma pH}) + (1 - \alpha)k_{phenolate} \quad (3')$$

The effect is hardly noticeable in Figure 2 because the difference between $k°_{CEP(a)}$ and $k°_{CEP(b)}$ is small. However, together with the somewhat different energetics due to changes in $E°$ and pK_a values for the substituted phenols (see Table 1), the titration of the carboxylic acid makes the contribution of the pH-independent ETPT mechanism at the lowest pH values unimportant in the experimental range examined (Figure 2). Otherwise, the pH-dependence for **1b** and **2b** is very similar to that for the unsubstituted phenol above.

The pH-dependence for the hydrogen-bonded phenols **1a** and **2a** instead is markedly different. In the region between the pK_a values of the carboxylic acid and the phenolic group a hydrogen bond can be formed between these groups. For salicylate (**2a**) this is known to result in a strong hydrogen bond.[16] In a pH interval above the carboxylic pK_a value, the rate constant for oxidation of the phenol was essentially independent of pH. This can be attributed to the effect of the hydrogen bond on the CEP reaction (see below). At even higher pH, the reaction of $[Ru(bpy)_3]^{3+}$ with the phenolate form becomes dominating, as was the case for the other phenols. The solid lines show fits to the data according to eq 4, which is a modification of eq 3 that includes one term (α $f_{HB}k_{HB}$) for the hydrogen-bonded phenol (the ETPT term could be neglected):

$$k = \alpha(f_{(a)}k°_{CEP}10^{\gamma pH} + f_{HB}k_{HB}) + (1 - \alpha)k_{phenolate} \quad (4)$$

The pH-dependent fractions of hydrogen-bonded (f_{HB}) and non-hydrogen-bonded ($f_{(a)}$) phenol are determined by the titration of the carboxylic acid group and were fixed in the fit according to the pK_a values (Table 1). A small fraction of non-hydrogen-bonded phenols remained also at higher pH due to limited

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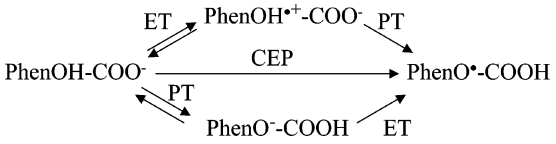
Scheme 2. Possible Mechanisms of PCET for **1a** and **2a**



thermodynamic stability of the hydrogen bond. This fraction amounted to only 0.2 for **1a** and 0.1 for **2a** and gave a weak pH-dependence also in this region ($f_{(a)} = 0.2$ and 0.1, respectively, also at a pH above the carboxylic acid pK_a; the small difference between $k°_{CEP(a)}$ and $k°_{CEP(b)}$, as in eq 3′, for this fraction was neglected). The pH-dependence for the non-hydrogen-bonded phenols, i.e., the value of γ, was fixed to the same value for **1b** and **2b**. The fractions α and $1 - \alpha$ are phenol and phenolate forms, as before.

Oxidation Mechanism of the Hydrogen Bonded Phenols. The fits of the data in Figure 2 (upper panel) to eq 4 are good, with four variable parameters: the three rate constants and the fraction $f_{(a)}$ remaining non-hydrogen bonding at pH > pK_{aCOOH}. It is obvious to the eye, in particular for **2a**, that the hydrogen-bonded phenols give (near) pH-independent rates in the region of intermediate pH values, where the hydrogen-bonded phenol species dominate the observed kinetics. As the main aim of the present paper is to investigate the effect of hydrogen bonds on the kinetics of PCET from phenols, we will continue by discussing the reason for the pH-independence of the hydrogen-bonded phenols in this pH-region, where the non-hydrogen-bonded phenols instead show a strong pH-dependence.

Three mechanisms were considered to explain the pH-independence of the hydrogen-bonded phenols (Scheme 2): (1) deprotonation to give the phenolate form, followed by electron transfer (PTET); (2) electron transfer generating the protonated phenoxy radical, followed by deprotonation (ETPT); or (3) a concerted reaction (CEP). As we show in the following paragraphs, however, the stepwise mechanisms can be excluded.

(1) In a PTET mechanism with a rapid proton pre-equlibrium the observed rate constant is given by the ET rate constant times the fraction of phenolate, and the latter is given by the difference in pK_a values of the phenol and the carboxylic acid: $k = k_{ET}10^{-\Delta pK_a}$. As the p$K_a$ values of the carboxylic groups are much lower than those for the phenols, this fraction is only 3×10^{-7} and 3×10^{-11} for **1a** and **2a**, respectively. To account for the observed rate constants, k_{ET} would have to be at least 4 orders of magnitude larger than a diffusion controlled rate constant.

In the other limit of PTET, the initial deprotonation is instead the slower rate-determining step. The deprotonation rate constant cannot be faster than approximately $k_{PT} = 6 \times 10^{12}\ 10^{\Delta pK_a}\ s^{-1}$, where the frequency factor $6 \times 10^{12}\ s^{-1}$ is given by absolute rate theory and the factor $10^{\Delta pK_a}$ gives the correct ratio of forward and reverse PT. This would give $k_{PT} \approx 2 \times 10^6$ and $2 \times 10^2\ s^{-1}$ for **1a** and **2a**, respectively, which is too slow to allow for the observed oxidation rates. These estimates show that a PTET mechanism is not consistent with the data.

(2) In an ETPT mechanism the initial, endergonic ET step to form PhenOH$^{•+}$ will be rate determining, because the subsequent deprotonation of this species (p$K_a \approx -2$[4b]) is very rapid. The relative rates for the phenols studied should then correlate with the PhenOH$^{•+}$/PhenOH potentials. A comparison with the ETPT rate constants for the non-hydrogen-bonded phenols would then reveal if such a correlation exists. Due to the low pK_a value for PhenOH$^{•+}$, the PhenOH$^{•+}$/PhenOH potentials are difficult to measure. Instead these were calculated from the PhenO$^{•}$/PhenO^{-} potentials under the reasonable assumption that the difference in potentials for the protonated and unprotonated redox couples is very similar for this series of phenols (see Experimental Section). In Figure 3, we plot the pH-independent rate constants around pH = 6 for **1a** and **2a** (solid symbols), the mechanism of which we are discussing. For **1b**, **2b**, and the unsubstituted phenol, we plot the observed rate constants at pH = 2 (solid symbols), which is due to ETPT for the unsubstituted phenol while it is an upper limit of ETPT for **1b** and **2b** that do not reach the ETPT region in the examined pH range. It is clear from Figure 3 that the plotted rate constants do not correlate with the PhenOH$^{•+}$/PhenOH potentials. This strongly suggests that the phenol oxidation in **1a** and **2a** does not follow an ETPT mechanism.

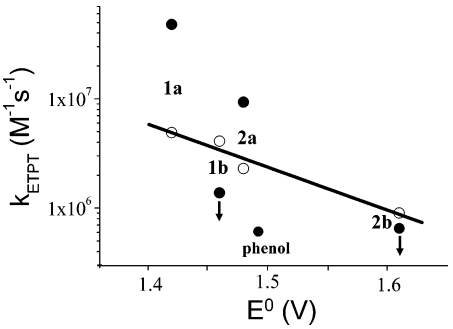


Figure 3. (○) Observed rate constant for phenol oxidation with $Br_2^{•-}$ as oxidant vs phenol potential ($E°_{PhenOH^{•+}/PhenOH}$). (●) Limiting rate constants for ETPT for phenols **1b** and **2b** and observed rate constants for the hydrogen-bonded phenols **1a** and **2a**, with $Ru^{III}(bpy)_3$ as oxidant, vs phenol potential (see text).

We also tested the predicted rate vs potential correlation for ETPT in pulse-radiolysis experiments. As we have previously shown and explained,[14] the use of a stronger oxidant favors ETPT over CEP. $Br_2^{•-}$ is a stronger oxidant than $[Ru(bpy)_3]^{3+}$ by about 0.35 V ($E°(Br_2^{•-}/2Br^-) = 1.6$ V, $E°([Ru(bpy)_3]^{3+/2+}) = 1.26$ V, vs NHE). With the $Br_2^{•-}$ oxidant, the rate of oxidation of the phenol form was pH-independent for all the phenols in the range examined (pH = 5−8), as expected for an ETPT mechanism. Moreover, the relative rates of phenol oxidation for the five compounds correlated well with the PhenOH$^{•+}$/PhenOH potential (Figure 3, open circles). These results are consistent with an ETPT mechanism for all compounds with the $Br_2^{•-}$ oxidant, and they suggest that the hydrogen bonds do not significantly affect the ETPT rate. This is in contrast to the results with the $[Ru(bpy)_3]^{3+}$ oxidant, where the effect of hydrogen bonds is strong and the rate does not correlate with the PhenOH$^{•+}$/PhenOH potential. Note that comparisons should be made only within each series with the same oxidant, because of different intrinsic reactivities of $Br_2^{•-}$ and $[Ru(bpy)_3]^{3+}$. The large qualitative difference observed between the series therefore strongly suggests that the pH-independence observed for oxidation of **1a** and **2a** by $[Ru(bpy)_3]^{3+}$ is not due to an ETPT mechanism.

(3) The stepwise mechanisms are inconsistent with our data, and we have to conclude that ET from the phenol form is concerted with proton transfer (CEP) also in **1a** and **2a**, but with an initial proton transfer to the base instead of directly to water. Thus, the CEP driving force depends on the pK_a of the base (see Experimental Section) and not on pH as in **1b** and **2b**

where the proton is directly transferred to bulk water in a concerted reaction. The presence of an intramolecular base as proton acceptor makes the driving force pH-independent and is thus the reason for the pH-independence of the rate observed in **1a** and **2a**. The proton is presumably released to the bulk in a secondary reaction step, as the pH is above the pK_a of the protonated base, but without affecting the rate limiting, initial CEP reaction.[17]

Having established that the PCET from the phenols to $[Ru(bpy)_3]^{3+}$ follows a CEP mechanism, we also investigated the kinetic isotope effect of exchanging the phenolic proton for a deuteron. For solutions prepared in H_2O and D_2O at pH or pD = 6, the following rate constant ratios were obtained: $k_H/k_D = 2.1$ for **1b** and **2b**, but $k_H/k_D = 1.6$ and 1.2 for **1a** and **2a**, respectively. Thus the effect is small, but there is still a significant difference between the phenols with and without internal hydrogen bonds.

Effect of the Hydrogen Bond on the CEP Rate: The presence of an internal hydrogen bond not only makes the rate pH-independent but also increases the rate, as compared to the case of a non-hydrogen-bonded phenol with the same driving force. The CEP driving force at pH = 7 is much higher for the compounds without hydrogen bonds, because proton release at pH = 7 is energetically more favorable than proton transfer to a base with pK_a = 3−4. Thus, $\Delta G^{\circ\prime} = -0.31$ eV for **1b** and −0.22 eV for **2b**, while it is −0.16 eV for **1a** and +0.13 eV for **2a**. The somewhat endergonic CEP reaction in **2a** is driven by the subsequent, rapid deprotonation of the carboxylic acid (see Experimental Section). Despite the much lower driving force, the oxidation rates of the phenol form at pH = 7 are very similar for all compounds: $(1-6) \times 10^7$ M^{-1} s^{-1} with **1a** giving the highest value. If all other parameters except $\Delta G^{\circ\prime}$ would be the same, eq 1 predicts instead that the rate constant, e.g., for **2a**, would be 3 orders of magnitude higher than that for **2b**.[18] This estimate clearly shows that some other parameter changes to promote CEP in the hydrogen-bonded complexes, which compensates for the lower driving force. In our analysis of temperature-dependent data for $Ru(bpy)_3$−tyrosine complexes, we have shown that the pre-exponential factor of eq 1 is not significantly different for a CEP, a pure ET from a phenol,[14] and for an ET from the phenolate,[6] making significant effects of a hydrogen bond on the pre-exponential factor of eq 1 unlikely. Neither are the diffusion constants of the present bimolecular reactions expected to be sensitive to the hydrogen bonds. This leaves two alternatives to explain the increase in rate at a given driving force: either a lower reorganization energy (λ) or an increase in the proton vibrational wave function overlap between the reactant and donor states. The latter factor may be temperature-dependent but appears explicitly in the pre-exponential factor in the rate expression in some treatments of CEP reactions (corresponding to eq 1).[5d−g] An increase in vibrational wavefuntion overlap is expected if the hydrogen bond results in a shorter proton transfer distance than when water is the proton acceptor. The effect of this can be diminished by fluctuations in the proton transfer distance, which can strongly enhance the effective overlap.[19] For the reorganization energy instead, we have argued, from an analysis of experimental data, that the reorganization energy for a CEP reaction of phenols is higher than that for a pure ET reaction in an aqueous solution.[6,7,14] Our conclusions were based on the temperature-dependence of the rate, and also on the fact that the CEP rate was less dependent on the strength of the oxidant than was the ETPT. The steeper driving-force-dependence for ETPT is expected for a reaction with lower reorganization energy (in the Marcus normal region, $-\Delta G^\circ < \lambda$). This effect allowed us to switch reaction mechanisms by altering the oxidant, as was also done in the present study. It has not been shown that this effect can be explained without assuming a larger reorganization energy for CEP. Moreover, a bidirectional CEP reaction, in which the electron and proton are transferred in different directions, has a greater solvent reorganization energy due to the larger separation of charges (as accounted for in ref 5d−g). However, the inner reorganization energy of the phenol group is also significant and can be estimated to several tenths of an eV[14] (0.35 eV in a recent calculation),[12e] which is similar to the difference in reorganization energy we reported between oxidation of the tyrosine in a CEP reaction (λ = 1.4 eV)[7,10] and that of tyrosinate (pure ET, λ = 0.9 eV).[6,7] From these results and discussion it is clear that the additional reorganization energy for a CEP reaction gives significant effects and cannot be neglected.

To estimate how much the reorganization energy may possibly be reduced by the hydrogen bonds, we will first assume that the pre-exponential factor (eq 1) is the same within this series of compounds (i.e., neglecting possible variations in vibrational overlap factors). Then we assume that λ = 1.4 eV in **1b** and **2b**, as for the intramolecular reaction in the Ru−tyrosine complex.[7] For **1a** and **2a** the reorganization energies then have to be smaller, because the driving force is also smaller, to obtain the observed rate constants. From eq 1 we obtain λ = 1.2 and 0.9 eV for **1a** and **2a**, respectively. The values follow the same trend as that of the hydrogen bond strengths. Although these values are approximate, they would suggest that the reorganization energy may be reduced in the hydrogen-bonded system to values between those for CEP with deprotonation to bulk water and for pure ET from the phenolate form. A possible explanation for a smaller CEP reorganization energy in the hydrogen-bonded system is a smaller proton transfer distance, which may reduce both the internal and the solvent reorganization energy. Nevertheless, further experimental and theoretical work is needed to clearly establish the importance of variations in reorganization energy and proton vibrational overlap, respectively, in systems exhibiting CEP reactions. Although the trend of the kinetic isotope effects at pH = 6 (see above) follows the hydrogen bond strengths, the isotope effects are small and cannot conclusively distinguish which parameters are responsible for the much larger effects on the rate induced by the internal hydrogen bonds.

Note that Mayer and co-workers recently studied the bimolecular oxidation kinetics for phenols with an internal hydrogen bond in acetonitrile.[12d,e] By varying the driving force, using different oxidants and a fit to eq 1, they obtained a reorganization energy of 1.4 eV[12d] and even higher values[12e] for CEP that is significantly larger than expected for a pure ET reaction, in

(17) As a control, in response to a reviewers' request, we compared the reaction rates of the hydrogen-bonded systems **1a** and **2a** at pH = 7 in both 10 and 100 mM buffer and observed no significant difference.

(18) From eq 1, $(\partial \ln \Delta k_{ET}/\partial \Delta G^\circ) = (1/2RT)[1 + (\Delta G^\circ/\lambda)] \approx 1/2RT$ around $\Delta G^\circ = 0$. The difference in ΔG° of 0.35 eV would then give a predicted rate difference of a factor of 1×10^3.

(19) Compare with the proton transfer theory of Hynes and co-workers in: (a) Kiefer, P. M.; Hynes, J. T. *Solid State Ionics* **2004**, *168*, 219−224 and references therein.

line with our previous results for the intramolecular Ru−tyrosine reaction. They did not directly compare with results for phenols lacking internal hydrogen bonds, however. Linschitz and coworkers[12a,c] on the other hand reported in a series of papers the bimolecular CEP kinetics of phenols in nonaqueous media, in the presence and absence of hydrogen bonding bases (pyridines, etc.). They observed an increase in rate for the hydrogen-bonded phenols but concluded that this was entirely caused by the increase in driving force due to the presence of the proton-accepting base in the nonaqueous solution. By comparing with results for more easily oxidized, non-hydrogen-bonded hydroquinones they reported that there was no effect on the rate by the hydrogen bond itself, except that of the driving force. Our present results, in an aqueous solution, are different and show new aspects of the effect of hydrogen bonds on CEP reactions.

In conclusion we have shown that hydrogen bonds can promote PCET through the concerted electron transfer−deprotonation (CEP) mechanism, resulting in much higher rates than those for the corresponding reaction with the same driving force but in the absence of an internal hydrogen bond. We suggest that the effect of the internal hydrogen bond is at least partly due to a decrease of the reorganization energy associated with the proton reaction coordinate. The hydrogen-bonded CEP reaction may thus allow for a low energy barrier path that can operate efficiently at low driving forces, even for endergonic reactions as in the case of **2a**, which is ideal for PCET reactions in biological systems. This is illustrated by the data of Figure 3, where the stronger oxidant $Br_2^{\bullet-}$ oxidizes the phenols in a stepwise ETPT mechanism, with a rate that correlates with the phenol ($PhenOH^{\bullet+}$/PhenOH) potential, while with the weaker oxidant $Ru(bpy)_3^{3+}$ oxidizes the same phenols via a CEP mechanism that utilizes all the available free energy in a single reaction step.[14]

Experimental Section

Laser Flash Photolysis with Transient Absorption Detection. The solution was buffered with 0.1 M Na_2HPO_4 (SigmaUltra 99%) and 0.1 M H_3BO_3 (SigmaUltra 99.5%), and the pH was adjusted with concentrated NaOH (Elektrokemiska Aktiebolaget, Pro Analysis) or HCl (P-H TAMM). 2-Hydroxy-benzoic acid (Aldrich), 4-hydroxy-benzoic acid (Aldrich), 2-hydroxy-phenyl-acetic acid (Aldrich), or 4-hydroxy-phenyl-acetic acid (Lancaster) was dissolved in the buffer solution to a concentration of 0.1 to 20 mM, and the pH was measured. $[Ru(bpy)_3]Cl_2$ (Molecular probes, Inc.) and methyl viologen (Sigma, highest grade commercially available) were added to the analyte solution to a concentration of 40−60 μM and 50 mM, respectively.

The bimolecular electron transfer from the phenol to $[Ru(bpy)_3]^{3+}$ was investigated using a flash−quench method[13b] described earlier.[13a] $[Ru(bpy)_3]^{2+}$ was excited with a <10 ns 460 nm laser pulse, and the excited state was oxidatively quenched by the methyl viologen MV^{2+} giving $[Ru(bpy)_3]^{3+}$ and $MV^{\bullet+}$. The concomitant bimolecular electron transfer from the phenol to $[Ru(bpy)_3]^{3+}$ was followed by the recovery of the $[Ru(bpy)_3]^{2+}$ signal at 450 nm. Recombination between $MV^{\bullet+}$ and $[Ru(bpy)_3]^{3+}$ or the oxidized phenol was controlled by monitoring the disappearance of the $MV^{\bullet+}$ absorption at 600 nm. The analyzing light was produced by a pulsed xenon lamp, and after passing the sample the light was detected as a function of time with a Hamamatsu R928 photomultiplier. Electron transfer from the phenol was kept rapid, by the use of a high phenol concentration, compared to the recombination reaction with $MV^{\bullet+}$, making $MV^{\bullet+}$ recombination insignificant for the recovery of $[Ru(bpy)_3]^{2+}$. The pseudo-first-order rate constant for the electron transfer between $[Ru(bpy)_3]^{3+}$ and phenol was determined by fitting the 450 nm transients to a single-exponential function, and the second-order rate constant was extracted from the pseudo-first-order rate constant by division of the phenol concentration. In all measurements the temperature was kept at 298 K using a Hetrofrig thermostat.

Pulse Radiolysis. The pulse radiolysis equipment consists of a linear accelerator delivering 3 MeV electrons and a computerized optical detection system. For dosimetry air-saturated 10^{-2} M KSCN solutions were employed. The $G\epsilon$ value of the $(SCN)_2^{\bullet-}$ radical was taken to be 2.2×10^{-4} m^2/J at 500 nm. All experiments were performed in N_2O-saturated aqueous solutions where the primary radiation chemical yield of $OH^{\bullet}$ radicals, G_{OH}, was set to 5.6×10^{-7} mol/J. Equilibrium measurements were run in 1 M NaOH, to keep the phenols in their fully deprotonated form, according to the procedure in ref 1 with 4-I-phenolate as the redox partner for the phenolates. The primary oxidation of the phenolates was achieved by $N_3^{\bullet}$ produced in the reaction of $OH^{\bullet}$ radicals with N_3^-, the latter being added (NaN_3 (Merck)) in sufficient excess to scavenge at least 99% of the $OH^{\bullet}$ radicals. Kinetic measurements were performed in buffered water solution (0.1 M phosphate buffer) at various phenol concentrations in the pH range 5.5−6.6 and with Br_2^-, produced in the reaction of $OH^{\bullet}$ radicals with $2Br^-$, as the oxidant. The reaction was followed by light absorption measurements using a halogen lamp as the light source. Pulses employed were 5×10^{-9} s long, generating total radical concentrations on the order of 5×10^{-6} M. The different phenols, KSCN, KBr, and NaOH (Aldrich, semiconductor grade) were employed without purification. Deionized water was further purified in a Millipore setup.

This choice of 4-I-phenolate as the redox partner in the equilibrium determinations was contingent on the strong absorption of the 4-I-$PhO^{\bullet}$ radical at 510 nm. At this wavelength the phenoxyl radicals studied in this work are transparent. The reduction potential for the phenolates could be determined from the measured equilibrium constant and the 4-I-$PhO^{\bullet}$ reduction potential, E° (4-I-$PhO^{\bullet}$/4-I-PhO^-) = 0.82 V[2] vs NHE, using eq 5 (Table 1).

$$E^{\circ\prime}(\mathrm{PhenO}^{\bullet}/\mathrm{PhenO}^-) = E^{\circ\prime}(\text{4-I-PhO}^{\bullet}/\text{4-I-PhO}^-) - RT\ln(K)/zF \quad (5)$$

Energetics for Proton Coupled Electron Transfer Reactions. The driving force for the electron transfer reactions ($-\Delta G^{\circ}$) can be determined from eq 6, assuming that the coloumbic interaction between the involved species is insignificant.

$$-\Delta G^{\circ} = zF(E^{\circ}_{\mathrm{red}} - E^{\circ}_{\mathrm{ox}}) \quad (6)$$

E°_{red} and E°_{ox} are the reduction potentials for the species being reduced and oxidized in the reaction, i.e., the $[Ru(bpy)_3]^{3+}$ and the phenol, respectively. The potential for the $[Ru(bpy)_3]^{3+/2+}$ couple in an aqueous solution is 1.26 V[14] vs NHE, independent of pH. Phenol oxidation on the other hand is coupled to deprotonation in the wide pH range between the pK_a for the oxidized phenol ($PhenOH^{\bullet+}$) and the pK_a of the reduced form (PhenOH); see Table 1. Thus the phenol reduction potential decreases with pH according to eq 7 (primed symbols $E^{\circ\prime}$ and $\Delta G^{\circ\prime}$ denote standard states but with the proton activity at the given pH).

$$E^{\circ\prime}_{\mathrm{PhenO}^{\bullet}/\mathrm{PhenOH}} = E^{\circ}_{\mathrm{PhenO}^{\bullet}/\mathrm{PhenO}^-} - RT\ln 10/zF \times (\mathrm{pH} - \mathrm{p}K_{a_{\mathrm{PhenOH}}}) \quad (7)$$

This pH-dependent potential is only relevant for a concerted electron transfer−deprotonation (CEP) reaction with proton release to bulk water. For an ETPT mechanism instead the phenol potential for the pure electron transfer step that is to be used in eq 6 is that for the $PhenOH^{\bullet+}$/PhenOH couple. As the phenoxy radical is only protonated at pH < −2, we could not determine these potentials or the values of p$K_{a\mathrm{PhenOH}^{\bullet+}}$. Instead we have to rely on the assumption that the difference in pK_a for the oxidized and reduced forms is equal and, thus, that the difference $E^{\circ\prime}_{\mathrm{PhenOH}^{\bullet+}/\mathrm{PhenOH}} - E^{\circ\prime}_{\mathrm{PhenO}^{\bullet}/\mathrm{PhenO}^-}$ is equal to that for the unsubstituted phenol. The latter shows a pK_a shift from 10.0[15] to −2[4b]

when oxidized, i.e., 12 units. In that case the potential for the oxidized phenol can be calculated from eq 8.

$$E^\circ_{\mathrm{PhenOH^{\bullet+}/PhenOH}} = E^\circ_{\mathrm{PhenO^\bullet/PhenO^-}} + 12 \times RT \ln 10/zF \quad (8)$$

In a hydrogen-bonded system the situation is slightly different. For the ETPT mechanism, where no proton is involved in the electron transfer step, the energetics is not expected to be significantly altered by the hydrogen bond. This is confirmed by the pulse-radiolysis results of Figure 3, which shows a good correlation including phenols both with and without internal hydrogen bonds. For the CEP mechanism on the other hand a hydrogen bond alters the energetics markedly. The proton is no longer released to the bulk in the CEP step but instead to the carboxylate base. Thus the free energy gain upon release of the proton from $\mathrm{TyrOH^{\bullet+}}$ is given by the difference in pK_a of the oxidized phenol and the base (B^-), and the phenol potential can be estimated by eq 9 (Table 1).

$$E^\circ_{\mathrm{PhenO^\bullet-HB/PhenOH-B^-}} = E^\circ_{\mathrm{PhenO^\bullet/PhenO^-}} - RT \ln 10/zF \times (\mathrm{p}K_{a_{\mathrm{HB}}} - \mathrm{p}K_{a_{\mathrm{PhenOH}}}) \quad (9)$$

For **2a** the initial CEP reaction is somewhat endergonic and is followed by the exergonic proton release from the carboxylic acid (eq 10).

$$\mathrm{Ru^{III}} + \mathrm{PhenOH-{}^-OOC} \underset{k_{-\mathrm{CEP}}}{\overset{k_{\mathrm{CEP}}}{\rightleftharpoons}} \mathrm{Ru^{II}} + \mathrm{PhenO^\bullet - HOOC} \xrightarrow{k_d} \mathrm{Ru^{II}} + \mathrm{PhenO^\bullet\ {}^-OOC} + \mathrm{H^+} \quad (10)$$

With a steady-state treatment of the intermediate, the observed rate constant is $k_{\mathrm{obs}} = k_{\mathrm{CEP}}\, k_d/(k_{-\mathrm{CEP}} + k_d)$. Deprotonation to H_2O with a pK_a value of 3.1 gives a rate constant of $k_d \approx 10^8\ \mathrm{s^{-1}}$, independent of pH.[20] In the limit where $k_{-\mathrm{CEP}} \ll k_d$, then $k_{\mathrm{CEP}} = k_{\mathrm{obs}} = 1 \times 10^6\ \mathrm{s^{-1}}$ as reported. Because $k_{\mathrm{CEP}}/k_{-\mathrm{CEP}} = \exp(-\Delta G^\circ/RT) \approx 0.01$, $k_{-\mathrm{CEP}}$ may be similar to k_d, which then implies that k_{CEP} is in fact somewhat larger that the observed k_{obs} for **2a**. This would enhance the reported effect of the hydrogen bond somewhat but does not affect the present, semiquantitative discussion.

Derivation of the Linear pH-Dependence of the Logarithm of the CEP Rate Constant. For small differences in ΔG° a Taylor expansion of eq 1 (the semiclassical Marcus equation in the high-temperature limit) around ΔG°_a with respect to ΔG° gives a linear dependence of ln k_{ET} on ΔG°:

$$\ln k_{\mathrm{ET}} = \ln \frac{2\pi {H_{\mathrm{rp}}}^2}{\hbar\sqrt{4\pi\lambda k_B T}} - \frac{(\Delta G_a^\circ + \lambda)^2}{4\lambda k_B T} + \frac{(\Delta G_a^\circ + \lambda)}{2\lambda k_B T}(\Delta G_a^\circ - \Delta G^\circ) \quad (11)$$

And since $\mathrm{d}\Delta G^{\circ\prime}_{\mathrm{CEP}}/\mathrm{dpH} = -0.059$ meV/pH we expect a linear dependence of ln k_{ET} on pH with a slope $\gamma = 0.059(\Delta G^{\circ\prime}_a + \lambda)/(2k_B T\lambda)$ for the CEP reaction with proton release to bulk.

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