Concerted Proton–Electron Transfer

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Concerted Proton–Electron Transfer in Pyridylphenols: The Importance of the Hydrogen Bond**

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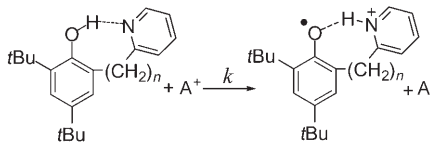
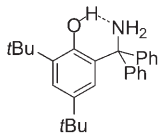
Proton-coupled electron transfer (PCET) reactions are of much current interest because of their role in many chemical and biological processes.[1] The oxidation of tyrosine residues to tyrosyl radicals, for example, is important in the function of a number of proteins.[2] The Kok S-state cycle of photosystem II involves oxidations of tyrosine-Z through long-range electron transfer to P_{680}^{+} whereby the phenolic proton is likely transferred to a hydrogen-bonded imidazole (H_{190}) in a single kinetic step,[3] called separated CPET (concerted proton–electron transfer).[4] This conclusion has been generally supported by studies of phenol model systems in which electron transfer (ET) is coupled to proton transfer (PT) to a different species.[4–9] Concerted transfer of e^- and H^+ is often preferred because ΔG°_{CPET} is more favorable than ΔG°_{ET} for initial electron transfer.[4–9] When the driving forces are equal, however, separated-CPET reactions typically occur with lower rate constants than related ET reactions. The origin of the slower rates has been discussed in theoretical treatments[1,10] and the importance of hydrogen bonding has been noted by Hammarström and co-workers.[6b] Herein, we report that the nature of the hydrogen bond has a large influence on the facility of CPET.

We recently described chemical and electrochemical oxidations of phenol base compounds HOAr-B (B = base) that proceed by intermolecular ET concerted with intramolecular PT to the hydrogen-bonded base (Scheme 1).[9] CPET reactions of pyridylphenol **1** are around 10^2 times faster than those of amine analogue **2** with the same type of oxidant and for the same value of ΔG°_{CPET}.[9] This result was unexpected because free pyridine is a weaker base than a primary amine ($pK_{BH^+} = 12$ and 18, respectively, in MeCN).[11] The difference between **1** and **2** is unlikely to be due to different outer-sphere (solvent) reorganization because these molecules are of comparable size and should have similar changes in solvation upon CPET. The average crystallographic proton donor–acceptor distance d(O···N) is slightly shorter in **1** than in **2** (by 0.01 Å).[9] However, this distance does not appear to be the dominant factor as a phenol–



1, $n = 0$; **3**, $n = 1$



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Scheme 1. Pyridylphenols and their one-electron oxidation. A^+ = oxidant.

imidazole analogue of **1** has a much longer d(O···N) than **2** (by 0.06 Å) yet is oxidized substantially faster.[9] The key feature seems to be that the faster phenol–pyridine and phenol–imidazole compounds contain resonance-assisted hydrogen bonds (RAHBs) owing to conjugation between the proton donor and acceptor. This conjugation leads to stronger hydrogen bonds and influences the NMR and IR spectra (see below).[9,12]

To test the apparent correlation between RAHBs and increased CPET rates, the nonconjugated phenol–pyridine 4,6-di-*tert*-butyl-2-(2′-pyridinylmethyl)phenol (**3**) was prepared. 2-Pyridylmagnesium chloride (2-pyMgCl) was added to benzyl ether protected 3,5-di-*tert*-butylsalicylaldehyde, followed by acylation of the resulting alcohol and catalytic hydrogenation. Compound **3** has been fully characterized, including by X-ray crystallography.[13] The presence of the inserted CH_2 group causes the pyridine ring to twist out of the plane of the phenol ring and makes the hydrogen bond longer and more linear than that in **1** [$d_{O\cdots N} = 2.6914(13)$ vs. 2.567(3) Å, $\sphericalangle$(OHN) = 167.7(15)° vs. 154(2)°].[9] The chemical shift of the phenolic proton in nonconjugated **3** is 3.7 ppm upfield of that in **1** ($\delta_{OH} = 11.15$ vs. 14.83 ppm in CD_3CN). IR spectra show that the ν_{OH} peaks of **3** (3094, 2772 cm^{-1} in MeCN) are blue-shifted relative to that of **1** (2650 cm^{-1}, $\nu_{OD} =$ 2000 cm^{-1}, Figure 1). The low-field ^1H NMR resonance and low-frequency ν_{OH} peak for **1** are characteristic of shorter, stronger RAHB systems.[12]

Cyclic voltammograms of **3** are chemically reversible and give a value of $E_{1/2} = 0.44$ V vs. $[Cp_2Fe]^{0/+}$ in MeCN (Cp = cyclopentadienyl). The peak separation ΔE_p is large relative to that of **1** (220 mV vs. 100 mV at $\nu = 0.2$ V s^{-1}), which suggests slower electrochemical kinetics.[9,13,14] Slow ET is also evident in the kinetics of **3** with a number of one-electron

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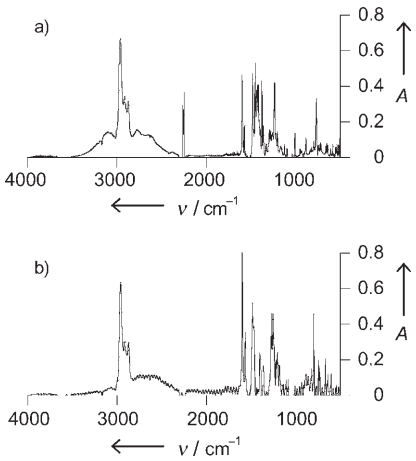


Figure 1. IR spectra of solutions of a) **3** and b) **1** in MeCN. The ν_{OH} peaks are the very broad absorptions between 2000 and 3500 cm^{-1}. The peak at around 2400 cm^{-1} in (a) is due to incomplete solvent subtraction.

oxidants in anaerobic MeCN (Table 1).[13] A primary kinetic isotope effect ($k_H/k_D = 5.9 \pm 0.8$ at 24 °C) is observed for the oxidation of [H/D]-**3** with $[Fe(Me_2bpy)_3]^{3+}$, which is indicative of a CPET mechanism. This k_H/k_D ratio is large relative to those measured for other HOAr-B oxidations (1.6–2.8).[9] Arrhenius analysis of the temperature dependence of k_H and k_D (Figure 2a, Table 2) gives values of $\log(A^H/A^D) = -1.0 \pm 0.8$ and $E_a^D - E_a^H = 2.3 \pm 1.2$ kcal mol^{-1} (estimated 2σ errors).

Table 1: Kinetic data for oxidation of **3** at 296 ± 2 K.[a]

Oxidant	E_{rxn} [V]	k [$M^{-1}s^{-1}$]
$[Fe(3,4,7,8\text{-}Me_4phen)_3]^{3+}$	0.02	$(2.3\pm0.2)\times10^4$
$[Fe(4,7\text{-}Me_2phen)_3]^{3+}$	0.09	$(2.5\pm0.3)\times10^5$
$[Fe(5,5'\text{-}Me_2bpy)_3]^{3+}$	0.14	$(1.7\pm0.2)\times10^5$
$[Fe(bpy)_3]^{3+}$	0.26	$(1.8\pm0.2)\times10^6$
$[N(p\text{-}C_6H_4OMe)_3]^{+\bullet}$	−0.28	$(8\pm2)\times10^2$
$[N(tol)_3]^{+\bullet}$	−0.06	$(1.2\pm0.1)\times10^5$
$[N(p\text{-}C_6H_4OMe)(p\text{-}C_6H_4Br)_2]^{+\bullet}$	0.04	$(5.3\pm0.5)\times10^5$

[a] bpy = 2,2′-bipyridine; phen = 1,10-phenanthroline; tol = tolyl.

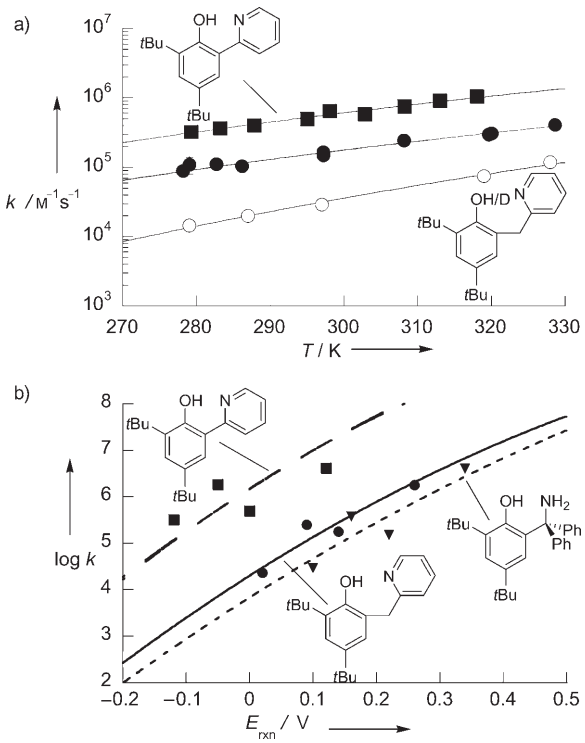


Figure 2. a) Plot of k versus T for the reactions of $[Fe(Me_2bpy)_3]^{3+}$ with [H/D]-**3** (● = k_H; ○ = k_D) and **1** (■).[9] Fits are to the Arrhenius equation: $k = A\exp[-E_a/RT]$. b) Plot of log k versus E_{rxn} for reaction of $[Fe(N\text{–}N)_3]^{3+}$ with **3** (●, solid line), **1** (■, long dashes),[9] and **2** (▼, short dashes).[9] The lines are fits to $k = Z\exp-[(\lambda - E_{rxn})^2/4\lambda k_B T]$ with values of $\log(Z/M^{-1}s^{-1}) = 9.9$ (for **1**), 10.4 (for **2**), and 9.5 (for **3**).[9,13,15]

Table 2: Arrhenius parameters for the reactions of **1** and [H/D]-**3** with $[Fe(Me_2bpy)_3]^{3+}$.

Phenol	$\Delta G°$ [kcal mol^{-1}][a]	k_{rt} [$M^{-1}s^{-1}$][b]	$\log(A$ [$M^{-1}s^{-1}$])	E_a [kcal mol^{-1}]
1	0 ± 0.7	$(6.6\pm1.0)\times10^5$	9.6 ± 0.7	5.3 ± 1.0
[H]-**3**	−3.2 ± 0.7	$(1.7\pm0.2)\times10^5$	9.2 ± 0.5	5.4 ± 0.8
[D]-**3**	−3.2 ± 0.7	$(2.9\pm0.2)\times10^4$	10.2 ± 0.6	7.7 ± 0.9

[a] Calculated from cyclic voltammetry data ($\Delta G° = -F E_{rxn}$). [b] Data collected at 298 K for **1** and 297 K for [H/D]-**3**.

The rate constants for CPET are plotted versus the reaction driving force ($E_{rxn} = E_{oxidant} - E_{HOAr\text{-}B}$) in Figure 2b and S13.[13] The lines to guide the eye assume the typical parabolic dependence of log k on E_{rxn}.[15] At the same driving force, values of k for **3** are similar to those for **2**, and 25–150 times slower than those found for **1**. Even though the proton acceptor in **3** is a pyridine ring, the reactivity of this nonconjugated phenol is much closer to that of the nonconjugated phenolamine **2** than that of the conjugated phenol–pyridine **1**.

What is the origin of the substantial differences in rate constants for **1** and **3**? The complete theoretical analysis needed to address this question—a non-adiabatic treatment with a fully quantum-mechanical transferring proton and rates averaged over the range of proton donor–acceptor (OH···N) distances—is beyond the scope of this communication. However, some insight can be gained from the data above and some initial calculations. For the oxidations of **1** and **3** with $[Fe(Me_2bpy)_3]^{3+}$, both the Arrhenius A and E_a values (Table 2) are the same within error, even though the reaction of **3** is energetically more downhill by 3.2 kcal mol^{-1}. The A^H/A^D and $E_a^D - E_a^H$ values for **3** + $[Fe(Me_2bpy)_3]^{3+}$ appear to be outside the semiclassical limits,[16] implying that tunneling plays a significant role and indicating that crossing from reactants to products could occur in different regions of the potential-energy surface for H versus D.[17]

To probe the differences in the potential-energy surfaces for oxidations of **1** and **3**, DFT calculations were performed using the "four-point" method developed by Nelsen et al. for ET reactions.[18] For a self-exchange reaction such as HOAr-B + $^{\bullet}$OAr-BH$^+$, this method gives the energy to take the reactants to the geometry of the products without allowing the electron to transfer—that is, the vertical reorganization

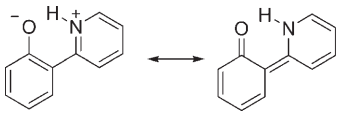
energy λ. With the assumption of parabolic surfaces, the crossing point between the reactant and product surfaces in this symmetrical case is $^1/_4\lambda$. This method implicitly defines the problem as an electron transfer with proton transfer contributing to the relaxation energies, and does not consider proton tunneling and the quantum nature of the proton. Therefore, any conclusions from this approach must be considered tentative pending a more complete analysis.

Nelsen's method estimates λ from calculations of four points of a cycle: 1) the neutral HOAr-B at its optimized geometry (E_{ng}^{0}), 2) vertical ionization to give the radical cation at the optimized geometry of the neutral compound (E_{ng}^{+}), 3) relaxation of the radical cation to its optimized, proton-transferred, geometry (E_{cg}^{+}), and finally, 4) the closed-shell neutral compound at the optimized cation geometry (E_{cg}^{0}). λ is the sum of the relaxation energies for the neutral compound and the cation $[(E_{ng}^{+}-E_{cg}^{+})+(E_{cg}^{0}-E_{ng}^{0})]$.[13,18] The calculations indicate that the value of λ for **1** is significantly smaller (by 8–11 kcal mol^{-1}) than those for **2** and **3** (Table 3). This difference arises mostly from E_{cg}^{0}, the energy of the neutral at the cation geometry, which is a zwitterionic structure in which the proton is nitrogen-bound.[13] This structure is stabilized by resonance in **1** [Eq. (1)] but not in **2** or **3** because of the saturated α carbon atom. Interestingly, the root-mean square displacements of the non-hydrogen atoms between neutral and cation ground states is almost identical in **1** and **3** (within 0.001 Å), so this is not the origin of the difference in λ.[13] Thus, the computations are consistent with the suggestion that the faster reactions of **1** are due to the conjugation between the proton donor and acceptor. Conjugated **1** has the shorter, stronger hydrogen bond, as indicated by the structural and spectroscopic data, which makes the proton-transfer potential flatter and results in more facile CPET.

Table 3: Calculations of λ.[a]

B		E_{ng}^{0}	E_{ng}^{+}	E_{cg}^{+}	E_{cg}^{0}	λ[b]
py	(**1**)	0	134	120	7	21
NH_2	(**2**)	0	135	118	12	29
CH_2py	(**3**)	0	136	117	13	32

[a] B3LYP/6-311+G**//B3LYP/6-31G* energies (in kcal mol^{-1} relative to E_{ng}^{0} for each system) with solvent (MeCN) modeled using PCM.[19] [b] $\lambda = E_{ng}^{+}-E_{cg}^{+}+E_{cg}^{0}-E_{ng}^{0}$.[18,19]



(1)

In conclusion, CPET reactions of the nonconjugated phenol–pyridine **3** are much slower than those of conjugated analogue **1** and are comparable to those of the nonconjugated aminophenol **2**. The nature of the base (NH_2 vs. py) is not critical. We suggest that the key feature in this case is the presence or absence of conjugation between the phenol and the basic nitrogen atom. This conjugation has a marked effect on the hydrogen bond, as indicated by ^{1}H NMR chemical shifts and IR stretching frequencies, as well as on the rates of CPET oxidation. These results may have implications in the understanding of biological and other CPET reactions; further experimental and computational studies are in progress.

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