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Effect of Basic Site Substituents on Concerted Proton-Electron Transfer in Hydrogen Bonded-Pyridyl Phenols

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Abstract

Separated concerted proton-electron transfer (sCPET) reactions of two series of phenols with pendent substituted pyridyl moieties are described. The pyridine is either attached directly to the phenol (**HOAr-pyX**) or connected through a methylene linker (**HOArCH₂pyX**) (X = 4-NO₂, 5-CF₃, 4-CH₃, 4-NMe₂). Electron-donating and -withdrawing substituents also have a substantial effect on the chemical environment of the transferring proton, as indicated by IR and ¹H NMR spectra, X-ray structures and computational studies. One-electron oxidation of the phenols occurs concomitantly with proton transfer from the phenolic oxygen to the pyridyl nitrogen. The oxidation potentials vary linearly with the p*K*_a of the free pyridine (pyX), with slopes slightly below the Nernstian value of 59 mV/p*K*_a. For the **HOArCH₂pyX** series, the rate constants *k*_{sCPET} for oxidation by NAr₃^{•+} or [Fe(diimine)₃]³⁺ vary primarily with the thermodynamic driving force (Δ*G*[°]_{sCPET}), whether Δ*G*[°] is changed by varying the potential of the oxidant or the substituent on the pyridine, indicating a constant intrinsic barrier λ. In contrast, the substituents in the **HOAr-pyX** series affect λ as well as Δ*G*[°]_{sCPET}, and compounds with electron-withdrawing substituents have significantly lower reactivity. The relationship between the structural and spectroscopic properties of the phenols and their CPET reactivity is discussed.

Keywords

Proton-coupled electron transfer; phenol; oxidation; structure-activity relations; tunneling distance; tyrosine-Z

INTRODUCTION

Proton-coupled electron transfer (PCET) reactions are of considerable current interest, due to their importance in fundamental biological processes, energy transduction, and other chemical transformations.^{1–6} Of particular importance is developing an understanding of the parameters that affect PCET reactivity. This report is focused on one class of PCET reactions, in which a proton and an electron are transferred to different sites in a single

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ASSOCIATED CONTENT:

Supporting Information. Syntheses and characterizations of **HOArCH₂pyX** and **HOAr-pyX** derivatives. Spectroscopic, X-ray crystallographic, electrochemical, and kinetic data, including ORTEPs and cyclic voltammograms. CIF files. Computational results, and the complete citation for reference 75. This material is available free of charge via the Internet at <http://pubs.acs.org>

kinetic step, termed separated concerted proton-electron transfer (sCPET)^{7,8} or alternatively multiple site electron-proton transfer (MS-EPT).² Such reactions play important roles in a variety of chemical and biological processes, from energy conversion to the generation of reactive oxygen species.¹ One important example is the oxidation of tyrosine to a neutral tyrosyl radical,^{9,10} for instance in the oxidation of water to O₂ by Photosystem II.^{11–15} This catalytic cycle involves oxidation of tyrosine-Z by long-range electron transfer to an oxidized chlorophyll P680 molecule concomitantly with transfer of the phenolic proton to a near-by hydrogen-bonded histidyl imidazole.^{16,17}

The understanding of separated CPET reactions is being developed through both experimental and theoretical studies. One of the goals of work reported here is to build stronger connections between experiment and theory, which is challenging because of the complexity of the theoretical formulations.^{5,18–23} Many of these formulations view sCPET as an outgrowth of the non-adiabatic form of the Marcus theory of electron transfer.^{24,25} Marcus theory relates the rate constant to a pre-exponential electronic coupling term V_{el} and exponentially to a free energy barrier ΔG^* that is related to the thermodynamic reaction driving force (ΔG°) and an intrinsic barrier or reorganization energy λ (eq. 2). Extending this formalism to sCPET requires taking into account the proton tunneling probability, which can be done with a Franck-Condon (FC) term describing the overlap between proton vibrational wavefunctions in the reactants and products. The rate expression in equations 1 and 2 is a simplistic version of this formalism, and provides a framework with which to interpret experimental results.

$$k \propto (FC)(V_{el})^2 e^{-\Delta G^*/k_B T} \quad (1)$$

$$\Delta G^* = (\Delta G^\circ + \lambda)^2 / 4\lambda \quad (2)$$

Phenol oxidations have been a focus of experimental studies of sCPET, apparently starting with Linschitz *et al.*'s study of photoexcited C₆₀ oxidizing a hydrogen-bonded adduct between phenol and pyridine.^{26,27} More recent studies by the groups of Hammarström, Meyer, Thorp, Nocera, Savéant and others have used photochemical and electrochemical approaches to study sCPET.^{28–39} These studies have primarily been performed in aqueous solution with external proton acceptors, typically a buffer ion or hydroxide. However, these studies are complicated by termolecular kinetics and a lack of definition of the proton transfer coordinate. Our approach has used stopped flow kinetic studies of phenols with well-defined intramolecular hydrogen bonds in aprotic media, using model systems consisting of a di-*tert*-butyl phenol with a base attached *ortho* to the phenolic oxygen.^{7,40–42} When an electron is removed by an outer-sphere oxidant, the phenolic proton is transferred intramolecularly to the basic site to give a distonic radical cation (Scheme 1). The use of a pendent basic site in aprotic media is advantageous for studying the effect of various parameters on sCPET reactivity because the free energy change, ΔG°_{sCPET} , is readily determined using cyclic voltammetry or chemical equilibration experiments. Also, the chemical environment of the transferring proton within the relatively strong O-H...N hydrogen bond can be probed experimentally and computationally.

In previous studies of phenol-pyridines, our laboratory has found that changing the pendent base can substantially affect the sCPET reactivity, and that rate constants (k_{sCPET}) across the whole series do not simply correlate with driving force.^{7,40} Specifically, phenols with pendent pyridyl and imidazolyl basic sites in conjugation with the phenol undergo sCPET with substantially higher rate constants than phenols with unconjugated pyridyl and primary amine basic sites, even at the same ΔG°_{sCPET} . This effect was initially attributed to a

lowering of λ in the conjugated systems due to stronger hydrogen bonding between the phenol and the basic site,⁴⁰ and recent results indicate that differences in the exponential prefactor vibrational and electronic overlap terms also contribute.⁴³

Herein, the properties of the phenol-pyridine molecules that affect their sCPET reactivity are examined in more detail. As shown in the bottom of Scheme 1, two series of di-*tert*-butyl phenols with pendent substituted pyridine bases have been synthesized and studied. The **HOAr-pyX** compounds (X = 4-NMe₂, 4-CH₃, 5-CF₃, 4-NO₂) have a substituted pyridine attached directly to the phenol, while the **HOArCH₂pyX** series (X = 5-CF₃, 4-CH₃, 4-NMe₂) have the pyridine attached to the phenol through a methylene linker. A preliminary account has described the chemistry of the unsubstituted compounds (X = H).⁴⁰ In this study, the substituents allow systematic variation of the sCPET driving force, the strength of the OH...N hydrogen bond, the proton transfer distance (d_{ON}), the X-H vibrational frequencies, and other parameters relevant to sCPET kinetics. There is a strong contrast between the behaviors of the conjugated (**HOAr-pyX**) vs. the non-conjugated (**HOArCH₂pyX**) compounds, in terms of how their reactivity depends on $\Delta G^\circ_{\text{sCPET}}$ and how their intrinsic reactivity (at $\Delta G^\circ_{\text{sCPET}} = 0$) is modulated by the substituents.

RESULTS AND DISCUSSION

Synthesis and Characterization

The non-conjugated pyridyl-methyl-phenols **HOArCH₂pyX** were synthesized by a modification of the previously reported method for the parent **HOArCH₂py**.⁴⁰ *Ortho*-lithiated substituted pyridines were prepared *in situ* from *n*-butyllithium and the corresponding substituted 2-halopyridine and were added to benzyl-ether protected 3,5-di-*tert*-butylsalicylaldehyde. The resulting alcohol was acylated, and catalytic hydrogenation removed both the acetate and the benzyl protecting group. The substituted pyridyl phenols **HOAr-pyX** were prepared via Suzuki couplings of 2,4-di-*tert*-butyl-methoxyphenyl-6-boronic acid with the appropriate halo-pyridine, followed by deprotection of the phenol. All the **HOArCH₂pyX** and **HOAr-pyX** compounds were characterized by ¹H and ¹³C NMR spectroscopy and mass spectrometry.

The substituents have a substantial effect on the ¹H NMR chemical shift of the phenolic proton (δOH) in 'dry' CD₃CN. In the pyridylmethyl series **HOArCH₂pyX**, this proton appears as a singlet with δOH from 10.19 ppm for the nitro derivative (X = NO₂) to 12.06 ppm for X = NMe₂. This singlet is far downfield from δOH for phenols without pendent basic sites, such as tri-*tert*-butyl phenol (δOH = 5.3 in this solvent). The phenolic resonances for **HOAr-pyX** are even further downfield, ranging from δ 14.01 to 15.45 ppm (Table 1).

These large differences in chemical shift reflect differences in the OH...py hydrogen bonding. In general, stronger hydrogen bonding leads to more downfield δOH resonances,⁴⁴ and the hydrogen bond strength increases as the $\text{p}K_{\text{a}}$ of the donor and [protonated] acceptor are more closely matched.⁴⁵ Determining the effective base strength of the pyridine in these strongly H-bonded compounds is problematic, so we use the $\text{p}K_{\text{a}}$ of the free pyridine as a measure of the substituent effect. The substituted pyridines **pyX** vary in basicity by nearly ten orders of magnitude, as the protonated pyridinium ions in acetonitrile solution have estimated $\text{p}K_{\text{a}}$ s ranging from 8.7 for 4-nitropyridinium to 18.5 for 4-dimethylaminopyridinium.^{46–52} The more electron-donating substituents raise the $\text{p}K_{\text{a}}$ of the pyridinium, bringing it closer to the $\text{p}K_{\text{a}}$ of the phenol ($\text{p}K_{\text{a}}$ of phenol = 27 in MeCN),⁵⁴ and thereby leading to stronger hydrogen bonding and more downfield resonances. Given the large range of basicity, there should be notable differences in the hydrogen bonding environment of the phenolic proton, so the variation in δOH is not surprising. Within each series of compounds, δOH varies roughly linearly with the $\text{p}K_{\text{a}}$ of the pyridinium (Figure

1a), and for the same substituent the chemical shift for **HOAr-pyX** is almost 4 ppm downfield of **HOArCH₂pyX**.

Another key parameter of the OH...N hydrogen bond is the donor-acceptor distance between the phenol oxygen and the pyridyl nitrogen, d_{ON} . X-ray crystal structures were obtained for all of the **HOAr-pyX** compounds and for all **HOArCH₂pyX** derivatives except for X = NMe₂ (Table 1). ORTEP drawings for two representative structures are given in Figure 2. The d_{ON} are ca. 0.2 Å longer for the **HOArCH₂pyX** vs. the **HOAr-pyX** compounds, because of the larger ring size for the **HOArCH₂pyX** derivatives. In most cases, smaller d_{ON} are found for compounds with more electron donating substituents, but the range of distances is small. A number of the structures have multiple independent molecules in the unit cell, which differ in their d_{ON} values by more than 0.01 Å, indicating that crystal packing plays a significant role in the observed d_{ON} .

Computed structures may give a better indication of the d_{ON} in solution, avoiding the influence of crystal packing forces. Density functional theory gas-phase B3LYP/6-31G(d,p) optimized geometries (Tables 1 and S18) correlate more strongly with the pK_a of the pyridyl group (Figure 1b). Calculated values of d_{ON} for **HOArCH₂pyX** vary by 0.056 Å, and for **HOAr-pyX** they vary by 0.026 Å. While d_{ON} is a useful parameter for assessing trends in hydrogen-bonding, this is only a proxy for the underlying factors that determining CPET reactivity, *i.e.* the Franck-Condon overlap factors. These overlaps depend on parameters such as the proton tunneling distance, the shape of the proton wavefunctions, and the linearity of hydrogen bond ($\angle_{\text{OHN}}$) as well as the geometry of the hydrogen bond (the location of the proton). For the phenols compounds discussed here, the seven-membered ring in **HOAr-CH₂pyX** allows for a more linear hydrogen bond. For instance, $\angle_{\text{OHN}} = 161^\circ$ in **HOAr-CH₂pyH** compared to $\angle_{\text{OHN}} = 149^\circ$ in the six-membered ring in **HOAr-pyH**.⁴⁰ Within each series, there is only a small variation in $\angle_{\text{OHN}}$ ($< 2^\circ$), with the more electron rich pyridines having more linear as well as shorter H-bonds. In the radical cations, the opposite trends in d_{ON} and $\angle_{\text{OHN}}$ are observed: more electron-withdrawing substituents lead to shorter, more linear O...H-N hydrogen bonds. This is because the low pK_a of the phenoxyl radical (ca. 0) means that stronger hydrogen bonding is expected with electron-withdrawing substituents due to better pK_a matching. The radical cations show a larger effect of substituents, for example d_{ON} varies by 0.08 Å and $\angle_{\text{OHN}}$ values span 4.8° for **•OArCH₂(H⁺)pyX**. Because of these opposing trends, the difference in the equilibrium proton position in the neutrals vs. the radical cations *decreases* with more electron-withdrawing substituents, by 0.043 Å and 0.12 Å in **HOAr-pyX** and **HOArCH₂pyX**. This is the opposite trend compared to d_{ON} in the neutral state. However, this calculation takes into account the movement of the heavy atoms (*e.g.* changes in d_{ON}) from reactants to products so it is not an accurate proton tunneling distance. A related study by Johannissen *et al.*^{32b} took into account $\angle_{\text{OHN}}$ of the radical cation but not the changes in d_{ON} , and found an *increase* in the tunneling distance with electron-withdrawing substituents, but the magnitude is less than the changes in d_{ON} (by a factor of 3 in each series). These results highlight the complexity of predicting geometric effects on CPET reactivity.

Calculated gas phase OH stretching frequencies ($\nu_{\text{OH,DFT}}$), another measure of hydrogen bond strength, also correlate with the pK_a of the base. These values are calculated from the second derivative of the potential energy surface at the minimum, and therefore do not capture the anharmonicity and mode mixing that strongly affect the experimental spectra.⁵⁵ The calculated $\nu_{\text{OH,DFT}}$ are ca. 250 cm⁻¹ higher for the **HOArCH₂pyX** compounds, and the values are higher with more electron withdrawing substituents (from 3053 cm⁻¹ for X = NMe₂ to 3224 cm⁻¹ for X = CF₃ for **HOArCH₂pyX**; Table 1).

Taken together, the d_{ON} , $\nu\text{OH}_{\text{DFT}}$, and δOH values indicate that there is weaker hydrogen bonding for the **HOArCH₂pyX** compounds, and weaker hydrogen bonding with more electron-withdrawing X groups. The changes in these parameters across each series are somewhat smaller than the differences *between* the two series: *i.e.*, **HOAr-pyNO₂** has a shorter d_{ON} , lower νOH , and higher δOH than does **HOArCH₂pyNMe₂**. Figures 1a and 1b also show that the effect of the substituent is more pronounced for the **HOArCH₂pyX** compounds than for **HOAr-pyX**. This could be due to the **HOArCH₂pyX** compounds having greater flexibility of their seven-membered rings, more linear O-H...N angles, or because the conjugation in **HOAr-pyX** allows for compensatory effects of the substituent on the $\text{p}K_{\text{a}}$ of the phenol, as discussed below.

Thermodynamics of HOArCH₂pyX and HOAr-pyX Oxidation

The potentials for oxidation of **HOArCH₂pyX** and **HOAr-pyX** were determined by cyclic voltammetry. Cyclic voltammograms (CVs) of **HOArCH₂pyX** and **HOAr-pyX** in acetonitrile containing 0.1 M [*n*-Bu₄N][PF₆] are chemically reversible, with roughly equal anodic and cathodic currents. The separations between the anodic and cathodic peaks (ΔE_{p}) are somewhat larger than the theoretical value of 0.059 V, as has been observed in related systems.^{6,7,40–42} These quasi-reversible CVs indicate that electrochemical oxidation is coupled to proton transfer to the pyridyl moiety. Reversible cyclic voltammograms have been observed for a variety of phenols with pendent bases in aprotic media,^{7,40–42,56} while the CVs of phenols without pendent bases in aprotic media are irreversible,⁵⁷ in part due to proton transfer to the bulk solution upon oxidation. Proton transfer from the phenol is energetically favorable because the phenol radical cation is very acidic, with a $\text{p}K_{\text{a}}$ in acetonitrile of ~ 0 .⁵⁷ CVs of compounds with weaker hydrogen bonds, *e.g.* **HOAr-pyNO₂**, **HOAr-pyCF₃**, and **HOArCH₂pyCF₃**, show decreased cathodic currents, indicating instability of the oxidized product on the timescale of the experiment. CVs of these compounds at increased scan rates show greater electrochemical reversibility (see Supporting Information Figures S2 – S3). This instability may be due to partial deprotonation of the weakly basic pendent pyridines on the timescale of the CV experiment.

The measured redox potentials ($E_{1/2}$) for **HOArCH₂pyX** vary with substituent, ranging from 0.16 to 0.62 V *vs.* Cp₂Fe⁺⁰ for X = NMe₂ and CF₃, respectively (Table 2). The redox potentials vary linearly with the estimated $\text{p}K_{\text{a}}$ of the pyridyl moiety (Figure 1c), indicating that the thermodynamics of oxidation depend on the energy to transfer the proton to the basic site. The slope of this relationship is $-0.051(2)$ V/ $\text{p}K_{\text{a}}$, just slightly lower than the predicted value of -0.059 V/ $\text{p}K_{\text{a}}$. This result underscores a key advantage of this system in the study of sCPET, as the thermodynamics of the proton transfer are varied in a systematic and well-defined way. The redox potentials of **HOAr-pyX** also vary linearly with the $\text{p}K_{\text{a}}$ of the pyridyl moiety (Table 2 and Figure 1c). The slope of this relationship, $-0.048(1)$ V/ $\text{p}K_{\text{a}}$, is slightly further from the predicted value than for **HOArCH₂pyX**. This somewhat greater deviation from the predicted value is likely due to the increased electronic communication between the phenol and the substituent on the pyridine in the conjugated compounds, which allows compensatory effects on the acidity of the phenol. For instance, an electron-donating substituent lowers the proton-coupled $E_{1/2}$ primarily by increasing the $\text{p}K_{\text{a}}$ of the pyridine, but this effect is partially offset by an increase in the $\text{p}K_{\text{a}}$ of the more distant phenol.

Kinetics of sCPET Oxidations of HOArCH₂pyX and HOAr-pyX

The kinetics of the reactions of **HOArCH₂pyX** and **HOAr-pyX** with one-electron chemical oxidants in acetonitrile at 295(2) K were measured by stopped-flow UV/Vis spectroscopy. The one-electron oxidants used were the hexafluorophosphate salts of a variety of *para*-substituted triarylamminium cations, [N(C₆H₄X)₃]⁺, and substituted tris(bipyridyl) and tris(phenanthroline) iron(III) complexes, [Fe(R₂bpy)₃]³⁺ and [Fe(Me_xphen)₃]³⁺. Reaction

kinetics were fit globally, but marked primarily by the disappearance of the blue ammonium oxidant in reactions using $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$ or by the appearance of the reduced Fe^{II} species in reactions performed with $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$ and $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$. Typical reactions were performed with *ca.* 0.01 mM oxidant and the phenol concentration varied from *ca.* 3 – 30 equivalents. Bimolecular rate constants were obtained by fitting to opposing second order kinetics using SpecFit™ global analysis software.⁵⁸ The results are summarized in Table 3.

A. Substituent and driving force effects on CPET kinetics of $\text{HOArCH}_2\text{pyX}$ —

Bimolecular rate constants have been determined for nine CPET reactions of the substituted $\text{HOArCH}_2\text{pyX}$ compounds with various $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$ oxidants. These rate constants span three orders of magnitude, while the ΔG° (from CV data) varies such that K_{eq} spans 10^6 , depending both on the choice of oxidant and internal base. A Brønsted plot, $\log(k)$ vs. $\log(K_{\text{eq}})$ (Figure 4a), of this data gives a strong linear correlation ($R^2 = 0.92$) with a slope of $\alpha = 0.54(5)$. This value of α , which is equivalent to $\Delta G^\circ_{\text{CPET}} / \Delta G^\circ$, is within error of the value of 0.5 predicted for CPET reactions in the limit where $\Delta G^\circ \ll 2\lambda$ (eq. 2). Thus the rate constants for CPET reactions of $\text{HOArCH}_2\text{pyX}$ depend primarily of the driving force of the reaction, despite the changes in proton transfer coordinate discussed above. A similar result was obtained in our related studies of phenol-imidazoles ($\alpha = 0.55$)⁴² and for a phenol-amine with oxidants of varying potential ($\alpha = 0.53$).⁷ Fecenko, Thorp, and Meyer have reported a slope of ~ 0.6 for oxidation of tyrosine in aqueous buffers.³¹ Such a dependence of the rate on driving force has previously been shown to indicate a concerted proton-coupled mechanism rather than stepwise electron transfer/proton transfer or proton transfer/electron transfer.^{7,31,59}

While the correlation of rate constants with driving force in Figure 4a is quite strong, there are some modest deviations. These deviations could indicate whether the rate constants are affected differently when $\Delta G^\circ_{\text{CPET}}$ is varied through the $\text{p}K_{\text{a}}$ of the base vs. $E_{1/2}$ of the outersphere oxidant. In the reactions of $\text{HOArCH}_2\text{pyCH}_3$ and HOArCH_2py , the ET component of ΔG° has been varied by changing the triarylaminium oxidant, $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$, as shown in the Brønsted plots of Figures 5a and 5b. These plots are linear ($R^2 = 0.99$ for both) with $\alpha = 0.46(5)$ and $0.49(6)$, respectively. Alternatively, ΔG° can also be varied by the substituent on the pyridine. This affects primarily the $\Delta G^\circ_{\text{CPET}}$ through well-defined changes in the $\text{p}K_{\text{a}}$ of the pyridine base (as indicated by the slope of the experimental $E_{1/2}$ vs. estimated $\text{p}K_{\text{a}}$). Figure 5c shows Brønsted plots for the oxidations of $\text{HOArCH}_2\text{pyX}$ ($\text{X} = \text{CF}_3$, H, and Me) by $[\text{N}(\text{C}_6\text{H}_4\text{OMe})(\text{C}_6\text{H}_4\text{Br})_2]^+$ (points on dashed line) or by $[\text{Fe}(\text{Me}_2\text{phen})_3]^{3+}$ (points on solid line). Both of these plots are linear, with $\alpha = 0.57(6)$ ($R^2 = 0.99$) for the ammonium reactions and $\alpha = 0.59(6)$ ($R^2 = 0.99$) for the iron reactions. At the same driving force, the ammonium reactions have rate constants roughly ten times larger than the iron reactions, due to the smaller ET intrinsic barrier for the $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$ reagents.⁷ The good agreement between the ammonium and iron values of α suggests that in these reactions α is independent of the structure of the oxidant used.

The Brønsted slopes are larger when ΔG° is varied by changing the pyridine substituent [$\alpha = 0.57(6)$, $0.59(6)$] than varying the oxidant [$\alpha = 0.46(5)$, $0.49(6)$]. This conclusion is tentative because the plots each involve only three points, and the uncertainties are significant (due primarily to the large estimated uncertainties in the redox potentials and K_{eq} values). However, the confidence level is raised by the agreement between the two series where the oxidant is varied ($\alpha = 0.48$), and between the two series where the substituent is varied ($\alpha = 0.58$). This result is in contrast to the previous study by Meyer *et al.*, in which $\alpha \sim 0.6$ was observed both when changing the oxidant potential and when changing the $\text{p}K_{\text{a}}$ of the buffer.³¹ There could be various reasons why the rate constants are more sensitive to variation in $\Delta G^\circ_{\text{CPET}}$ from changes in the $\text{p}K_{\text{a}}$ of the base vs. changes in the $E_{1/2}$ of the oxidant. In a purely classical picture, this could reflect an asymmetry in the reaction

coordinate, with the transition structure involving more proton transfer.⁶⁰ In the context of PCET theory (eq 1), changing the pyridine substituent could affect k_{sCPET} via changes in the intrinsic barriers λ or quantum mechanical prefactor terms V_{el} and FC . This is discussed in more detail below. The net result is that more electron withdrawing substituents result in smaller rate constants than would be predicted if the substituent affected only $\Delta G^{\circ}_{\text{sCPET}}$.

B. Substituent and driving force effects on CPET kinetics of HOAr-pyX—The reactions of the conjugated **HOAr-pyX** compounds are significantly faster than those of **HOArCH₂pyX** at the same driving force, as was observed for the parent X = H compounds.⁴⁰ This results in the reactions of **HOAr-pyX** with triarylamminiums being too fast to measure with our approach, because they are complete within the mixing time of the stopped-flow instrument even at the lowest practical concentrations. Still, the kinetics for ten reactions with $[\text{Fe}(\text{N-N})_3]^{3+}$ oxidants have been measured (Table 3), with values of E_{rxn} which vary by 0.24 V (or 10^4 in K_{eq}) and rate constants that vary by a factor of 250. The majority of these are slightly uphill reactions ($\Delta G^{\circ}_{\text{CPET}} > 0$), and have been measured with approach-to-equilibrium kinetics.

The Brønsted plot of $\log(k)$ vs. $\log(K_{\text{eq}})$ for oxidations of **HOAr-pyX** shows substantial scatter, as shown in Figure 4b above. The linear fit is very poor, with $R^2 = 0.53$. For example, the reactions of **HOAr-py** + $[\text{Fe}(4,7\text{-Me}_2\text{phen})_3]^{3+}$ and **HOAr-pyCF₃** + $[\text{Fe}(\text{bpy})_3]^{3+}$ have very similar driving forces ($E_{\text{rxn}} = -0.05$ and -0.06 V) but their rate constants differ by a factor of 50. Thus for the **HOAr-pyX** series, other parameters besides the thermodynamic driving force play an important role in determining the sCPET rate. This contrasts with the non-conjugated **HOArCH₂pyX** system, as well as the previous reports of sCPET phenol oxidations mentioned above.^{28–33,39,40,42}

Examining the rate constants in Table 3, including the intrinsic rate constants k° described in the next section, it is apparent that the oxidation reactions with $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$ are significantly faster than the reactions with $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$. For instance, the oxidations of **HOAr-pyCF₃** and **HOAr-pyNO₂** are 4.3 and 3.6 times faster with $[\text{Fe}(\text{phen})_3]^{3+}$ than with $[\text{Fe}(\text{bpy})_3]^{3+}$ even though they are 10 mV less favorable. A small part of this is the *ca.* three-times larger electron transfer self-exchange reaction rate constants for $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$ vs. $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$.⁶¹ However, this should only account for a factor of about 1.7 (using the Marcus cross relation), which is almost exactly counterbalanced by the difference in driving force (accounting for a factor of 0.7 with $\alpha = 1/2$). This effect was noted previously for **HOAr-py**,⁷ but it is not observed in the reactions of **HOArCH₂pyX**. In the context of Marcus models for CPET such as equation 1 above, the observation of a pyridyl-phenol reacting faster with $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$ than with $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$ at essentially the same driving force must be an effect of the electronic coupling V_{el} (also called H_{AB} in ET theory). The other parameters that affect CPET rates are the Franck-Condon factors (FC) and the intrinsic barrier λ . The FC term is a property of the pyridyl-phenol, independent of the oxidant at the same $\Delta G^{\circ}_{\text{CPET}}$, and the ET intrinsic barriers of the two oxidants are very similar based on the self-exchange rate constants given above.

The electronic coupling V_{el} is probably larger for the phenanthroline compounds than the bipyridine ones because the larger conjugated π system of phenanthroline provides a better conduit for electron transfer. The reason that this effect is seen for **HOAr-pyX** and not for **HOArCH₂pyX** is most likely related to the conjugation of the phenol and substituted pyridine rings in **HOAr-pyX**. The optimal electron transfer pathway from the phenol to the oxidant could be via the pyridine since the phenol has two sterically protecting tertiary butyl groups. The significant interaction between the pyridyl and phenol groups in the **HOAr-pyX** compounds is indicated by the dependence of the CPET redox potential on the basicity of the pyridine, $-0.048(1)$ V/p K_{a} , which is lower than the 0.059 V/p K_{a} predicted for non-

interacting fragments (see above). In addition, the hydrogen bonds are significantly stronger for the **HOAr-pyX** compounds, as indicated by the O...N distances being *ca.* 0.2 Å shorter, the stretching frequencies being ~ 200 cm⁻¹ lower, and the δOH being 3–4 ppm lower.

Understanding the substituent effect on sCPET kinetics

A. Intrinsic rate constants k° —To understand the effects of pyridine substitution on k_{sCPET} , it is helpful to separate the thermodynamic contribution from other factors. The reactions described here all have $|\Delta G^\circ| \ll 2\lambda$,⁷ and in this limit the barrier $\Delta G^\ddagger$ becomes linear with ΔG° and equation 1 reduces to equation 3. Separating out the thermochemical driving force from the intrinsic kinetic terms yields an “intrinsic rate constant” k° (eqs 4, 5). In essence, k° is the rate constant extrapolated to $\Delta G^\circ = 0$.⁶² This analysis is analogous to the derivation of the standard electrochemical rate constant by extrapolation to zero driving force using the Tafel slope, which is equivalent to the Brønsted α and is typically taken as 1/2, as in equations 3 and 4.

$$k \propto (FC)(V_{el})^2 e^{-(\Delta G^\circ/2 + \lambda/4)/k_B T} \quad (3)$$

$$k = k^\circ e^{-\Delta G^\circ/2k_B T} \quad (4)$$

$$k^\circ \propto (FC)(V_{el})^2 e^{-\lambda/4k_B T} \quad (5)$$

Plotting k^0 vs. the pK_a of the pyridyl moiety (Figure 6) illustrates clearly the difference between the **HOArCH₂pyX** and **HOAr-pyX** reactions. For the oxidations of **HOArCH₂pyX** by ammonium ions, changing the pyridine substituent has almost no effect on k° . The slope of a linear fit is within error of zero [0.04(4), $R^2 = 0.34$], with some scatter. This indicates that the FC , V_{el} , and λ change only slightly with the pyridine substituent, so that all of the rate constants are fairly well predicted by a single value of k° and the $\Delta G^\circ_{\text{sCPET}}$. This is consistent with the tightness of the Brønsted plot in Figure 4 above. For the three reactions of **HOArCH₂pyX** with $[\text{Fe}(4,7\text{-Me}_2\text{phen})_3]^{3+}$, there appears to be a small increase in k^0 with the pK_a of the base [slope = 0.07(5), $R^2 = 0.88$], in agreement with the deviation from $\alpha = 1/2$ in the Brønsted plots in Figure 5c.

In contrast, there is a strong dependence of k° on pyridine pK_a for the reactions of **HOAr-pyX** with iron oxidants. First, it is immediately apparent that the reactions of $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$ have four-to-ten times greater k° values than reactions with $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$, as discussed above. Once the two iron oxidants are plotted separately, as in Figure 6, it is evident that k° depends strongly on the electron donating character of the substituent. The apparent scatter in the Brønsted plot (Figure 4b) is due to this variation. The values of k° vary by a factor of approximately seven over the *ca.* five orders of magnitude in pyridine pK_a . Plots of $\log(k^\circ)$ versus the pK_a of the pendant base for oxidations of **HOAr-pyX** can be fit by a linear trend, with slopes of 0.19(10) ($R^2 = 0.79$) and 0.24(4) ($R^2 = 0.98$) for the bpy and phen reactions, respectively. Substituent effects on k° account for as much as 50% of the variation in rate constants for the reactions of **HOAr-pyX** with $[\text{Fe}(4,7\text{-Me}_2\text{phen})_3]^{3+}$, while changes in k° account for at most 5% of the variation in reactions of **HOArCH₂pyX** with the same oxidant.

B. Analysis of the origin of the substituent effects—Experimental values for the intrinsic barriers λ , the electronic couplings V_{el} , and Franck-Condon proton transfer terms

FC are not readily accessible.⁶³ However, insight may be gained by looking for correlations of k° and computed values of λ with the available parameters d_{ON} , ν_{OH} , and δOH (Table 1).

First, it is remarkable that there is so little substituent effect on sCPET kinetics for the **HOAr-CH₂pyX** compounds, apart from the effect of substituents on ΔG° . k° shows little change over this series despite changes in the base strength by nearly five orders of magnitude and the resulting changes in the hydrogen bond, *e.g.* the 170 cm⁻¹ shift in calculated ν_{OH} .

In contrast, sCPET reactions of the conjugated **HOAr-pyX** compounds show a much larger variation of k° values with substituents – by roughly an order of magnitude – despite the fact that the variation in the key parameters is smaller for this series. The ranges, for **HOArCH₂pyX** vs. **HOAr-pyX**, are 0.056 vs. 0.026 Å for d_{ON} , 171 vs. 161 cm⁻¹ for ν_{OH} , and 1.87 vs. 1.44 for δOH . Thus the simple correlations of sCPET rates with structure and spectroscopy do not hold across all of the compounds discussed here. The k° values for the **HOAr-pyX** compounds are significantly smaller for those with more electron-withdrawing substituents, which have longer calculated d_{ON} , stiffer O–H modes, and weaker hydrogen bonds as indicated by the lower chemical shift for the hydroxyl protons δOH . This is consistent with the expected trends for both the Franck-Condon (*FC*) and λ parameters. The *FC* term describes the overlap of initial and final proton vibrational wavefunctions, the proton tunneling component of the CPET process. *FC* is known to be smaller for longer proton-donor acceptor tunneling distances,^{5,18,19} so it would be expected to be smaller for molecules with longer ground state O···N distances d_{ON} . This is only an approximate argument, however, because the proton actually tunnels at configurations of the molecules that have smaller d_{ON} than the ground state.^{5,19,21,32b,64} Still, molecules with longer ground state d_{ON} should have higher reorganization energies to reach good tunneling configurations, so they should still have smaller k° . The **HOArCH₂pyX** compounds may not show this substituent effect in part because they have a hydrogen bond in a seven-membered ring, which is more flexible and allows a more linear OH···N structure. Calculations show that the energy to distort d_{ON} is smaller for **HOArCH₂pyX** than for **HOAr-pyX**.⁵⁵

Hammarström and co-workers recently reported a correlation between $\ln(k^0)$ and crystallographic d_{ON} values for photo-initiated sCPET oxidations of four related phenol-base compounds.³⁰ Their k^0 values span 10^{2.4} for compounds in which the crystallographic d_{ON} vary by ca. 0.2 Å, yielding a slope of *ca.* –27 Å⁻¹, consistent with a theoretical prediction.²¹ This is a first approximation to the relationship between k^0 and d_{ON} , because the reactive configurations have smaller d_{ON} than the ground state structures (as noted above), and because the crystallographic values are influenced by crystal packing (the structure which has the longest d_{ON} has an unusual bifurcated hydrogen bond in the crystal lattice and another of the compounds has four independent molecules in two structures, with d_{ON} which span 0.08 Å⁴²). This is why we prefer to use computed d_{ON} values.⁴² Recasting the data in Figure 6 as $\ln(k^0)$ vs. $d_{\text{ON}}(\text{DFT})$, the weak dependence of k^0 on substituent for the **HOArCH₂pyX** compounds is described by a distance dependence similar to that reported by Hammarström. However, for the reactions of the **HOAr-pyX** compounds that have the much larger intrinsic substituent effects, plots of $\ln(k^0)$ vs. $d_{\text{ON}}(\text{DFT})$ have slopes roughly five times larger, *ca.* –150 Å⁻¹ (see SI p. 27).

We have previously shown that DFT calculations of the inner-sphere reorganization energies λ_i qualitatively explained the two-order of magnitude faster sCPET reactions of **HOAr-py** versus **HOArCH₂py**.⁴⁰ Both inner-sphere and solvent reorganizations are involved in the intrinsic barrier λ , which is the energy to move the reactants into the geometry of the products. The solvent contributions are expected to be similar for all the reactions analyzed

here because of the similar size of the phenol-pyridines. The calculations of λ_i (sCPET) followed Nelson's four-point method for ET reorganization energies,^{65,66} with the proton transfer included in the reorganization energy, as we⁴⁰ and others⁶⁷ have done previously. The energies of the neutral molecule and radical cation (denoted E^0 and E^+ , respectively) are calculated at the optimized neutral and cation geometries (denoted ng and cg , respectively), and λ_i (sCPET) is taken as the sum of the neutral and cation relaxation energies (denoted E_{relax}^0 and E_{relax}^+ , respectively).⁶⁵ This calculation provides an approximation of λ_i for the self-exchange reaction of the phenol-pyridine with its radical cation. While quantitative accuracy is not achieved from this simple model, which ignores the quantum mechanical character of the proton and the dynamic effects of promoting vibrations, its success for the parent compounds ($X = H$)⁴⁰ encouraged us to apply it to the substituted derivatives. DFT (B3LYP/6-311+G(d,p)) was used to calculate the four needed energies for each of **HOArCH₂pyX**, $X = 4\text{-CH}_3$, 5-CF_3 , 4-NMe_2 , and **HOAr-pyX**, $X = 4\text{-NO}_2$, 4-NMe_2 using a polarizable continuum solvent model (PCM) for acetonitrile (Table 4). The λ_i (sCPET) values for **HOAr-pyX** are calculated to be *ca.* 10 kcal mol⁻¹ lower than those for **HOArCH₂pyX** (20–23 *vs.* 31–32 kcal mol⁻¹), corresponding to a difference in k° of a factor of *ca.* 10 for reactions with oxidants of similar λ_i (k° is proportional to $\lambda/4k_B T$, eq. 5). This difference in k° is roughly an order of magnitude less than the difference in k° observed experimentally, indicating that other factors make significant contributions to the differences k° . The calculated values of λ_i (sCPET) predict a slight decrease in λ_i (and thus faster rates) for the compounds with electron withdrawing substituents, the opposite of the experimentally observed trends Figure 6. However, the variation in these λ_i values is very small due to compensating effects on E_{relax}^+ and E_{relax}^0 . The insignificant variation of λ_i are consistent with the constant k° for the **HOArCH₂pyX** series and suggests that this is not the origin of the substituent effects in **HOAr-pyX**.

The DFT calculations show one other substantial difference between the **HOAr-pyX** and **HOArCH₂pyX** series of compounds. The HOMOs of **HOAr-pyX** and **HOArCH₂pyX**, and SOMOs of the corresponding radical cations, have most of their density in the π system of the phenol, but for **HOAr-pyX** significant electron density is delocalized onto the pyridine via the conjugated π system. More electron donating substituents may slightly increase the density of the HOMO and SOMO on the pyridine ring. For instance, the HOMO of **HOAr-pyNMe₂** has 8.8% pyridine contribution by Mulliken population analysis, compared to 7.3% for **HOAr-pyNO₂** (Figure 7).⁶⁸ If the pathway for electron transfer is via the pyridine, this suggests that more electron donating substituents would be expected to lead to increased electronic coupling (larger V_{el}), and thereby increase k° as is observed experimentally. In contrast, the DFT calculated HOMO and SOMO orbitals for **HOArCH₂pyX** ($X = 4\text{-CH}_3$, 5-CF_3 , 4-NMe_2) have relatively little density on the pyridine ring. Changing the substituent on the pyridine ring in **HOArCH₂pyX** has almost no effect on the HOMO or SOMO, which are localized on the phenol ring. For example, even with $X = 4\text{-NMe}_2$, only 1.5% of the electron density of the HOMO is on the pyridine (Figure 7). This would be expected to lead to small differences in V_{el} with substituent and therefore small differences in k° , consistent with experiment. While accurate calculations of V_{el} would require a more thorough theoretical analysis, the substituent effects on the phenol molecular orbitals seem likely to be a part of the origin of the differences between the conjugated and non-conjugated systems. However, the differences in orbital character with substituents are subtle, and it seems unlikely that these differences entirely account for observed substituent effect. There may also be a substituent effect on the proton transfer coordinate that has not been captured by these calculations.

CONCLUSIONS

Studies of phenols with pendent substituted pyridines and $-\text{CH}_2\text{pyridines}$, including the kinetics of their oxidations, reveal new features of separated concerted proton-electron transfer (sCPET). The substituent groups vary the $\text{p}K_{\text{a}}$'s of the pyridinyl groups by almost 10 $\text{p}K_{\text{a}}$ units, causing substantial differences in the phenol-pyridine hydrogen bond strength, the proton transfer distance, and the proton-coupled oxidation potential. With the methylene linker between the phenol and the pyridine, there is little electronic communication between the two sites and they act almost as separate molecules, as evidenced by the $-51(2)$ mV per unit change in the estimated $\text{p}K_{\text{a}}$ of the substituted pyridine. The rate constants for oxidation of **HOArCH₂pyX** vary primarily with the changes in ΔG° , as has been found in related studies of phenol-imidazoles⁴² and aqueous phenol oxidations.³¹ There are, however, small differences in the effects of varying ΔG° via changes in the oxidant vs. the base, as indicated by different slopes in Brønsted plots of $\log(k_{\text{sCPET}})$ vs. $\log(K_{\text{sCPET}})$. Much larger substituent effects are observed for the **HOAr-pyX** series of compounds, in which the pyridine and phenol are in conjugation. The importance of this conjugation is evident in the smaller dependence of oxidation potential on pyridyl $\text{p}K_{\text{a}}$ ($-48(1)$ mV/ $\text{p}K_{\text{a}}$), the stronger hydrogen bonds, and the nature of the frontier molecular orbitals. Extracting an intrinsic rate constant k° by extrapolating to $\Delta G^\circ = 0$ shows that substituents can have a substantial effect on the intrinsic reactivity, with electron donating groups leading to faster reactions. Surprisingly, while the **HOAr-pyX** compounds show greater sensitivity of their intrinsic sCPET rate constants to substituents, the **HOArCH₂pyX** series shows a greater effect of substituents on ground state properties such as the proton-donor acceptor distance and the phenol proton chemical shift. The substituent effects in the two systems have been analyzed in the context of sCPET rate theory. Variations in electronic couplings V_{el} with substituent appear to be significant for reactions of the **HOAr-pyX** compounds.

EXPERIMENTAL

General Considerations

Unless otherwise noted, reagents were purchased from Aldrich, solvents from Fischer, and deuterated solvents from Cambridge. Acetonitrile was purchased from Burdick and Jackson (low-water brand) and stored in an argon-pressurized stainless steel drum plumbed directly into a glovebox. *n*-BuLi (1.6M in hexanes) was purchased from Acros. CD_3CN was dried by stirring over CaH_2 overnight, then distilled onto P_2O_5 , followed by another distillation from CaH_2 , and was stored in a glove box. The iron-bipyridyl and phenanthroline complexes were synthesized according to literature procedures⁶⁹ and were used as PF_6^- salts. 3,5-Di-*tert*-butyl-2-(benzyloxymethyl)benzaldehyde⁷⁰ and 2-bromo-5-trifluoromethylpyridine⁷¹ were synthesized according to literature procedures. Triarylamminium hexafluorophosphate salts were prepared from the corresponding amines as described previously.⁷ ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AV300 or AV500 spectrometers at ambient temperatures; chemical shifts are reported relative to TMS in ppm by referencing to the residual solvent signals. Column chromatography used silica gel as the stationary phase. Mass spectrometry was performed on a Bruker Esquire Ion Trap Mass Spectrometer using electrospray ionization and on a Hewlett Packard 5971A Gas Chromatograph/Mass Spectrometer using electron impact ionization, and are reported as m/z with relative abundance in parentheses when multiple peaks were observed.

Syntheses

The syntheses of **HOArCH₂pyX** and **HOAr-pyX** derivatives were carried out in a similar manner to the syntheses of the parent $\text{X} = \text{H}$ compounds.⁴⁰ Experimental details as well as spectroscopic and crystallographic refinement data for these compounds are given in the

Supporting Information. ORTEPs of the crystal structures are presented in Figures 2 and S1 (in the SI).

Electrochemistry

Cyclic voltammetry (CV) was performed under N₂ using an E2 Epsilon apparatus (BASi) equipped with Pt disc or glassy carbon working electrode (3.0 mm dia), platinum wire auxiliary electrode, and Ag/Ag(NO)₃ (0.01 M) reference electrode. CV was carried out in acetonitrile with 0.1 M [*n*-Bu₄N][PF₆] as supporting electrolyte with *ca.* 5 mM substrate. [*n*-Bu₄N][PF₆] was recrystallized three times from EtOH and dried *in vacuo* for two days at 110 °C prior to use. Ferrocene was added as an internal standard and all potentials are reported vs. the Cp₂Fe⁺⁰ couple. For each compound, CVs were collected at a range of scan rates, from *ca.* 25 to 500 mV/s. Representative voltammograms can be found in Supporting Information.

Kinetics

All kinetics experiments were performed at room temperature in low-water acetonitrile using an OLIS USA stopped-flow instrument with an OLIS rapid scanning monochromator and UV-vis detector. Kinetic data were analyzed using SpecFit™ global analysis software,⁵⁸ and were fit to opposing second order kinetics. Kinetic experiments using the iron oxidants were run in acetonitrile with 0.1 M [Bu₄N][PF₆] because the potentials of these compounds vary with ionic strength.^{72–74}

DFT Calculations

All calculations were performed with *Gaussian03*.⁷⁵ In all cases, *tert*-butyl groups were replaced with methyl groups to save computational time. All optimized geometries were confirmed to be local minima by vibrational analysis (NImag = 0). Four-point analysis of λ was performed following reference 65. Optimizations of the neutral and cation geometries of **HOArCH₂pyX** and **HOAr-pyX** were performed at the B3LYP/6–31G(d,p) level of theory. Single point energies calculated for determination of λ on these geometries were performed at the B3LYP/6–311+G(d,p) level of theory with acetonitrile solvent modeled by a polarizable continuum model (PCM). In all cases, geometries corresponding to the non-proton-transferred radical cations ([HOAr-B]^{•+}) or the zwitterions (–OAr-BH⁺) are not local minima. Energies are not corrected for zero-point vibrational energy. Cartesian coordinates of the optimized geometries of all species are given in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Variation of thermochemical and structural parameters in $\text{HOArCH}_2\text{pyX}$ (blue $\blacklozenge$) and HOAr-pyX (red $\blacksquare$) versus the estimated pK_a of the pyridinium (see Ref. 46).

Figure 2.
ORTEPs of HOArCH₂pyCH₃ (left) and HOAr-pyCH₃ (right).

Figure 4. Brønsted plots for (a.) reactions of $\text{HOArCH}_2\text{pyX}$ with $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$, and (b.) reactions of HOAr-pyX with $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$ and $[\text{Fe}(\text{Me}_x\text{phen})_3]^{3+}$.

Figure 5. Brønsted plots for reactions of (a.) $\text{HOArCH}_2\text{pyCH}_3$ with $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$, (b.) $\text{HOArCH}_2\text{pyH}$ with $[\text{N}(\text{C}_6\text{H}_4\text{X})_3]^+$, and (c.) $\text{HOArCH}_2\text{pyX}$ with $[\text{N}(\text{C}_6\text{H}_4\text{OMe})(\text{C}_6\text{H}_4\text{Br})_2]^+$ (points on dashed blue line) and $[\text{Fe}(\text{Me}_2\text{phen})_3]^{3+}$ (points on solid red line).

Figure 6.

Intrinsic kinetic rate constants k° (Table 3) plotted vs. the pK_a of the pyridine (Table 1), for reactions of **HOArCH₂pyX** and **HOAr-pyX** with different oxidants. The estimated error on $\log(k^\circ)$ is ± 0.3 .

Figure 7.
Kohn-Sham molecular orbital diagrams for the HOMOs of (a.) **HOAr-pyNMe₂**, (b.) **HOAr-pyNO₂**, and (c.) **HOArCH₂pyNMe₂**.

Scheme 1.
sCPET reactivity of phenols with pendent bases, and the phenols with pendent pyridines used in this study, **HOAr-pyX** and **HOArCH₂pyX**.

Table 1

Structural and spectroscopic properties of **HOArCH₂pyX** and **HOAr-pyX**.

	X	p <i>K</i> _a ^a	δOH ^b	d _{ON} (X-ray) ^c	d _{ON} (DFT) ^c	νOH _{DFT} ^d
-CH ₂ pyX	4-NMe ₂	18.5	12.06	-	2.726	3053
	4-CH ₃	14.1	11.31	2.724(3)	2.753	3137
	H ^e	12.9	11.15 ^e	2.6914(13) ^e	2.761	3160
	5-CF ₃	9.5	10.19	[2.778(5), 2.766(5)] ^f	2.782	3224
-pyX	4-NMe ₂	18.5	15.45	2.500(4)	2.551	2838
	4-CH ₃	14.1	14.95	2.531(3)	2.560	2897
	H ^g	12.9	14.83	[2.561(3), 2.567(3), 2.573(3)] ^f	2.565	2918
	5-CF ₃	9.5	14.26	[2.565(4), 2.547(4), 2.570(4)] ^f	2.569	2958
	4-NO ₂	8.7	14.01	2.548(3)	2.578	2999

^a Estimated, from Ref. 46.

^b In ppm, in CD₃CN.

^c In Å.

^d In cm⁻¹, corrected following to Ref. 53.

^e Ref. 40.

^f multiple independent molecules in the unit cell.

^g Ref. 7.

Table 2Thermochemical properties of **HOArCH₂ pyX** and **HOAr-pyX**.

	X	p<i>K</i>_a(pyX)^a	<i>E</i>_{1/2}^b(Δ<i>E</i>_p)^c
-CH ₂ pyX	4-NMe ₂	18.5	60.16 (0.12) ^d
	4-CH ₃	14.1	0.40 (0.21) ^d
	H ^e	12.9	0.44 (0.22)
	5-CF ₃	9.5	0.62 (0.12) ^d
-pyX	4-NMe ₂	18.5	0.32 (0.09)
	4-CH ₃	14.1	0.53 (0.11)
	H ^f	12.9	0.58 (0.10)
	5-CF ₃	9.5	0.76 (0.08)
	4-NO ₂	8.7	0.79 (0.09)

^a Estimated, from Ref. 46.^b vs. Cp₂Fe^{+/0} in MeCN, estimated error is ± 0.02 V.^c In V, scan rate = 0.2 V/s.^d Scan rate = 0.1 V/s.^e Ref. 40.^f Ref 7.

Table 3

Kinetic data for oxidations of **HOArCH₂pyX** and **HOAr-pyX**.

Phenol	Oxidant	$E_{\text{rxn}}(\text{V})$	$k (\text{M}^{-1} \text{s}^{-1})$	$k^\circ (\text{M}^{-1} \text{s}^{-1})^a$
-CH ₂ pyNMe ₂	[N(C ₆ H ₄ OMe) ₃] ⁺⁺	0.00	$5.4 \pm 0.5 \times 10^5$	5.4×10^5
-CH ₂ pyCH ₃	[N(C ₆ H ₄ OMe)(C ₆ H ₄ Br) ₂] ⁺⁺	0.08	$8.0 \pm 0.9 \times 10^5$	1.7×10^5
	[N(C ₆ H ₄ Me) ₃] ⁺⁺	-0.02	$1.4 \pm 0.2 \times 10^5$	2.2×10^5
	[N(C ₆ H ₄ OMe) ₂ (C ₆ H ₄ Br)] ⁺⁺	-0.08	$4.4 \pm 0.5 \times 10^4$	2.2×10^5
	[Fe(4,7-Me ₂ phen) ₃] ³⁺	0.13	$5.0 \pm 0.5 \times 10^5$	4.0×10^4
-CH ₂ py	[N(C ₆ H ₄ OMe)(C ₆ H ₄ Br) ₂] ⁺⁺ ^b	0.04	$5.3 \pm 0.5 \times 10^5$	2.4×10^5
	[N(C ₆ H ₄ Me) ₃] ⁺⁺ ^b	-0.06	$1.2 \pm 0.1 \times 10^5$	3.9×10^5
	[N(C ₆ H ₄ OMe) ₃] ⁺⁺ ^b	-0.28	$8 \pm 2 \times 10^2$	1.9×10^5
	[Fe(4,7-Me ₂ phen) ₃] ³⁺ ^b	0.09	$2.5 \pm 0.3 \times 10^5$	4.3×10^4
CH ₂ pyCF ₃	[N(C ₆ H ₄ Br) ₃] ⁺⁺	0.05	$7.5 \pm 1.5 \times 10^5$	2.8×10^5
	[N(C ₆ H ₄ OMe)(C ₆ H ₄ Br) ₂] ⁺⁺	-0.14	$7.6 \pm 0.8 \times 10^3$	1.2×10^5
	[Fe(4,7-Me ₂ phen) ₃] ³⁺	-0.09	$3.4 \pm 0.3 \times 10^3$	2.0×10^4
-pyCH ₃	[Fe(5,5'-Me ₂ bpy) ₃] ³⁺	0.05	$2.2 \pm 0.2 \times 10^6$	8.3×10^5
-py	[Fe(bpy) ₃] ³⁺ ^c	0.12	$5.2 \pm 0.8 \times 10^6$	5.0×10^5
	[Fe(5,5'-Me ₂ bpy) ₃] ³⁺ ^c	0.00	$5.8 \pm 0.9 \times 10^5$	5.8×10^5
	[Fe(4,4'-Me ₂ bpy) ₃] ³⁺	-0.07	$4.5 \pm 0.9 \times 10^5$	1.8×10^6
	[Fe(4,7-Me ₂ phen) ₃] ³⁺ ^c	-0.05	$1.9 \pm 0.4 \times 10^6$	5.0×10^6
	[Fe(3,4,7,8-Me ₄ phen) ₃] ³⁺ ^c	-0.12	$3.3 \pm 0.6 \times 10^5$	3.4×10^6
	[Fe(4,4'-tBu ₂ bpy) ₃] ³⁺	-0.06	$4.6 \pm 0.5 \times 10^4$	1.5×10^5
-pyCF ₃	[Fe(bpy) ₃] ³⁺	-0.06	$3.7 \pm 0.4 \times 10^4$	1.2×10^5
	[Fe(phen) ₃] ³⁺	-0.07	$1.6 \pm 0.2 \times 10^5$	6.3×10^5
-pyNO ₂	[Fe(bpy) ₃] ³⁺	-0.09	$2.1 \pm 0.2 \times 10^4$	1.2×10^5
	[Fe(phen) ₃] ³⁺	-0.10	$7.5 \pm 1.5 \times 10^4$	5.3×10^5

^a Intrinsic rate constants, corrected to $\Delta G^\circ = 0$ (see text).^b Ref. 40.^c Ref. 7.

Table 4

Calculation of λ_1 (sCPET) by four-point method.^a

X	E_{ng}^0	E_{ng}^+	E_{eg}^0	E_{eg}^+	E_{relax}^0	E_{relax}^+	λ_1
HOAr-CH₂pyX	4-NMe ₂	0	134	9	111	9	32
	4-CH ₃	0	135	13	117	13	31
	5-CF ₃	0	137	17	123	17	31
HOAr-pyX^c	4-NMe ₂	0	133	6	116	6	23
	4-CH ₃	0	135	8	121	8	22
	4-NO ₂	0	139	10	129	10	20

^aEnergies in kcal mol⁻¹ relative to E_{ng}^0 , from calculations at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) level of theory.