

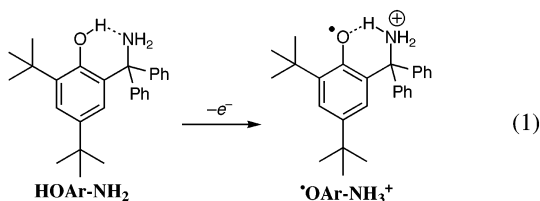
## One-Electron Oxidation of a Hydrogen-Bonded Phenol Occurs by Concerted Proton-Coupled Electron Transfer

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Proton-coupled electron transfer (PCET) is of much current experimental and theoretical interest.<sup>1</sup> When an e<sup>-</sup> and a H<sup>+</sup> transfer together from one reactant to another (AH + B → A + HB), the reaction is hydrogen-atom transfer.<sup>1b,c</sup> There are also processes in which e<sup>-</sup> and H<sup>+</sup> both transfer but are separated, such as AH + B + C → A + HB<sup>+</sup> + C<sup>-</sup>. An important example of this second class of PCET reactions is the formation of tyrosyl radicals in proteins from tyrosine residues, by long-range electron transfer coupled to deprotonation by a nearby base.<sup>2</sup> In photosystem II, oxidation of tyrosine Z (Y<sub>Z</sub>) by P680<sup>++</sup> likely occurs with transfer of the tyrosyl proton to a hydrogen-bonded histidine.<sup>3</sup> In a number of systems, the mechanisms of such processes are controversial, especially whether e<sup>-</sup> and H<sup>+</sup> transfer occurs in two steps (ET and PT) or in a single concerted PCET process.<sup>1-3</sup> Described here are outer-sphere oxidations of a phenol with a pendent base (abbreviated **HOAr-NH<sub>2</sub>**, eq 1), both as a model both for the oxidation of Y<sub>Z</sub> and as a prototype for this class of PCET reactions. Mechanistic studies indicate that the e<sup>-</sup> and H<sup>+</sup> transfer in one kinetic step, with no intermediate along the reaction coordinate. Analysis of these unusual reactions with Marcus theory gives large apparent intrinsic barriers (λ > 30 kcal mol<sup>-1</sup>).



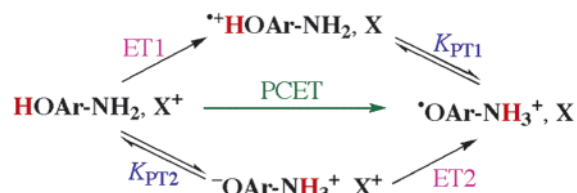
**HOAr-NH<sub>2</sub>** was prepared by addition of benzophenone to dilithiated 2,4-di-*tert*-butylphenol and then by treatment with HCl and finally ammonia.<sup>4</sup> An X-ray crystal structure (Figure S3)<sup>4</sup> confirms the structure and shows an OH...N hydrogen bond, as is typical for such Mannich bases.<sup>5a</sup> The O-H and N...H distances are 0.90(3) and 1.75(3) Å (averages of two independent molecules). Cyclic voltammetry of **HOAr-NH<sub>2</sub>** using a glassy carbon working electrode reveals a quasi-reversible wave at 0.36 ± 0.02 V (0.1 M TBAPF<sub>6</sub>, MeCN, vs Cp<sub>2</sub>Fe<sup>+0</sup>, ΔE<sub>p</sub> = 163 mV). Related α-alkyl-amino phenols undergo similar oxidations to the corresponding phenoxyl radical/protonated base.<sup>6</sup> The potentials for these oxidations are much lower than those for phenol oxidations without proton movement (e.g., E = 1.09 V for 2,4,6-tri-*tert*-butylphenol (<sup>t</sup>Bu<sub>3</sub>-ArOH)<sup>7</sup>). Monitoring the chemical oxidation of **HOAr-NH<sub>2</sub>** by [N(*p*-C<sub>6</sub>H<sub>4</sub>Br)<sub>3</sub>]<sup>++</sup> (E = +0.67 V) in CD<sub>3</sub>CN shows the disappearance of the <sup>1</sup>H NMR signals for **HOAr-NH<sub>2</sub>** and the appearance of N(*p*-C<sub>6</sub>H<sub>4</sub>Br)<sub>3</sub>; UV-vis spectra show bleaching of the blue aminium ion. An EPR spectrum of a reaction mixture in CH<sub>2</sub>Cl<sub>2</sub> shows a new complex multiplet presumably due to **OAr-NH<sub>3</sub><sup>+</sup>**.<sup>4</sup>

**Table 1.** Rate and Equilibrium Constants for Oxidations of **HOAr-NH<sub>2</sub>**

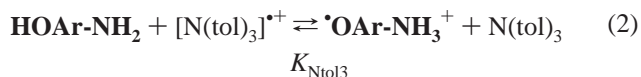
| oxidant  | E <sub>1/2</sub> <sup>a</sup> | k<br>(M <sup>-1</sup> s <sup>-1</sup> ) | K <sub>eq</sub> <sup>b</sup>   |
|--|-------------------------------|---|--------------------------------|
| [Fe(bpy) <sub>3</sub> ] <sup>3+</sup>  | 0.70                          | (4 ± 1) × 10 <sup>6</sup>               | > 10 <sup>2</sup>              |
| [N( <i>p</i> -C <sub>6</sub> H <sub>4</sub> Br) <sub>3</sub> ] <sup>++</sup>   | 0.67                          | (4 ± 2) × 10 <sup>7</sup>               | > 10 <sup>2</sup>              |
| [Fe(5,5'-Me <sub>2</sub> bpy) <sub>3</sub> ] <sup>3+</sup>   | 0.58                          | (1.5 ± 0.2) × 10 <sup>5</sup>           | > 10 <sup>2</sup>              |
| [N( <i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe)( <i>p</i> -C <sub>6</sub> H <sub>4</sub> Br) <sub>2</sub> ] <sup>++</sup> | 0.48                          | (8 ± 1) × 10 <sup>5</sup>               | <sup>c</sup>                   |
| [N(tol) <sub>3</sub> ] <sup>++</sup>   | 0.38                          | (1.1 ± 0.2) × 10 <sup>5</sup>           | 2.0 ± 0.5                      |
| [N( <i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe) <sub>2</sub> ( <i>p</i> -C <sub>6</sub> H <sub>4</sub> Br)] <sup>++</sup> | 0.32                          | (2.7 ± 0.3) × 10 <sup>4</sup>           | 0.21 ± 0.06                    |
| [N( <i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe) <sub>3</sub> ] <sup>++</sup>  | 0.16                          | (1.1 ± 0.1) × 10 <sup>3</sup>           | (2.9 ± 0.3) × 10 <sup>-4</sup> |

<sup>a</sup> Potentials (V) vs FeCp<sub>2</sub><sup>+0</sup> (±0.02 V) in MeCN.<sup>4</sup> <sup>b</sup> K<sub>eq</sub> = [**OAr-NH<sub>3</sub><sup>+</sup>**][Red]/[**HOAr-NH<sub>2</sub>**][Ox]. <sup>c</sup> Not determined.

**Scheme 1.** Mechanisms for Electron Transfer from **HOAr-NH<sub>2</sub>** to X<sup>+</sup>



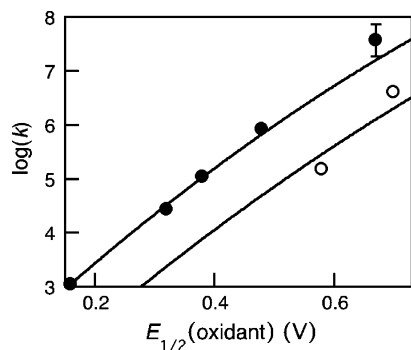
Reaction of **HOAr-NH<sub>2</sub>** with [N(*p*-C<sub>6</sub>H<sub>4</sub>Me)<sub>3</sub>]<sup>++</sup> ([N(tol)<sub>3</sub>]<sup>++</sup>, E<sub>1/2</sub> = 0.38 V), forms an equilibrium mixture (eq 2). Addition of N(tol)<sub>3</sub>



shifts the equilibrium to the left, as does the addition of triflic acid (by protonating and thereby removing **HOAr-NH<sub>2</sub>**). These independent experiments give K<sub>Ntol3</sub> = 2.0 ± 0.5.<sup>8</sup> This and equilibrium constants derived from similar reactions with [N(*p*-C<sub>6</sub>H<sub>4</sub>OMe)<sub>3</sub>]<sup>++</sup> and [N(*p*-C<sub>6</sub>H<sub>4</sub>OMe)<sub>2</sub>(*p*-C<sub>6</sub>H<sub>4</sub>Br)]<sup>++</sup> confirm the +0.36 V redox potential of **HOAr-NH<sub>2</sub>** (Table 1). These equilibration experiments indicate the stability of the phenoxyl radical **OAr-NH<sub>3</sub><sup>+</sup>**, as expected for a phenoxyl radical with tertiary substituents at the 2, 4, and 6 positions (e.g., <sup>t</sup>Bu<sub>3</sub>ArO<sup>•</sup>).<sup>9</sup>

The kinetics of outer-sphere oxidations of **HOAr-NH<sub>2</sub>** have been measured in anaerobic MeCN using stopped-flow spectrophotometry. Under pseudo-first-order conditions, the disappearance of [N(tol)<sub>3</sub>]<sup>++</sup> follows first-order kinetics, and the k<sub>obs</sub> varies linearly with the phenol concentration, indicating a second-order rate law with k<sub>Ntol3</sub> = (1.1 ± 0.2) × 10<sup>5</sup> M<sup>-1</sup> s<sup>-1</sup>. Rate constants for different oxidants are shown in Table 1. With [N(*p*-C<sub>6</sub>H<sub>4</sub>Br)<sub>3</sub>]<sup>++</sup>, electron transfer is complete within 20 ms even with near stoichiometric amounts of **HOAr-NH<sub>2</sub>**, giving k<sub>N(ArBr)3</sub> = (4 ± 2) × 10<sup>7</sup> M<sup>-1</sup> s<sup>-1</sup>.

The three most likely mechanisms for the oxidation of **HOAr-NH<sub>2</sub>** to **OAr-NH<sub>3</sub><sup>+</sup>** are shown in Scheme 1. Initial outer-sphere electron transfer (top path, ET1-PT1) would form the radical cation **HOAr-NH<sub>2</sub><sup>•+</sup>**, which would rapidly rearrange to **OAr-NH<sub>3</sub><sup>+</sup>** by proton transfer. Alternatively, in the bottom PT2-ET2 path, initial preequilibrium proton transfer (too rapid to be rate limiting) would give the zwitterion **OAr-NH<sub>3</sub><sup>+</sup>** as the species that undergoes



**Figure 1.**  $\log(k)$  vs  $E_{1/2}(\text{oxidant})$  for oxidation of **HOAr-NH<sub>2</sub>** by  $\text{NAr}_3^{+}$  (●) and  $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$  (○). The curves are fits to  $k = 10^{11} \exp(-[1/\lambda(1 + \Delta G^\circ/\lambda)^2]/kT)$  with  $\lambda = 34$  and  $40 \text{ kcal mol}^{-1}$ , respectively.

electron transfer. Finally, the transfer of both the electron and proton could occur by concerted PCET, in a single kinetic step.

Three lines of evidence indicate that oxidation proceeds by the concerted PCET pathway, without involving an intermediate. First, a primary kinetic isotope effect  $k_{\text{H}}/k_{\text{D}} = 2.4 \pm 0.2$  is found upon oxidation of **DOAr-ND<sub>2</sub>** by  $[\text{N}(\text{tol})_3]^{+}$ . Neither rate-limiting electron transfer (ET1–PT1) nor preequilibrium proton transfer (PT2–ET2) are consistent with this result.

Second, the rates are too fast to be consistent with high-energy intermediates along the pathway. The  $\Delta G^\circ_{\text{ET1}}$  for the first step in the ET1–PT1 mechanism, **HOAr-NH<sub>2</sub>** +  $[\text{N}(\text{tol})_3]^{+} \rightarrow \cdot^+\text{HOAr-NH}_2 + [\text{N}(\text{tol})_3]$ , is  $+16.4 \text{ kcal mol}^{-1}$ ,  $K_{\text{eq,ET1}} = 10^{-12}$ , estimated using  $E(\text{Bu}_3\text{ArOH}^{+0})^7$  as a model for  $E(\text{HOAr-NH}_2/\cdot^+\text{HOAr-NH}_2)$ .<sup>4</sup> The  $\Delta G^\circ_{\text{ET1}}$  is larger than  $\Delta G^\ddagger = 11 \text{ kcal mol}^{-1}$  from the Eyring equation.<sup>10</sup> From another perspective,  $K_{\text{eq,ET1}} = 10^{-12}$  means that the forward rate constant  $k_{\text{ET1}}$  cannot be  $10^5 \text{ M}^{-1} \text{ s}^{-1}$  because back ET would have occurred with an unreasonable  $k_{\text{ET-1}} = 10^{17} \text{ M}^{-1} \text{ s}^{-1}$ . A very short-lived successor complex  $[\cdot^+\text{HOAr-NH}_2][\text{NAr}_3]$  is conceivable but unlikely for similar reasons.<sup>11</sup> In the PT2–ET2 pathway, an upper limit of  $K_{\text{PT2}} < 10^{-4}$  for the initial preequilibrium PT can be estimated following studies of other Mannich bases.<sup>5</sup> Optical spectra of saturated solutions of **HOAr-NH<sub>2</sub>** in MeCN show no evidence for the zwitterion  $^-\text{OAr-NH}_3^+$  (using the spectrum of the phenoxide  $^-\text{OAr-NH}_2$  as a model for this species<sup>4,5</sup>). With  $K_{\text{PT2}} < 10^{-4}$ , the observed  $k > 10^7 \text{ M}^{-1} \text{ s}^{-1}$  for  $[\text{N}(p\text{-C}_6\text{H}_4\text{Br})_3]^{+}$  would require  $k_{\text{ET2}}$  from  $^-\text{OAr-NH}_3^+$  to occur at  $> 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ , faster than the diffusion limit.

Third, concerted PCET is indicated by the dependence of the rate constants on driving force,  $\Delta\Delta G^\ddagger/\Delta\Delta G^\circ = 0.53$ .<sup>4</sup> This indicates that the reactions are in the regime  $|\Delta G^\circ| \ll \lambda$  expected for the PCET path. In the stepwise paths,  $k_{\text{ET-1}}$  and  $k_{\text{ET2}}$  would need to be close to (if not faster than) the diffusion limit (see above), a regime where  $|\Delta G^\circ| \cong \lambda$  and  $\Delta\Delta G^\ddagger/\Delta\Delta G^\circ$  is far from  $1/2$ .<sup>12</sup>

The oxidations of **HOAr-NH<sub>2</sub>** therefore occur by concerted proton and electron transfer (note that *concerted* does not imply *synchronous*). Concerted PCET is advantageous because it avoids the higher free energy intermediates  $\cdot^+\text{HOAr-NH}_2$  and  $^-\text{OAr-NH}_3^+$ . This contradicts the frequent intuition that stepwise mechanisms are in general preferred to concerted PCET.

**HOAr-NH<sub>2</sub>** is an unusual electron-transfer reagent because of its intramolecular proton transfer. Using Marcus theory to analyze PCET reactions is of experimental<sup>13</sup> and theoretical interest.<sup>14</sup>  $k(\text{HOAr-NH}_2 + [\text{NAr}_3]^{+})$  are well fit by the adiabatic Marcus equation (Figure 1), with an intrinsic barrier  $\lambda = 34 \text{ kcal mol}^{-1}$ . The limited data for  $[\text{Fe}(\text{R}_2\text{bpy})_3]^{3+}$  give  $\lambda \approx 40 \text{ kcal mol}^{-1}$ , consistent with the higher intrinsic barrier for iron complexes.<sup>15</sup> These intrinsic barriers are significantly larger than those for most organic molecules, such as  $\lambda = 12 \text{ kcal mol}^{-1}$  for  $[\text{N}(\text{tol})_3]^{+0}$  self-

exchange (that should have a comparable donor/acceptor distance).<sup>15b</sup> Hammarström et al. have reached a similar conclusion, reporting  $\lambda = 55 \text{ kcal mol}^{-1}$  for the related aqueous PCET oxidation of tyrosine to tyrosyl radical +  $\text{H}_3\text{O}^+$  by a tethered  $\text{Ru}(\text{bpy})_3^{3+}$ .<sup>13a,14c</sup> These analyses assume adiabatic ET; nonadiabatic behavior would give lower values of  $\lambda$ . In either case, the concerted PCET is intrinsically more difficult than related ET reactions, either because of a larger  $\lambda$  or due to increased nonadiabaticity.

In sum, the mechanism of one-electron oxidation of the phenol-amine **HOAr-NH<sub>2</sub>** involves intramolecular proton transfer concerted with transfer of the electron in a single kinetic step. Stepwise mechanisms involving initial ET or PT are disfavored because they involve high-energy intermediates, which overshadows the larger intrinsic barrier for the proton-coupled electron transfer. The oxidation of **HOAr-NH<sub>2</sub>** is a prototype of PCET reactions in which the  $\text{e}^-$  and  $\text{H}^+$  are separated. It is also a good model for biologically important oxidations of tyrosine residues to tyrosyl radicals. Further studies to define the characteristics of this class of PCET reaction are in progress.

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**Supporting Information Available:** Synthetic details for **HOAr-NH<sub>2</sub>**, experimental details for equilibration and kinetics studies, and electrochemistry. Crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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