Comments on “How Single and Bifurcated Hydrogen Bonds Influence Proton-Migration Rate Constants, Redox, and Electronic Properties of Phenoxyl Radicals”**

*Ian J. Rhile and James M. Mayer**

Stichwörter:
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In a recent communication, Thomas et al. studied the oxidations of three hydrogen-bonded phenols.[1] Such compounds serve as interesting models for hydrogen-bonded tyrosine and tyrosyl radical residues in biological systems. EPR data and DFT calculations provided strong evidence for the nature of the phenoxyl radical products of one-electron oxidation. The cyclic voltammetry (CV) data were simulated and interpreted using a model with initial interfacial electron transfer and subsequent slow proton transfer. Herein we show that this mechanistic interpretation of the CV results is problematic on both thermochemical and kinetic grounds.

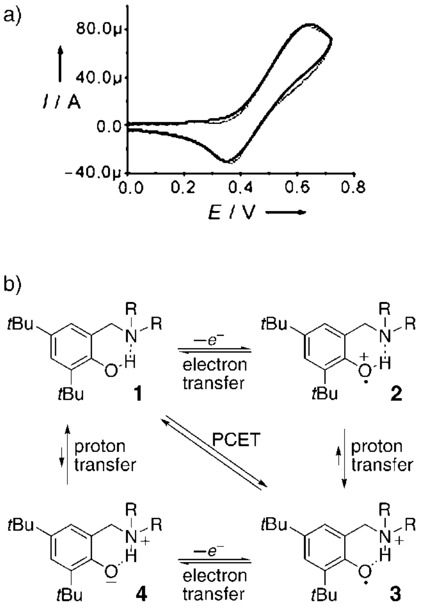
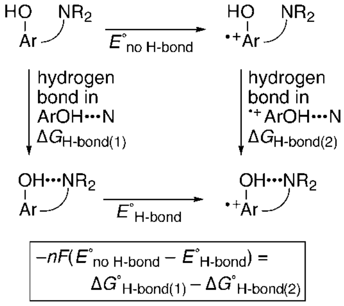


Figure 1. a) CV curve of HL^{Benz} reproduced from Reference [1]. Conditions: HL^{Benz} (2.4 mM in CH_2Cl_2), tetrabutylammonium perchlorate (0.1 M), 298 K, scan rate: 0.1 $V s^{-1}$; solid line: experimental; dotted line: simulation. b) Square scheme showing various pathways for oxidation of phenol-amine HL^{Benz} ($R = CH_2Ph$).[1]

Figure 1 shows the CV curve of the simplest phenol-amine studied by Thomas et al., HL^{Benz}, together with chemical structures of the various forms of the phenol and phenoxyl radical. The CV curve was modeled using DigiSim and involved transfer coefficients, redox potentials, heterogeneous electron-transfer rate constants (e.g. $k_{1\to 2}$), and subsequent proton-transfer rate constants (e.g. $k_{2\to 3}$). The peak potential of the oxidation wave ($E_{p(a)}$) is cited as 0.48 V less positive than that for the related 2,4,6-tri-*tert*-butylphenol, which does not contain an intramolecular hydrogen bond.[1] The explanation for the very large difference in redox potentials between the two phenols, $0.48\ V = 46\ kJ\,mol^{-1}$, was that “the hydrogen bonding increases the electron density on the phenolic oxygen making it easier to be oxidized.” A thermochemical cycle (Scheme 1) shows that the shift in potential results (in this model) from the *difference* in the strength of the hydrogen bond between the phenol-amine and the (phenol radical cation)-amine. A value of 46 $kJ\,mol^{-1}$ would be a large *total* hydrogen-bond energy and would be a very large difference between two structurally similar OH···N hydrogen bonds.



Scheme 1. Thermochemical cycle showing the influence of hydrogen-bonding on redox potentials. R = Aryl, *F* = Faraday constant.

Thermochemically, it is much more likely that the electrochemical oxidation occurring at $E_{p(a)}$ forms the radical in which the proton has transferred, **1**→**3**. Phenol radical cations such as **2** are extremely acidic, with pK_a values of less than 0 in aqueous solution.[2] Ammonium cations have pK_a values of approximately 10–11 in aqueous solution.[3] Proton transfer from a phenol radical cation to an amine, such as the intramolecular proton transfer **2**→**3**, is thus very favorable. The equilibrium constant (K_{eq}) value of 10^{10} in water serves

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[*] Dr. I. J. Rhile, Prof. J. M. Mayer
Department of Chemistry
University of Washington
Box 351700, Seattle, WA 98195-1700
(USA)
Fax: (+1) 206-543-2086
E-mail: mayer@chem.washington.edu

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as an estimate for $K_{eq}(\mathbf{2}\rightleftarrows\mathbf{3})$ in CH_2Cl_2. The $K_{eq}(\mathbf{2}\rightleftarrows\mathbf{3})$ value of $10^{3.3}$ derived by Thomas et al. from simulation of the CV curve[1] does not appear to be reasonable for proton transfer from a phenol radical cation to an amine.[2b] The K_{eq}-$(\mathbf{2}\rightleftarrows\mathbf{3})$ value of about 10^{10} implies that **3** is more stable than **2** by $\Delta\Delta G^{\circ} \approx -57\,\text{kJ}\,\text{mol}^{-1}$, which is close to the difference of $-46\,\text{kJ}\,\text{mol}^{-1}$ observed between the oxidation potentials of **1** and 2,4,6-tri-*tert*-butylphenol.[4]

Besides the thermodynamic issues, the CV simulation yields remarkably slow proton-transfer rates. The model yields downhill proton-transfer rate constants for $\mathbf{2}\rightarrow\mathbf{3}$ and $\mathbf{4}\rightarrow\mathbf{1}$ of $10^{7.4\pm0.5}\,\text{s}^{-1}$ and $10^{5.3\pm0.1}\,\text{s}^{-1}$, respectively,[1] equivalent to half-lives of 30 ns and 3 μs. We know of no precedent for such long timescales for simple exoergic proton transfer within a hydrogen bond between electronegative atoms, as in **2** and **4**. Proton transfers from oxygen to nitrogen are extremely facile and occur almost without a barrier.[5] A rate constant of $10^{5.3\pm0.1}\,\text{s}^{-1}$ would indicate a remarkably large proton-transfer energetic barrier, $\Delta G^{\neq} = 43\,\text{kJ}\,\text{mol}^{-1}$. Excited-state proton-transfer reactions occur on ultrafast timescales (picosecond and subpicosecond).[6] It is not reasonable to assign the low chemical rate constants from the CV simulation to exoergic proton-transfer reactions.

Thus, for both kinetic and thermodynamic reasons, the large peak separation in the CV curve of **1** is unlikely to be a result of an electrochemical mechanism in which the chemical step is proton transfer from **2** to **3**. Similar arguments apply to the oxidations of other phenols in the communication. The electrochemistry of other hydrogen-bonded phenols in acetonitrile show various shapes of CV curves and have usually been interpreted as phenol–amine$-e^{-}\rightarrow$phenoxyl–ammonium, similar to $\mathbf{1}\rightarrow\mathbf{3}$.[7] Quasi-reversible CV curves can typically be simulated with more than one kinetic model, so other data are required to corroborate a mechanism.[8] A number of effects could be responsible for the shape of the CV traces reported in Reference [1]. Methylene chloride is not regarded as an ideal solvent for electrochemical measurements because of its low dielectric constant, its propensity for ion pairing, and its high resistance.[9] Slow heterogeneous electron-transfer kinetics, owing to the solvent or other factors, could affect the shape of the CV curve.[10] If electron transfer to the electrode is concerted with intramolecular proton transfer—a proton-coupled electron-transfer (PCET) reaction[11]—it could display slow kinetics. Hammarström and coworkers[12] and ourselves[7b] have found that homogeneous electron-transfer reactions of related systems occur by concerted PCET with large intrinsic energetic barriers.

In conclusion, the oxidations of hydrogen-bonded phenols reported by Thomas et al.[1] are very interesting models for biochemical tyrosine oxidations, but thermodynamic and kinetic arguments raise serious questions about the mechanistic interpretation of the cyclic voltammetry data.

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[4] Agreement between the $\Delta\Delta G^{\circ}$(proton transfer) value and the shift in potential would likely be better if $E_{1/2}$ values were used and if the $\Delta\Delta G^{\circ}$ values were derived from pK_a values in the same solvent.

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