

Conformational Change with Steric Interactions Affects the Inner Sphere Component of Concerted Proton–Electron Transfer in a Pyridyl-Appended Radical Cation System

Evan A. Welker,[†] Brittney L. Tiley,[†] Crina M. Sasaran,[†] Matthew A. Zuchero,[†] Wing-Sze Tong,[†] Melissa J. Vettleson,[†] Robert A. Richards,[†] Jonathan J. Geruntho,[†] Stefan Stoll,[‡] Jeffrey P. Wolbach,^{*,§} and Ian J. Rhile^{*,†}

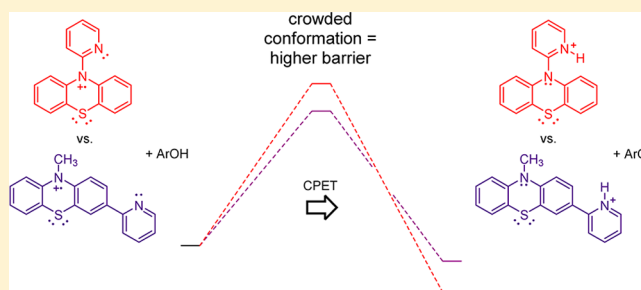
[†]Department of Chemistry and Biochemistry, Albright College, Reading, Pennsylvania 19610-5234, United States

[‡]Department of Chemistry, University of Washington, Seattle, Washington 98195-1700, United States

[§]Eurofins Lancaster Laboratories, Lancaster, Pennsylvania 17601, United States

S Supporting Information

ABSTRACT: Proton-coupled electron transfer (PCET) model systems combine one-electron oxidants and bases to generate net hydrogen atom acceptors. We have generated two persistent pyridyl-appended radical cations: 10-(pyrid-2-yl)-10H-phenothiazinium (**PPT**^{•+}) and 3-(pyrid-2-yl)-10-methyl-10H-phenothiazinium (**MPTP**^{•+}). EPR spectra and corresponding calculations indicate phenothiazinium radical cations with minimal spin on the pyridine nitrogen. Addition of hindered phenols causes the radical cations to decay, and protonated products and the corresponding phenoxyl radicals to form. The ΔG° values for the formation of intermediates (determined through cyclic voltammetry and pK_a measurements) rule out a stepwise mechanism, and kinetic isotope effects support concerted proton–electron transfer (CPET) as the mechanism. Calculations indicate that the reaction of **PPT**^{•+} + ^tBu₃PhOH undergoes a significant conformational change with steric interactions on the diabatic surface while maintaining the hydrogen bond; in contrast, **MPTP**^{•+} + ^tBu₃PhOH maintains its conformation throughout the reaction. This difference is reflected in both experiment and calculations with $\Delta G_{\text{MPTP}^{\bullet+}}^\ddagger < \Delta G_{\text{PPT}^{\bullet+}}^\ddagger$ despite $\Delta G_{\text{MPTP}^{\bullet+}}^\circ > \Delta G_{\text{PPT}^{\bullet+}}^\circ$. Experimental results with 2,6-di-*tert*-butyl-4-methoxyphenol are similar. Hence, despite the structural similarity between the compounds, differences in the inner sphere component for CPET affect the kinetics.



INTRODUCTION

Radical chemistry is a dominant paradigm in organic chemistry, and hydrogen atom transfer (HAT) is an important mechanism in this paradigm. In HAT, the H⁺ and e⁻ transfer from the same bond. HAT has been contrasted to concerted proton–electron transfer (CPET) for which the H⁺ is transferred between lone pairs in a hydrogen bond and the e⁻ is transferred between different orbital systems.¹ Some examples include reactions with phenols,² oximes,³ flavins,⁴ tryptophan,⁵ guanosine,⁶ and structurally related compounds. CPET also extends to cases not usually considered as HAT, such as reactions for which the H⁺ and e⁻ are transferred to or from multiple reagents, sites, or orbitals, and is sometimes qualified with “bidirectional”.⁷ (However, the orbital distinction between CPET and HAT can be ambiguous,⁸ and it has been suggested that the degree of nonadiabaticity is a better criterion.⁹)

Tethering a one-electron oxidant and a base generates a reagent that is capable of undergoing CPET. Several groups are using these systems to investigate what structures allow for CPET and how the structure affects the rate and thermody-

namics for the reactions. For example, insertion of a spacer between the oxidant and base¹⁰ or increasing the distance of H⁺ transfer¹¹ slows the overall kinetics. Here we describe two radical cations with appended bases (**PPT**^{•+} and **MPTP**^{•+}, Figure 1) and investigate their reactivity with hindered phenols. (Hindered phenols were employed since the corresponding phenoxyl radicals are persistent and do not appear to couple with the radical cations or each other. They are common reaction partners in studies of CPET, in part because they are hydrogen bond donors and because they have high-energy intermediates for the potential stepwise mechanisms.^{8b}) As described below, **PPT**^{•+} undergoes a significant conformational shift during its reaction with hydrogen atom donors; this conformational shift results in a larger barrier for reaction compared with **MPTP**^{•+}, which does not undergo as dramatic a shift. This is interpreted as a difference in the inner sphere reorganization, in parallel to electron transfer.

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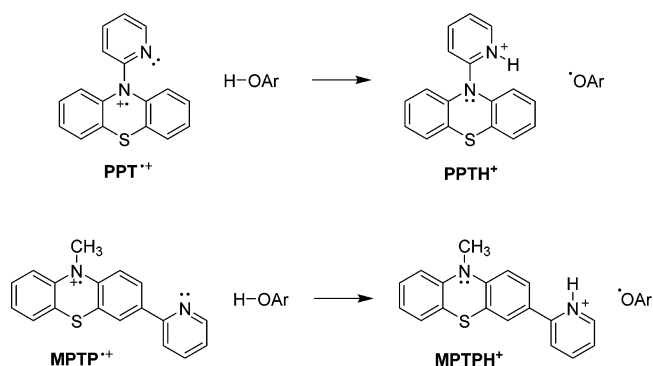


Figure 1. Reactions with 10-(2-pyridyl)-10*H*-phenothiazinium (PPT^{•+}) and 3-(pyrid-2-yl)-10-methyl-10*H*-phenothiazinium (MPTP^{•+}).

RESULTS

The radical cations were synthesized by palladium-catalyzed couplings and one-electron oxidation. Radical cation precursor 10-(pyridin-2-yl)-10*H*-phenothiazine (PPT)¹² was synthesized by a Buchwald–Hartwig amination,¹³ and 3-(pyrid-2-yl)-10-methyl-10*H*-phenothiazine (MPTP) was synthesized from the known pinacol borane¹⁴ via a Suzuki coupling.¹⁵ Cyclic voltammetry (CV) of the neutral compounds provided a reversible wave at 0.39 ± 0.03 and 0.32 ± 0.03 V, for PPT^{•+/0} and MPTP^{•+/0}, respectively, vs Cp₂Fe⁺⁰ in 0.1 M NBu₄PF₆ in MeCN (Figures S6 and S7). Similar systems undergo reversible CV.¹⁶ Forming the radical cations in solution requires an oxidant with a reduction potential higher than that of the radical cation–neutral pair. Lewis acidic oxidants such as metal ions and other strong electrophiles (e.g., NO⁺) reacted with the pyridine lone pair. Oxidations with limiting tris(4-bromophenyl)aminium hexafluorophosphate ($E = 0.67$ V vs Cp₂Fe⁺⁰; $E_{\text{rxn}} = 0.28$ V $\equiv K_{\text{eq}} = 5.2 \times 10^4$ for $\text{NAr}^{\text{Br}_3\text{•}+} + \text{PPT} \rightleftharpoons \text{NAr}^{\text{Br}_3} + \text{PPT}^{\bullet+}$; and $E_{\text{rxn}} = 0.35$ V $\equiv K_{\text{eq}} = 1.2 \times 10^8$ for $\text{NAr}^{\text{Br}_3\text{•}+} + \text{MPTP} \rightleftharpoons \text{NAr}^{\text{Br}_3} + \text{MPTP}^{\bullet+}$) provide colored solutions, red for PPT^{•+} and purple for MPTP^{•+}. Absorptions at 515 ($\epsilon = 1.0 \times 10^4$), 779 (1.5×10^3), and 890 nm (1.4×10^3 M⁻¹ cm⁻¹) for PPT^{•+} (Figure S2) and 580 (9.8×10^3), 779 (2.0×10^3), and 864 nm (1.9×10^3 M⁻¹ cm⁻¹) in MeCN for MPTP^{•+} (Figure S5) in the UV–vis spectrum are indicative of phenothiazinium radical cations.¹⁸ Solutions of PPT^{•+} at ≤ 10 mM maintain their absorbance in the UV–vis over several days in air (loss of absorbance per day ~ 2 –3%). EPR spectra were recorded in CH₂Cl₂ (Figure S9 and Tables S1 and S2), and ¹H NMR spectra in CD₃CN are silent. The persistence of the radical cation echoes that of substituted phenothiazinium¹⁹ and related aminium radical cations²⁰ in the presence of pyridine.

Hindered phenols were employed as hydrogen atom donors (Figure 1). Addition of excess 2,4,6-tri-*tert*-butylphenol (^tBu₃PhOH, 1–10 mM) to the radical cations (0.1–0.3 mM) in CH₃CN causes a decay in the absorptions and appearance of peaks for ^tBu₃PhO• at 400 and 626 nm.²¹ For PPT^{•+}, the resulting solutions were colorless with no significant absorptions for PPTH⁺; the concentration of ^tBu₃PhO• was small enough to not provide visible color. For MPTP^{•+}, resulting solutions are intensely yellow corresponding to MPTPH⁺ ($\lambda_{\text{max}} = 415$ nm, $\epsilon = 9.6 \times 10^3$ M⁻¹ cm⁻¹), confirmed by the protonation of MPTP with dimethylformamide–triflic acid complex. The decay was monitored by stopped flow under pseudo-first-order conditions. Rate constants were determined through global fitting. Plots of k_{obs}

vs the concentration of phenol in excess provided second-order rate constants: 12 ± 1 and 790 ± 80 M⁻¹ s⁻¹ for PPT^{•+} and MPTP^{•+}, respectively. Similar kinetics with ^tBu₃PhOD provide kinetic isotope effects: $k_{\text{D,PPT}^{\bullet+}} = 4.7 \pm 0.5$ M⁻¹ s⁻¹ $\equiv k_{\text{H}}/k_{\text{D}} = 2.6 \pm 0.4$; $k_{\text{D,MPTP}^{\bullet+}} = 90 \pm 9$ M⁻¹ s⁻¹ $\equiv k_{\text{H}}/k_{\text{D}} = 8.7 \pm 1.2$. Activation parameters were determined for PPT^{•+} + ^tBu₃PhOH over a range of 13.4–62.6 °C: $\Delta H^\ddagger = 7.5 \pm 0.3$ kcal mol⁻¹ and $\Delta S^\ddagger = -28.4 \pm 0.9$ cal K⁻¹ mol⁻¹. Similar kinetics using 2,6-di-*tert*-butyl-4-methoxyphenol (^tBu₂(OMe)PhOH) as the hydrogen donor afford rate constants of $(7.5 \pm 0.7) \times 10^3$ and $(9.0 \pm 0.9) \times 10^4$ M⁻¹ s⁻¹ for PPT^{•+} and MPTP^{•+}, respectively.

Additional experiments provide thermodynamic parameters. An acid–base equilibration study with thymol blue ($\text{p}K_{\text{a}} = 13.4$)²² and PPT provided $\text{p}K_{\text{a}}[\text{PPT}\{\text{H}^+/0\}] = 10.9 \pm 0.2$. Addition of triflic acid to PPT in electrolyte solution caused a shift in the CV attributed to PPTH^{2+/+} at 0.67 V. (CVs of protonated 10-ammoniumalkyl-10*H*-phenothiazines are reversible, even in water.²³) An equilibration study with tris(4-tolyl)aminium ($E = 0.38$ V)¹⁷ provides an equilibrium constant of 0.63, consistent with $E[\text{PPT}^{\bullet+}/0] = 0.39$ V. These data provide an effective bond dissociation free energy (BDFE) for PPTH⁺ → PPT^{•+} + H• of 79 ± 1 kcal/mol. The $\text{p}K_{\text{a}}$ of MPTP^{•+/0} was determined by titration with pyridinium ($\text{p}K_{\text{a}} = 12.6$)²³ and monitoring the growth of MPTPH⁺ to provide $\text{p}K_{\text{a}} = 11.9$. Further parallel experiments provided $E[\text{MPTPH}^{2+/+}] = 0.51$ V and the effective BDFE for MPTPH⁺ → MPTP^{•+} + H• of 79 ± 1 kcal/mol. The kinetic and thermodynamic data are summarized in Table 1.

Table 1. Experimental and Calculated Parameters for Radical Cations

	PPT ^{•+}	MPTP ^{•+}
$\text{p}K_{\text{a}}(\text{XPTH}^+ \rightarrow \text{XPT} + \text{H}^+)$	10.9 ± 0.1	11.9 ± 0.1
$E(\text{XPT}^{\bullet+}/0, \text{V})$	0.39 ± 0.03	0.32 ± 0.01
BDFE (kcal/mol)	78.8 ± 0.8	78.6 ± 0.8
$E(\text{XPTH}^{2+/+}, \text{V})$	0.67 ± 0.03	0.51 ± 0.03
$k_{2,4,6\text{-}^t\text{Bu}_3\text{PhOH}} (\text{M}^{-1} \text{s}^{-1})$	12 ± 1	790 ± 80
$k_{2,4,6\text{-}^t\text{Bu}_3\text{PhOD}} (\text{M}^{-1} \text{s}^{-1})$	4.7 ± 0.5	90 ± 9
$k_{\text{H}}/k_{\text{D}}$	2.6 ± 0.4	8.7 ± 1.2
$k_{2,6\text{-}^t\text{Bu}_2(\text{MeO})\text{PhOH}} (\text{M}^{-1} \text{s}^{-1})$	7.5×10^3	9×10^4

Since PPT^{•+}, MPTP^{•+}, and MPTPH⁺ have significant absorptions in the visible region, several equilibration experiments were performed between the sets of compounds to determine proton, electron, and proton–electron equilibrium constants (Table 2). For example, an equilibration experiment provides an alternate method to find the BDFE for MPTPH⁺. The equilibrium constant for ^tBu₃PhOH + MPTP^{•+} \rightleftharpoons ^tBu₃PhO• + MPTPH⁺ of 9.8 ± 0.9 provides $\Delta G^\circ = -1.1 \pm 0.1$ kcal/mol, and the literature BDFE for ^tBu₃PhOH of 77.1 kcal/mol^{8b} provides a consistent BDFE of 78.8 ± 1.3 kcal/mol.

Table 2. Experimentally Determined Equilibrium Constants and ΔG°

equilibrium	K_{eq}	ΔG° (kcal/mol)
$\text{PPT} + \text{MPTPH}^+ \rightleftharpoons \text{PPTH}^+ + \text{MPTP}$	0.17	-1.1 ± 0.1
$\text{PPT} + \text{MPTP}^{\bullet+} \rightleftharpoons \text{PPT}^{\bullet+} + \text{MPTP}$	0.031	-2.1 ± 0.1
$\text{PPTH}^+ + \text{MPTP}^{\bullet+} \rightleftharpoons \text{PPT}^{\bullet+} + \text{MPTPH}^+$	0.32	-0.7 ± 0.1
$\text{MPTP}^{\bullet+} + ^t\text{Bu}_3\text{PhOH} \rightleftharpoons \text{MPTPH}^+ + ^t\text{Bu}_3\text{PhO}^\bullet$	9.8	1.4 ± 0.1

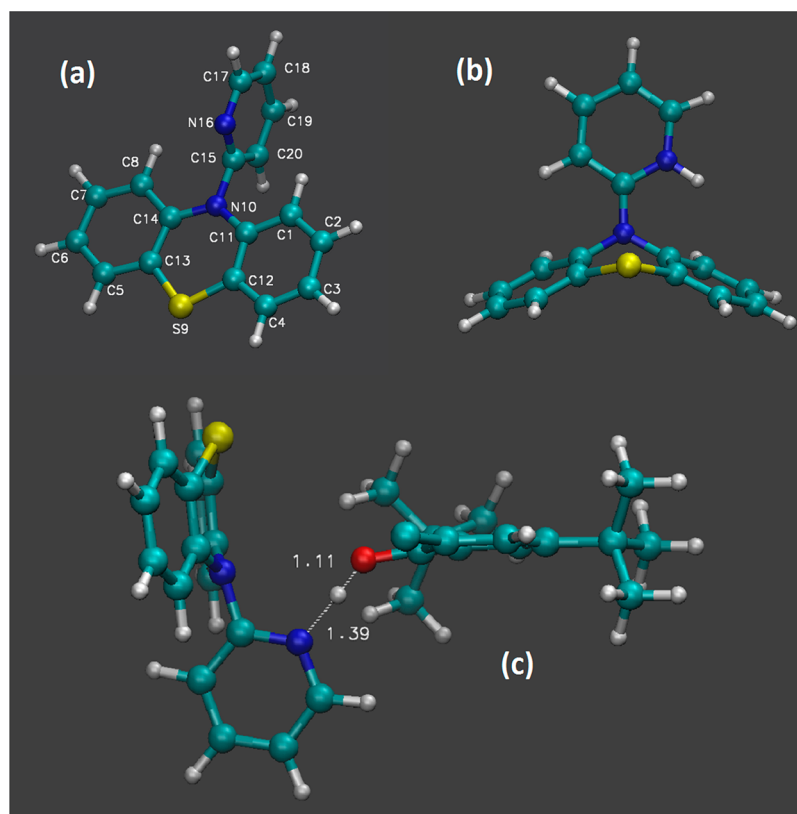


Figure 2. (a) $\text{PPT}^{\bullet+}$ with numbering, (b) PPTH^+ , and (c) calculated TS for $\text{PPT}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH} \rightarrow \text{PPTH}^+ + {}^t\text{Bu}_3\text{PhO}^\bullet$. One *tert*-butyl group has been truncated to a single carbon to aid in visualizing the TS geometry.

(Reactions with $\text{PPT}^{\bullet+}$ were slow to come to equilibrium at the appropriate concentrations to measure the corresponding equilibrium constant.)

Calculations were performed on the radical cations, the protonated products, ${}^t\text{Bu}_3\text{PhOH}$, and both pre- and post-reaction hydrogen bonded complexes (i.e., ${}^t\text{Bu}_3\text{PhOH} \cdots \text{PPT}^{\bullet+}$, ${}^t\text{Bu}_3\text{PhO}^\bullet \cdots \text{PPTH}^+$, ${}^t\text{Bu}_3\text{PhOH} \cdots \text{MPTP}^{\bullet+}$, and ${}^t\text{Bu}_3\text{PhO}^\bullet \cdots \text{MPTPH}^+$). In addition, the classical transition states (TS) were located. All calculations were performed in Gaussian 09²⁴ using the B972 model chemistry²⁵ and the 6-31+G(d,p) basis set.²⁶

The pyridine ring of $\text{PPT}^{\bullet+}$ is orthogonal to the planar phenothiazine ring (Figure 2) as in other 10-aryl-10H-phenothiazinium radical cations.²⁷ The conformations of 9-phenylanthracene and related compounds are similar.²⁸ The singly occupied molecular orbital (SOMO) contains significant electron density on the phenothiazine ring but negligible density on the pyridine ring. (A more complete analysis of the molecular orbitals and spin densities appears in the Supporting Information.) The EPR spectrum has a small hyperfine coupling for the pyridyl N (2.75–3.00 MHz), indicating a 0.5–0.6% spin population on it; DFT calculations are consistent with this value. Figure S28 displays the spin density of $\text{PPT}^{\bullet+}$, contoured at an isovalue of 0.0025 au; the spin density is completely confined to the phenothiazine ring at this level. Qualitatively, the planar conformation allows the charge and spin density to be delocalized over the phenothiazine ring with minimal steric interaction with the hydrogens at positions 1 and 8. In PPTH^+ , the phenothiazine N has pyramidalized. The phenothiazine is boat-like with the pyridine pseudoaxial, and the pyridine no longer bisects the phenothiazine ring. This

conformation parallels many neutral 10-aryl-10H-phenothiazines.²⁹ The progression of the backbone conformational change during the CPET reaction is illustrated in Figures S30 and S31.

The TS geometry is intermediate between PPT and PPTH^+ . The phenothiazine ring at the TS resembles the boat-like phenothiazine geometry of PPTH^+ . However, the pyridine ring remains orthogonal as in $\text{PPT}^{\bullet+}$, but pseudoequatorial instead of pseudoaxial. This conformation is required to maintain the hydrogen bond while minimizing steric clashing with ${}^t\text{Bu}_3\text{PhO}^\bullet$; the smallest *tert*-butyl hydrogen–sulfur distance is 3.42 Å, only slightly larger than what is expected from van der Waals radii. Vibrational frequency evaluation of the TS produced a single imaginary frequency (882.5 cm^{-1}). No stationary point was found for placing the pyridine in the pseudoaxial position. Starting from isolated ${}^t\text{Bu}_3\text{PhOH}$ and $\text{PPT}^{\bullet+}$, the calculated *in vacuo* ΔG^\ddagger is 14.7 kcal/mol, including a basis set superposition error of 1.8 kcal/mol. Static solvation of the *in vacuo* isolated reactant and TS geometries with the SMD³⁰ implicit solvation model resulted in a calculated ΔG^\ddagger of 21.8 kcal/mol. Calculations also were performed on the stable intermediates for both electron transfer (ET) and proton transfer (PT). Solvating the *in vacuo* optimized geometries of each reactant and stable intermediate with the SMD implicit solvation model provides $\Delta G_{\text{PT}} = 34.8$ kcal/mol (190.7 kcal/mol *in vacuo*) and $\Delta G_{\text{ET}} = 10.5$ kcal/mol (14.5 kcal/mol *in vacuo*). The value for *in vacuo* PT is extremely high due to charge-separation in the gas phase in contrast to ET or CPET.

The analogous reaction with $\text{MPTP}^{\bullet+}$ proceeds with a much less significant conformational change (Figure 3). The phenothiazine ring of $\text{MPTP}^{\bullet+}$ is nearly planar, and the

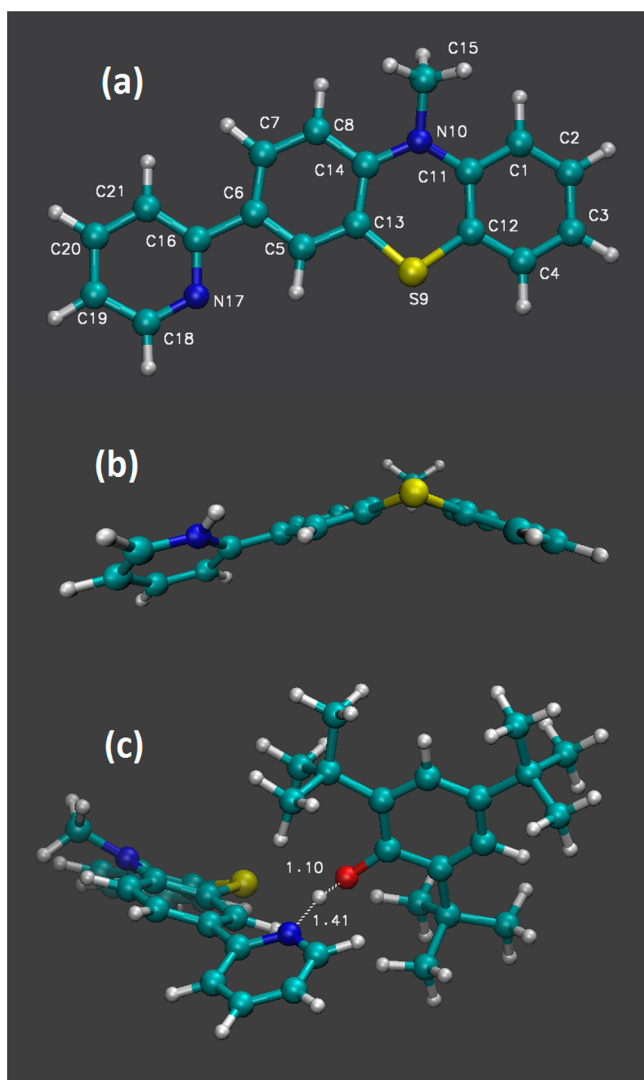


Figure 3. (a) $\text{MPTP}^{\bullet+}$ with numbering, (b) MPTPH^+ , and (c) calculated TS for $\text{MPTP}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH} \rightarrow \text{MPTPH}^+ + {}^t\text{Bu}_3\text{PhO}^\bullet$.

pyridine and phenothiazine rings are nearly coplanar in the radical cation, in contrast to the orthogonal positioning in $\text{PPT}^{\bullet+}$. Optimizations started with the pyridine orthogonal to the phenothiazine system resulted in the described pseudoplanar geometry. Experimentally, the hyperfine coupling to the phenothiazine nitrogen and the attached methyl group dominate the EPR spectrum, although a small amount of spin density is present on the attached, coplanar pyridine in the calculation (Figure S29). As for PPTH^+ , the phenothiazine ring of MPTPH^+ is boat-like, but the methyl group is in the pseudoequatorial position. The pyridine ring in MPTPH^+ is tilted relative to the attached phenothiazine, occupying a position neither coplanar nor orthogonal to the phenothiazine ring.

In the TS, the geometry of the acceptor component remains similar to MPTPH^+ . The phenothiazine ring is boat-like at the TS, the phenothiazine methyl is pseudoequatorial, and the pyridine is tilted out of the plane of the phenothiazine with a $\text{N}_{17}\text{--C}_{16}\text{--C}_6\text{--C}_5$ torsion angle of 39.4° . The transferring hydrogen remains closer to the O with $\text{O}\cdots\text{H}$ and $\text{N}\cdots\text{H}$ distances of 1.10 and 1.41 Å, respectively. These distances are similar to those at the TS for ${}^t\text{Bu}_3\text{PhOH} + \text{PPT}^{\bullet+}$. Vibrational

frequency evaluation of the ${}^t\text{Bu}_3\text{PhOH}\cdots\text{MPTP}^{\bullet+}$ TS produced a single imaginary frequency (709.3 cm^{-1}). Starting from isolated ${}^t\text{Bu}_3\text{PhOH}$ and $\text{MPTP}^{\bullet+}$, the calculated *in vacuo* ΔG^\ddagger is 10.1 kcal/mol (basis set superposition error 1.5 kcal/mol) and the solvated ΔG^\ddagger is 21.8 kcal/mol; calculations on the stable intermediates, including solvation, for both ET and PT provide $\Delta G_{\text{PT}} = 27.0$ kcal/mol (170.6 kcal/mol *in vacuo*) and $\Delta G_{\text{ET}} = 12.9$ kcal/mol (16.9 kcal/mol *in vacuo*).

DISCUSSION

In this work, two persistent and structurally similar base-appended radical cations are reacted with hindered phenols as hydrogen atom donors to explore the mechanism and compare the two compounds. Each compound combines a phenothiazinium radical cation and a pyridine, and hence each has the components to accept an e^- and a H^+ . We will consider the mechanism for the two sets of reactions and then compare the two cases.

From experimental and literature data,^{8b,31} ΔG° for ET and PT intermediates can be estimated and the ΔG^\ddagger can be calculated (from the Eyring equation) to explore the mechanism (see Table 3 and Experimental Section). The

Table 3. Experimental and Computational Free Energies (kcal/mol)

reactant pair	experimental			computational		
	ΔG^\ddagger	$\Delta G_{\text{ET}}^\circ$	$\Delta G_{\text{PT}}^\circ$ (est.)	ΔG^\ddagger	$\Delta G_{\text{ET}}^\circ$	$\Delta G_{\text{PT}}^\circ$ ^a
$\text{PPT}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH}$	15.9	18.2	29.9	14.7	14.5	34.8
$\text{PPT}^{\bullet+} + {}^t\text{Bu}_2(\text{OMe})\text{PhOH}$	12.1	14.3	32.6			
$\text{MPTP}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH}$	13.4	19.8	26.4	10.1	16.9	27.0
$\text{MPTP}^{\bullet+} + {}^t\text{Bu}_2(\text{OMe})\text{PhOH}$	10.7	15.9	29.2			

^aCalculated including implicit solvation.

data indicate ΔG_{ET} for $\text{PPT}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH} \rightarrow \text{PPT} + {}^t\text{Bu}_3\text{PhOH}^{\bullet+}$ of 18.2 ± 1.4 kcal/mol and an estimated ΔG_{PT} for $\text{PPT}^{\bullet+} + {}^t\text{Bu}_3\text{PhOH} \rightarrow \text{PPTH}^{2+} + \text{Bu}_3\text{PhO}^-$ of 29.9 kcal/mol. These ΔG° values are larger than the measured ΔG^\ddagger of 15.9 ± 0.7 kcal/mol. The corresponding data for ${}^t\text{Bu}_2(\text{OMe})\text{PhOH} + \text{PPT}^{\bullet+}$ are similar: $\Delta G_{\text{ET}} = 14.3 \pm 1.4$ kcal/mol; $\Delta G_{\text{PT}} \approx 32.6$ kcal/mol; $\Delta G^\ddagger = 12.1 \pm 0.7$ kcal/mol. $\text{MPTP}^{\bullet+}$ has a similar pattern for the corresponding values: For reaction with ${}^t\text{Bu}_3\text{PhOH}$, $\Delta G^\ddagger = 13.4 \pm 0.7$ kcal/mol, $\Delta G_{\text{ET}} = 19.8 \pm 1.4$ kcal/mol, and $\Delta G_{\text{PT}} \approx 26.4$ kcal/mol, and with ${}^t\text{Bu}_2(\text{OMe})\text{PhOH}$, $\Delta G^\ddagger = 10.7 \pm 0.7$ kcal/mol, $\Delta G_{\text{ET}} = 15.9 \pm 1.4$ kcal/mol, and $\Delta G_{\text{PT}} \approx 29.2$ kcal/mol; these data are summarized in Table 3. These data suggest that CPET is the mechanism. (While ΔG_{ET} is close to being within error of the experiment, ET is unlikely to be barrierless.) Experimentally, $\Delta G^\ddagger < \Delta G_{\text{ET}}^\circ \ll \Delta G_{\text{PT}}^\circ$; the computed *in vacuo* values for $\Delta G_{\text{ET}}^\circ$ and ΔG^\ddagger , and the computed solvated value of $\Delta G_{\text{PT}}^\circ$ are in reasonable agreement. The computed *in vacuo* difference between the barriers ($\Delta\Delta G^\ddagger$) of 4.6 kcal/mol echoes the experimental results (2.5 kcal/mol), with $\text{MPTP}^{\bullet+}$ reacting with a smaller barrier; including the effects of solvation in the calculations results in the barriers for both reactions being equal.

The kinetic isotope effects for the reactions with ${}^t\text{Bu}_3\text{PhOH}$ of 2.6 ± 0.4 and 8.9 ± 1.2 for $\text{PPT}^{\bullet+}$ and $\text{MPTP}^{\bullet+}$, respectively, indicate that the proton is involved in the rate-determining step. The latter value is likely out of the classical range³²

suggesting a tunneling event, although measured kinetic isotope effects vary from small (~ 2)³³ to very large (>400)³⁴ for CPET reactions.³⁵ The difference between the two systems could be ascribed to a balance among several factors (e.g., hydrogen vibrational wave function overlap, frequency, reorganization energy, and ΔG°)^{1a,36} and cannot be separated with the reported experimental and computational data.

Despite reactions with the $\text{MPTP}^{\bullet+}$ occurring with lower barriers than those with $\text{PPT}^{\bullet+}$, the $\text{MPTP}^{\bullet+}$ reactions are less favored thermodynamically. The ΔG° for the reaction can be determined in two ways from the thermodynamic data. (1) Using the $E[\text{XPT}^{\bullet+}/0]$ and $\text{p}K_a[\text{XPT}\{\text{H}^{+/0}\}]$ values, one obtains BDFEs of 79.1 ± 0.8 and 78.6 ± 0.8 kcal/mol, respectively, for $\text{PPTH}^+ \rightarrow \text{PPT}^{\bullet+} + \text{H}^\bullet$ and $\text{MPTPH}^+ \rightarrow \text{MPTP}^{\bullet+} + \text{H}^\bullet$, implying that the reactions with the phenols are 0.5 ± 1.6 kcal/mol ($\Delta\Delta G^\circ$) further downhill for $\text{PPT}^{\bullet+}$ compared with $\text{MPTP}^{\bullet+}$. (2) A direct and more precise comparison can be determined from the equilibrium constant for $\text{PPTH}^+ + \text{MPTP}^{\bullet+} \rightleftharpoons \text{PPT}^{\bullet+} + \text{MPTPH}^+$; $K_{\text{eq}} = 0.32$ implies $\Delta\Delta G^\circ = 0.7 \pm 0.1$ kcal/mol. (This is also consistent with the value determined from combining the ET and PT equilibria, providing $\Delta\Delta G^\circ = 1.0 \pm 0.3$ kcal/mol.) The difference in the activation energies for reaction $\Delta\Delta G^\ddagger$ follow the reverse trend, -2.5 ± 1.4 kcal/mol for reaction with ${}^t\text{Bu}_3\text{PhOH}$ and -1.4 ± 1.4 kcal/mol for reaction with ${}^t\text{Bu}_2(\text{OMe})\text{PhOH}$. For most CPET reactions with reagents of similar structure, the driving force and activation energy are correlated for similar reactions, with a lower activation energy for a more exergonic reaction such as in a Marcus relationship.³⁷ Hence, although both $\text{PPT}^{\bullet+}$ and $\text{MPTP}^{\bullet+}$ have a pyridine appended to a phenothiazinium radical cation, the order of activation energies is reversed.

The contrast between the geometry changes for the two systems explains the mismatch between the driving force of reaction and kinetics. As in other 10-aryl-10H-phenothiazine radical cations,²⁷ the calculations suggest that the pyridine ring of $\text{PPT}^{\bullet+}$ is orthogonal to the phenothiazine ring. This conformation allows for maximum overlap in the phenothiazine π system including the N p-type orbital.²⁷ The molecule resembles 10-phenylanthracene, which has a similar orthogonal conformation and a large barrier (>20 kcal/mol) to rotation with a distorted TS.²⁸ The nitrogen pyramidalizes upon accepting the e^- as in neutral, closed-shell phenothiazines.²⁹ This is reflected in the TS with a partially pyramidalized N. The hydrogen bond between ${}^t\text{Bu}_3\text{PhOH}$ and $\text{PPT}^{\bullet+}$ must be maintained for the H^+ to be transferred, and hence placing the pyridine in the pseudoaxial position would produce severe steric interactions for the phenothiazine ring and the *tert*-butyl groups. The pyridine is thus forced into the crowded pseudoequatorial position in the TS. In contrast, the geometry of $\text{MPTP}^{\bullet+}$ closely resembles that of MPTPH^+ with fewer constraints at the TS. That the $\text{MPTP}^{\bullet+}$ reactions are inherently faster than the $\text{PPT}^{\bullet+}$ reactions despite a lower driving force suggests that the inner sphere reorganization reflected in the conformational changes are the best explanation for the differences in these compounds, paralleling similar effects in electron transfer reactivity.³⁸ (However, the calculations reflect a diabatic surface, while the CPET reaction is likely to be nonadiabatic.)

Recently, distances between electron donating and accepting sites have been related to kinetics, with an increased distance slowing the reaction.¹⁰ In the CPET reactions presented here, the distances between electron donating and accepting sites and

between proton donating and accepting sites are not significantly different. The electron transfer distance is difficult to compare; however, the pyridine ring acts as a discrete spacer between the phenothiazine and the phenols for both the $\text{PPT}^{\bullet+}$ and $\text{MPTP}^{\bullet+}$ radical cations. Furthermore, the frontier orbitals are similar in terms of contributions between the two components.

In conclusion, a persistent pyridyl-appended radical cation abstracts a net hydrogen atom from a phenol by CPET, with separate sites for accepting the H^+ and e^- . The systems have different conformation changes: reaction with $\text{PPT}^{\bullet+}$ requires a more constrained TS than for $\text{MPTP}^{\bullet+}$, and this difference in inner-sphere reorganization increases the TS energy.

EXPERIMENTAL SECTION

General Considerations. Acetonitrile for kinetics and equilibration studies was purchased dry and used under N_2 . Toluene was either distilled from Na/benzophenone under N_2 or taken from a solvent drying column before use. Methylene chloride was taken from a solvent drying system. Triethylamine was distilled from sodium hydroxide under nitrogen, and 1,4-dioxane was also refluxed and dried over benzophenone and Na under nitrogen. The cyclic voltammogram for 1,3-di-*tert*-butyl-2,5-dimethoxybenzene was taken under nitrogen in a glovebox.

Room-temperature electron paramagnetic resonance (EPR) measurements were taken using 140 μL of solution in a 4 mm o.d. quartz tube. Samples were prepared and filled into quartz tubes in the glovebox and capped with a rubber septum and parafilm, and the EPR spectrum was measured immediately after. Complete analysis of the EPR spectra is given in the Supporting Information.

Synthesis. 2,4,6-Tri-*tert*-butylphenol-O-*d* was synthesized by the procedure of Stack and co-workers.³⁹ 1,3-Di-*tert*-butyl-2,5-dimethoxybenzene was synthesized by deprotonating the phenol with NaH in DMF and alkylating with methyl iodide.⁴⁰ Tri-(*p*-tolyl)aminium hexafluorophosphate and tri-(*p*-bromophenyl)aminium hexafluorophosphate were synthesized using the neutral amine and AgPF_6 and I_2 ⁴¹ or with NOPF_6 .⁴² 10-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10H-phenothiazine was synthesized by the procedure of Müller and co-workers.¹⁴

Synthesis of 10-(Pyridin-2-yl)-10H-phenothiazine.^{43–46} To 25 mL of dry toluene was added phenothiazine (1.794 g, 9.00 mmol), sodium *tert*-butoxide (1.394 g), DPPF (1,1'-bis(diphenylphosphino)ferrocene, 32.2 mg), 2-bromopyridine (0.996 mL, 1.643 g, 10.4 mmol), and $\text{Pd}_2(\text{dba})_3$ (40.2 mg; dba = dibenzylideneacetone), in that order. The reaction was refluxed overnight. Additional $\text{Pd}_2(\text{dba})_3$ (38 mg) and DPPF (30 mg) were added after 24 h, and the mixture was refluxed overnight. The reaction was filtered through silica, which was washed with ethyl acetate, and the solvent was removed under reduced pressure. The compound was subjected to column chromatography (20/1 to 12/1 v/v hexanes/ethyl acetate gradient) to afford a solid (1.829 g, 73.5%). ^1H NMR (300 MHz, CDCl_3 , Figure S1): δ 8.28 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.56 (d, $J = 13.3$ Hz, 2H), 7.52–7.44 (m, 1H), 7.38 (dd, $J = 12.8, 2.0$ Hz, 2H), 7.32–7.24 (m, 2H), 7.18–7.11 (m, 2H), 6.93 (d, $J = 14.1$ Hz, 1H), 6.87 (dd, $J = 11.7, 8.5$ Hz, 1H). Mp 109.6–110.4 $^\circ\text{C}$.⁴⁵ The compound was recrystallized twice to a colorless solid from 1/1 v/v hexanes/ethyl acetate before use in kinetics and equilibration studies.

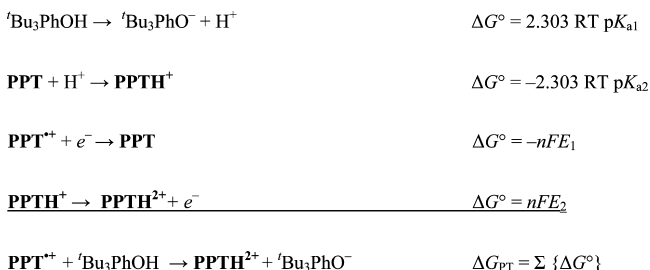
Synthesis of 10-Methyl-3-(pyridin-2-yl)-10H-phenothiazine.¹⁵ A combination of 10-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-10H-phenothiazine (5.6 g, 1.64 mmol), $\text{Pd}_2(\text{dba})_3$ (0.0329 g, 0.0573 mmol), and DPPF (0.0295 g, 0.0532 mmol) was added to a 2.0 M aqueous solution of Na_2CO_3 (2.454 mL) and 2-propanol (12 mL), which was degassed by bubbling with nitrogen. This reaction was stirred and refluxed under nitrogen for 56 h at 70 $^\circ\text{C}$, when the reaction was deemed complete by TLC. Water was added to this reaction mixture, and the organic layer was extracted with three portions of Et_2O . These organic layers were collected, combined, and dried over MgSO_4 . Column chromatography was used to purify the

compound (hexanes/ethyl acetate, 20:1 to 8:1), which results in isolated compound as a solid (0.376 g, 1.26 mmol, 46%). ¹H NMR (300 MHz, CDCl₃, Figure S3) δ 6.66 (m, 1H), 7.87 (m), 7.74 (m), 7.67(m), 7.19 (m), 6.96 (m), 6.89 (m), 3.44 (s, 3H) ppm. ¹³C NMR (400 MHz, CDCl₃, Figure S4) δ 35.4, 114.09, 114.14, 119.6, 121.7, 122.7, 123.1, 123.8, 125.4, 126.0, 127.2, 127.5, 133.7, 136.7, 145.4, 146.5, 149.6, 156.3 ppm. Anal. Calcd for C₁₈H₁₄N₂S: C, 74.45; H, 4.86; N, 9.65. Found: C, 74.06; H, 4.84; N, 9.56.

In Situ Generation of Radical Cation. The radical cation was synthesized by combining a solution of tris(*p*-bromophenyl)aminium hexafluorophosphate and a solution of excess PPT in acetonitrile. Concentrations for kinetics were typically ~0.2 mM in PPT and ~0.1 mM for tris(*p*-bromophenyl)aminium hexafluorophosphate, although concentrations up to 1 mM were stable. The reaction was assumed to reach completion. Higher concentrations of PPT did not affect the kinetics. Solutions for EPR were made similarly in CH₂Cl₂.

Cyclic Voltammetry. Cyclic voltammetry was performed in 0.1 M Bu₄NPF₆ in acetonitrile with a glassy carbon working electrode, Ag/AgNO₃ (0.01 M) reference electrode, and platinum wire auxiliary electrode. Ferrocene was added as an internal standard. Cyclic voltammograms are provided in the SI (Figures S6–S8).

Thermodynamic Parameters for ^tBu₃PhOH and ^tBu₂(OMe)-PhOH and Calculation of ΔG_{ET} and ΔG_{PT}. Thermodynamic parameters for ^tBu₃PhOH are known: E[^tBu₃PhOH^{•+/0}] = 1.18 V and pK_a[^tBu₃PhO{H/⁻}] = 28.^{8b,31} E[^tBu₂(OMe)PhOH^{•+/0}] can be estimated to be 1.01 V from a experimentally determined CV on neutral ^tBu₂(OMe)PhOMe referencing to Cp₂Fe⁺⁰ (Figure S8). The pK_a for 2,6-di-*tert*-butyl-4-methoxyphenol was estimated by the method of Kütt et al.⁴⁷ using a value of 18.2 in DMSO:^{8b,48} 0.980 × 18.2 + 12.31 = 30.1. The free energy difference for ET is determined by, for example, ΔG_{ET} = -nF(E[^tPPT^{•+/0}] - E[^tBu₃PhOH^{•+/0}]). The free energy difference for PT is determined by a thermodynamic cycle as follows:



Values of ΔG[‡] were determined using the rate constants and the Eyring equation (ΔG[‡] = -RT ln[(*kh*)/(*k_BT*)] and are reported at 298 K.

Equilibration Studies. Graphs and UV–vis spectra are provided in the Supporting Information for these experiments. Reaction between PPT^{•+} and ^tBu₃PhOH was too slow to provide an accurate equilibrium constant. Errors are estimated at 10% for these experiments. Linear fits were to *y* = *mx* + *b*, but the *y*-intercepts were negligible in all cases.

Electron Transfer Equilibrium. The equilibrium constant for tris(4-tolyl)aminium and PPT was determined by adding 50 μL aliquots of a 12.1 mM solution of PPT to 3.0 mL of a 0.079 mM solution of tris(4-tolyl)aminium hexafluorophosphate solution. The absorbance at 668 nm, corresponding to an absorption of the aminium, was used to determine [NAr^{Me}₃^{•+}] (at equilibrium) after correcting for volume (Figure S10). The other concentrations were determined by mass balance. The slope of a plot of [PPT^{•+}][NAr^{Me}₃]/[NAr^{Me}₃^{•+}] vs [PPT] provided the equilibrium constant (Figure S11).

The equilibrium constant for PPT + MPTP^{•+} ⇌ PPT^{•+} + MPTP was determined by adding 50 μL aliquots of a 20.7 mM solution of PPT to 3.0 mL of a 83.7 μM solution of MPTP^{•+}. The absorbances at 515 and 580 nm, corresponding to λ_{max} of PPT^{•+} and MPTP^{•+}, were used to determine their concentrations (by solving abs₅₁₅ = ε_{515,PPT^{•+}}[PPT^{•+}] + ε_{515,MPTP^{•+}}[MPTP^{•+}] and abs₅₈₀ = ε_{580,PPT^{•+}}[PPT^{•+}] + ε_{580,MPTP^{•+}}[MPTP^{•+}]; Figure S16). The other concentrations were

determined by mass balance. The slope of a plot of [PPT^{•+}][MPTP]/[MPTP^{•+}] vs [PPT] provided the equilibrium constant (Figure S17).

Proton Transfer Equilibrium. The equilibrium constant for PPT + MPTP^{•+} ⇌ PPTH⁺ + MPTP was determined by adding 50 μL aliquots of a 25.4 mM solution of PPT to 3.0 mL of an 83.3 μM solution of MPTP^{•+}. The absorbance at 415 nm, corresponding to an absorption of the MPTP^{•+} (ε = 9.6 × 10³ M⁻¹ cm⁻¹), was used to determine [MPTP^{•+}] at equilibrium after correcting for volume (Figure S18). The other concentrations were determined by mass balance. The slope of a plot of [PPTH⁺][MPTP]/[PPTH⁺] vs [PPT] provided the equilibrium constant (Figure S19).

Proton–Electron Transfer Equilibrium. The equilibrium constant for PPTH⁺ + MPTP^{•+} ⇌ PPT^{•+} + MPTPH⁺ was determined by adding 50 μL aliquots of a 3.58 mM solution of PPTH⁺ to 3.0 mL of an 81.3 μM solution of MPTP^{•+}. Absorbances at 422, 515, and 580 nm were used to determine the concentrations of MPTPH⁺, PPT^{•+}, and MPTP^{•+} (by solving abs₄₂₂ = ε_{422,PPT^{•+}}[PPT^{•+}] + ε_{422,MPTP^{•+}}[MPTP^{•+}] + ε_{422,PPTH⁺}[MPTPH⁺]; abs₅₁₅ = ε_{515,PPT^{•+}}[PPT^{•+}] + ε_{515,MPTP^{•+}}[MPTP^{•+}] + ε_{515,PPTH⁺}[MPTPH⁺]; and abs₅₈₀ = ε_{580,PPT^{•+}}[PPT^{•+}] + ε_{580,MPTP^{•+}}[MPTP^{•+}] + ε_{580,PPTH⁺}[MPTPH⁺]; Figure S20). [PPT] was determined by mass balance. The slope of a plot of [PPT^{•+}][MPTPH⁺]/[MPTP^{•+}] vs [PPTH⁺] provided the equilibrium constant (Figure S21).

The equilibrium constant for MPTP^{•+} + ^tBu₃PhOH ⇌ MPTPH⁺ + ^tBu₃PhO[•] was determined by adding 50 μL aliquots of a 1.75 mM solution of ^tBu₃PhOH to 3.0 mL of a 71.8 μM solution of MPTP^{•+} under N₂. The absorbances at 422 and 580 nm were used to determine the concentrations of MPTPH⁺ and MPTP^{•+} (by solving abs₄₂₂ = ε_{422,MPTP^{•+}}[MPTP^{•+}] + ε_{422,PPTH⁺}[MPTPH⁺] and abs₅₈₀ = ε_{580,MPTP^{•+}}[MPTP^{•+}] + ε_{580,PPTH⁺}[MPTPH⁺]; Figure S22). Concentrations of ^tBu₃PhOH and ^tBu₃PhO[•] were determined by mass balance. The slope of a plot of [MPTPH⁺][^tBu₃PhO[•]]/[MPTP^{•+}] vs [^tBu₃PhOH] provided the equilibrium constant (Figure S23).

Acid–Base Equilibrium for pK_a Determination. The equilibrium constant for PPT and thymol blue (pK_a[TH₂ ⇌ TH⁻ + H⁺, MeCN] = 13.4²²) was determined by adding 50 μL aliquots of a 12.1 mM solution of PPT to 3.0 mL of a 0.89 mM solution of thymol blue solution. The absorbance at 395 nm (λ = 1.65 × 10⁴ M⁻¹ cm⁻¹), corresponding to an absorption of the deprotonated thymol blue (TH⁻),²² was used to determine [TH⁻] after correcting for volume, and the other concentrations were determined by mass balance (Figure S12). The slope of a plot of [PPTH⁺][TH⁻]/[TH₂] vs [PPT] provided the equilibrium constant (Figure S13).

Similarly, the equilibrium constant for MPTP and pyridinium was determined by adding 50 μL aliquots of 29.2 mM pyridinium hexafluorophosphate (pK_a = 12.6)⁴⁹ to 3.00 mL of 98.7 μM MPTP. The absorbance at 415 nm (ε = 9.6 × 10³ M⁻¹ cm⁻¹) was used to determine MPTPH⁺, and the other concentrations were determined by mass balance (Figure S14). The slope of a plot of [MPTH⁺][pyr]/[pyrH⁺] vs [MPTP] provided the equilibrium constant (Figure S15).

Kinetics Studies. Solutions of radical cation were generated as above in concentrations of 0.1–0.2 mM in acetonitrile in a glovebox, and hydrogen atom donors (2,4,6-tri-*tert*-butylphenol or 2,6-di-*tert*-butyl-4-methoxyphenol) were prepared at 5–100× these concentrations. Solutions were combined in a stopped flow spectrophotometer, and the absorbance over a 200 nm range centered at 515 nm was observed. The decay of the spectra was fit globally to a first-order decay using Spec-Fit. The slope of *k*_{obs} vs concentration of hydrogen atom donor provided the second-order rate constants. Sample plots of data are given in Figures S24–S26.

Eyring Analysis. Kinetics were performed at five temperatures between 13.4 and 62.6 °C as above. The activation parameters (ΔH[‡] and ΔS[‡]) were determined from a plot of ln(*k*/T) vs 1/T (Figure S27).

Computational Procedures. All calculations were performed using the keyword int=ultrafine in Gaussian09. This produces a pruned grid of 99 radial shells with 590 points per shell for numerical integration. Frequency evaluations also included the keyword int=(Acc2e=11) to force tighter convergence (10⁻¹¹) of the two-electron integrals as part of solving the CPHF equations.

The BSSE at the transition state was calculated as the average of two counterpoise calculations using two fragments each. In the first calculation, the transferring hydrogen atom was assigned to ^tBu₃PhOH (the two fragments were ^tBu₃PhOH and the radical cation form of the acceptor), and in the second the transferring hydrogen was assigned to the hydrogen acceptor (the two fragments were ^tBu₃PhO[•] and the cationic form of the acceptor).

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01427.

Experimental and computational details (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: JeffreyWolbach@eurofinsUS.com.

*E-mail: irhile@albright.edu.

Notes

The authors declare no competing financial interest.

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