Article

Stereoelectronic and Resonance Effects on the Rate of Ring Opening of N-Cyclopropyl-Based Single Electron Transfer Probes

Michelle Grimm, Naushadalli Kamrudin Suleman, Amber N Hancock, Jared N. Spencer, Travis Dudding, Rozhin Rowshanpour, Neal Castagnoli, and James M. Tanko

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b12617 • Publication Date (Web): 08 Jan 2020

Stereoelectronic and Resonance Effects on the Rate of Ring Opening of *N*-Cyclopropyl-Based Single Electron Transfer Probes

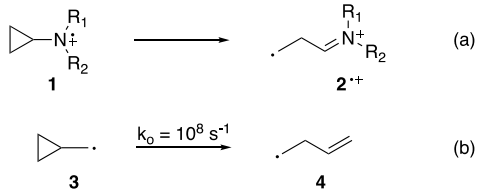
Michelle L. Grimm, N. Kamrudin Suleman,[†] Amber N. Hancock,[‡] Jared N. Spencer,[§] Travis Dudding,[⊥] Rozhin Rowshanpour,[⊥] Neal Castagnoli Jr., and James M. Tanko*

Department of Chemistry, Virginia Tech, Blacksburg, VA

ABSTRACT: *N*-cyclopropyl-*N*-methylaniline (**5**) is a poor probe for single electron transfer (SET) because the corresponding radical cation undergoes cyclopropane ring opening with a rate constant of only 4.1 x 10^4 s^{-1}, too slow to compete with other processes such as radical cation deprotonation. The sluggish rate of ring opening can be attributed to either (*i*) a resonance effect in which the spin and charge of the radical cation in the ring-closed form is delocalized into the phenyl ring, and/or (*ii*) the lowest energy conformation of the SET product (**5**$^{\bullet+}$) does not meet the stereoelectronic requirements for cyclopropane ring opening. To resolve this issue, a new series of *N*-cyclopropylanilines were designed to lock the cyclopropyl group into the required bisected conformation for ring opening. The results reveal that the rate constant for ring opening of radical cations derived from 1'-methyl-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinoline] (**6**) and 6'-chloro-1'-methyl-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinoline] (**7**) are 3.5 x 10^2 s^{-1} and 4.1 x 10^2 s^{-1}, effectively ruling out the stereoelectronic argument. In contrast, the radical cation derived from 4-chloro-*N*-methyl-*N*-(2-phenylcyclopropyl)aniline (**8**) undergoes cyclopropane ring opening with a rate constant of 1.7 x 10^8 s^{-1}, demonstrating that loss of the resonance energy associated with the ring-closed form of these *N*-cyclopropylanilines can be amply compensated by incorporation of a radical-stabilizing phenyl substituent on the cyclopropyl group. Product studies were performed, including a unique application of EC-ESI/MS (Electrochemistry/ElectroSpray Ionization Mass Spectrometry) in the presence of $^{18}O_2$ and $H_2{}^{18}O$ to elucidate the mechanism of ring opening of **7**$^{\bullet+}$ and trapping of the resulting distonic radical cation.

Introduction

N-Cyclopropylamines have been widely used as mechanistic probes to detect single electron transfer (SET) pathways for amine oxidations in both chemical and biological systems. *N*-cyclopropyl substrates have been used to probe for single electron transfer for amine oxidations induced chemically,[1-6] and catalyzed by enzymatic systems such as monoamine oxidase,[7-9] cyctochrome P450,[10-23] horse radish peroxidase,[24, 25] and others.[17, 23, 26] In such studies, it is supposed that if a single electron transfer mechanism is operative, the resulting aminyl radical cation will undergo rapid ring opening to generate the corresponding distonic radical cation (Scheme 1, **1** → **2**$^{\bullet+}$). In analogy to the cyclopropylcarbinyl → homoallyl neutral radical rearrangement (Scheme 1, **3** → **4**), ring opening is assumed to be rapid and irreversible. The isolation/detection of cyclopropane ring-opened products, or the loss of catalytic activity for an enzyme-mediated process, provides evidence for radical cation intermediacy—consistent with an electron transfer mechanism.

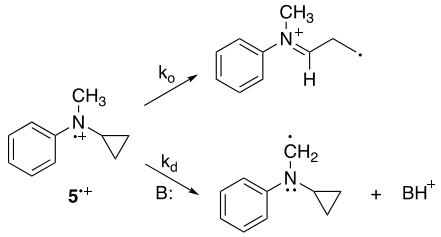


Scheme 1. Ring opening of *N*-cyclopropyl aminyl radical cations and the cyclopropyl carbinyl neutral radical

There are little kinetic data available pertaining to the ring opening of *N*-cyclopropyl aminyl radical cations. In most mechanistic studies it is simply assumed that the rate of ring opening would be extremely fast, as is the case for the neutral cyclopropylcarbinyl radical. For *N*-cyclopropyl radical cations generated from aliphatic amines (Scheme 1a, R^1, R^2 = alkyl or H), this assumption is likely valid based upon indirect evidence[27, 28] and molecular orbital calculations,[21, 29, 30] the latter of which indicate little to no barrier for ring opening.

In 2007, the first absolute rate constant for ring opening of an *N*-cyclopropylanilinyl radical cation was reported, and found to be *much* lower than anticipated. Specifically, the radical cation generated from *N*-cyclopropyl-*N*-methylaniline (**5**) was found to undergo ring opening with a rate constant of 4.1×10^4 s^{-1} at room temperature.[31] This result was particularly significant because *N*-cyclopropyl-*N*-methylaniline (**5**), or close derivatives thereof, had been used as SET probes in several mechanistic studies.[1-4, 6, 11, 12, 14-17, 21-25]

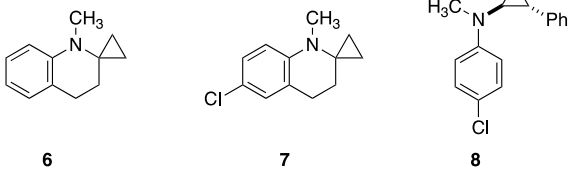
As noted, use of a radical cation probe requires that ring opening is rapid relative to other competing processes, typically radical cation deprotonation for most enzyme-catalyzed and chemically-induced amine oxidations (Scheme 2). If $k_o << k_d[B:]$, then the ring opening is not competitive and thus a *bona fide* electron transfer process would fail to be detected by this approach.



Scheme 2. Competition between ring opening and deprotonation in *N*-cyclopropylaminyl radical cation ($5^{\bullet+}$)

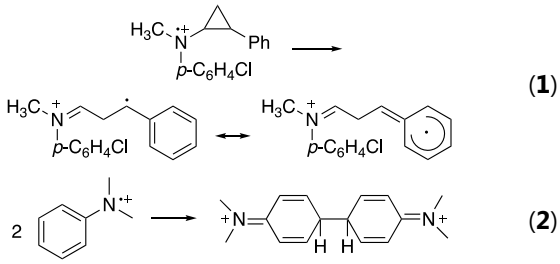
Two factors may explain the sluggish rate of ring opening of $\mathbf{5}^{\bullet+}$ (Scheme 3): (*i*) a resonance effect, in which the spin and charge of the radical cation in the ring closed form is delocalized into the phenyl ring, stabilizing the ring-closed radical cation, and thus diminishing the overall rate of the ring opening reaction, and/or (*ii*) the lowest energy conformation of the molecule does not meet the stereoelectronic requirements for a ring opening pathway. (In order to undergo ring opening, the cyclopropyl group must be in the bisected conformation).[30, 32-34]

To test which factors were responsible for the sluggish rate of ring opening of $\mathbf{5}^{\bullet+}$, a broader structural range of substrates (**6** → **8**) were examined. Compounds **6** and **7** were designed to effectively lock the cyclopropyl group in the required bisected conformation, and the derived radical cations were anticipated to ring open faster than $\mathbf{5}^{\bullet+}$ if stereoelectronic factors were important.



6 **7** **8**

Compound **8** tests whether resonance effects are important, as ring opening leads to a resonance-stabilized (benzylic) distonic radical cation, thereby compensating for the resonance energy of the ring closed form (Eq. 1). It should also be noted that another factor in the selection of **7** and **8** is that the *p*-Cl substituent essentially shuts down a potentially competing dimerization pathway, illustrated in Eq. 2 for *N,N*-dimethylaniline radical cation.[35]



(**1**)

(**2**)

Results

Direct Electrochemistry

Direct electrochemical techniques such as cyclic and linear sweep voltammetry (CV and LSV, respectively) are formidable tools for studying the chemistry of radical ions. Through these methods, a substrate (**A**) is oxidized or reduced at an electrode surface generating a radical ion (**B**, Figure 1); let k_s represent the standard heterogeneous rate constant for this step. This radical ion undergoes a follow-up chemical reaction, presumably cyclopropyl ring opening for these systems, with rate constant k_o. In principle, either of these two steps can be rate-limiting.

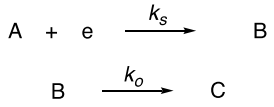
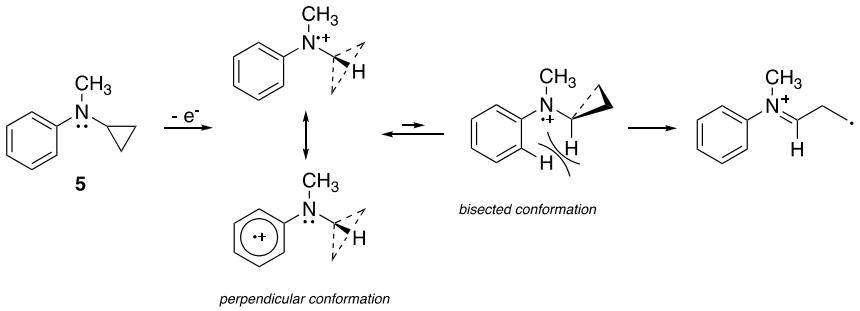


Figure 1. Direct electrochemistry: Substrate A is reduced on the electrode surface with heterogeneous rate constant k_s; electrogenerated species B undergoes a subsequent (homogeneous) chemical reaction with rate constant k_o.

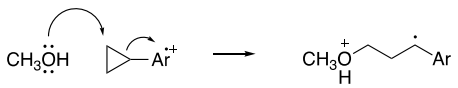
These techniques typically examine the effect of sweep rate and substrate concentration on the electrochemical response. When the chemical step is rate-limiting, it is possible to obtain information such as the formal reduction/oxidation potential of the substrate, the rate law for the chemical step, and its rate constant k_o. When heterogeneous electron transfer is rate-limiting, it is possible to measure k_s and the transfer coefficient α.[36] The Supporting Information provides details pertaining to the synthesis of these compounds, and sample voltammograms, pertinent plots, and more for the experiments summarized below.



Scheme 3. Resonance vs. stereoelectronic effects to explain the sluggish rate of ring opening of *N*-cyclopropylaminyl radical cation ($5^{\bullet+}$)

1'-Methyl-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinoline] (**6**). Several experiments were performed at various sweep rates (v = 100 - 1000 mV/s) and at various concentrations of substrate. Characteristic features of the voltammograms included: (*i*) No reverse wave was observed, (*ii*), peak potentials (E_p) of *ca.* 270 mV at 100 mV/s, (*iii*) peak widths ($E_p - E_{p/2}$) between 50-60 mV, and (*iv*) a change in peak potential with respect to the scan rate ($\partial E_p/\partial \log v$) of 27 ± 3 mV/decade. These results suggest that the follow-up chemical step—not heterogeneous electron transfer— was rate limiting, and that the follow up chemical step was likely first order in radical cation.

To verify that the follow up reaction was indeed first order in radical cation (*vs*. second order as would be found for a dimerization process, *i.e.*, 2 B → dimer), experiments were performed, measuring peak potentials at varying substrate concentrations and scan rates. Finally, additional experiments were conducted to verify that the ring opening of *N*-cyclopropylaniline radical cations was actually unimolecular, as opposed to bimolecular via a potential nucleophile-assisted pathway as is observed for the ring opening of cyclopropyl arene radical cations (Eq. 3).[37-39] These experiments entailed varying methanol concentration and holding the substrate concentration and sweep rate constant.



(3)

In Table 1, the results of all these experiments are summarized and compared to the theoretical parameters for three rate laws: 1) 1st order in radical cation and methanol (k[B][X]), 2) second order in radical cation (k[B]^2), and 3) first order solely in radical cation (k[B]).[36] The results clearly show that the follow up chemical step is solely first order in radical cation, consistent with the unimolecular ring opening of the cyclopropyl group. In principle, the rate constant for ring opening (k_o) could be determined from the variation of E_p with sweep rate in accordance with Eq. 4,[40] if E^o were known; n, F, R, and T are the number of electrons transferred, Faraday's constant, the ideal gas constant, and temperature, respectively.

$$E_p = E^o - \left(\frac{0.78RT}{nF}\right) + \frac{RT}{2nF} ln\left(\frac{k_o RT}{vnF}\right) \qquad \textbf{(4)}$$

6'-Chloro-1'-methyl-3',4'-dihydro-1'*H*-spiro[cyclopropane-1,2'-quinoline] (**7**). As was the case for **6**, **7** was exhaustively studied by CV/LSV at multiple scan rates (v = 100 - 1000 mV/s) and substrate concentrations. Characteristic features of the voltammograms included: (*i*) No reverse wave was observed, (*ii*) peak potentials (E_p) on the order of 310 mV at 100 mV, (*iii*) Peak widths ($E_p - E_{p/2}$) between 50 - 60 mV, and (*iv*) a change in peak potential with respect to the scan rate ($\partial E_p/\partial \log v$) of 27 ± 1 mV/decade—all consistent with first order radical cation decay. In light of the results for **6**, additional experiments to test for a nucleophile-assisted cyclopropane ring opening pathway or a dimerization mechanism were not attempted.

4-Chloro-*N*-methyl-*N*-(2-phenylcyclopropyl)aniline (**8**). Cyclic voltammograms of **8** were recorded at multiple scan rates (v = 100 - 1000 mV/s) and at multiple substrate concentrations. In all cases, no reverse wave was observed. Other characteristic features of the voltammograms included: (*i*) Peak potentials (E_p) on the order of 375 mV at 100 mV/s, (*ii*) Peak widths ($E_p - E_{p/2}$) between 78 - 85 mV, and (*iii*) a change in peak potential with respect to the scan rate ($\partial E_p/\partial \log v$) of 45 ± 3 mV/decade. The broadness of the waves and variation of E_p with sweep rate were greater than expected if the chemical step were rate limiting (*vide supra*), but less than expected if electron transfer were rate limiting (for α =

0.5, $\partial E_p/\partial \log v$ = 59 mV/decade, and $E_p - E_{p/2}$ = 95 mV). Consequently, mixed kinetic control was suspected.

For systems under mixed kinetic control, theoretical working curves that account for the variation in peak width ($E_p - E_{p/2}$) and peak potential (E_p) with respect to the scan rate have been derived.[41] The simultaneous variation of E_p and $E_p - E_{p/2}$ as a function of sweep rate (ν) are reconciled to the working curves (assuming α = 0.5), optimizing the floating parameters C_1 and C_2 (Eqs. 3 and 4) with C_1 = 2.396 V and C_2 = -0.254 V; F, R, and T were defined earlier. *D* represents the diffusion coefficient.

Table 1. Theoretical response for various mechanisms of radical cation decay compared to experimentally observed values from CVs of 6 and 7

	$\frac{\partial E_p}{\partial \log v}$ (mV/decade)	$\frac{\partial E_p}{\partial \log[A]}$ (mV/decade)	$\frac{\partial E_p}{\partial \log[CH3OH]}$ (mV/decade)
Mechanism	Predicted		
B → C	**30**	**0**	**0**
2 B → B2	**19.7**	**19.7**	**0**
B + X → C	**30**	**0**	**30**
(X = CH_3OH)			
Compound	Observed		
6	**27 ± 2**	**1.8 ± 10.5**	**0.0 ± 1.2**
7	**27 ± 2**	**1.1 ± 2.7**	**---**

Combining these two equations results in a single equation (Eq. 5) with two unknowns, $\underline{k_o}$ and E_o. Additional information is needed to solve this system, which fortunately was available using homogeneous redox catalysis (*vide infra*).

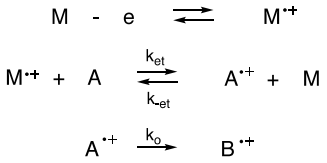
$$C_1 = log\left(\frac{F}{2RT}\frac{k_o D^2}{k_s^4}\right) \quad (5)$$

$$C_2 = E^o + \left(\frac{RT}{F}ln10\right)log\left(\frac{k_o D}{k_s^2}\right) \quad (6)$$

$$E^o + \left(\frac{RT}{2F}ln10\right)logk_o = C_2 - \left(\frac{RT}{2F}ln10\right)\left(C_1 - log\left[\right.\right. \quad (7)$$

Indirect electrochemistry (homogeneous redox catalysis)

Homogeneous redox catalysis (HRC) is a useful electrochemical method for studying the chemistry of highly reactive intermediates produced via electron transfer. As shown in Scheme 4, rather than the substrate, an electron-transfer mediator or catalyst **M** is oxidized at the electrode surface. Two requirements must be met: 1) The mediator must be more easily oxidized than the substrate, and 2) this oxidation must be reversible. Oxidation of the substrate **A** occurs in solution (homogeneous) *via* electron transfer to the oxidized form of the mediator to give oxidized product $\mathbf{A}^{\bullet+}$.



Scheme 4. Homogeneous redox catalysis.

Effects of substrate addition on this reversible electron transfer are manifested experimentally by an increase in peak current and a loss of reversibility if catalysis is occurring. Kinetic control may be governed by either the homogeneous electron transfer step (k_{et}) or the chemical step (k_o). The system is governed by the dimensionless kinetic parameters λ, λ_1, λ_{-1} (Eqs. 8 - 10), and the ratio of substrate to mediator, γ = [A]/[M].[42, 43]

$$\lambda = \left(\frac{RT}{F}\right)\left(\frac{k_o}{v}\right) \quad (8)$$

$$\lambda_1 = \left(\frac{RT}{F}\right)\left(\frac{k_{et}[M]}{v}\right) \quad (9)$$

$$\lambda_{-1} = \left(\frac{RT}{F}\right)\left(\frac{k_{-et}[M]}{v}\right) \quad (10)$$

Working curves relating the experimental observables: i_p (the current in the presence of mediator and substrate) and i_{pd} (the current in the presence of mediator alone) to the sweep rate and mediator concentration allow the pertinent rate constants to be extracted. If the rate of the chemical step is faster than back electron transfer, then the electron transfer step is rate-limiting and k_{et} can be determined. If the chemical step is slow relative to back electron transfer, the chemical step is rate limiting with the electron transfer step as a rapid pre-equilibrium, and it is possible to determine k_o. Oftentimes, joint application of both direct and indirect electrochemical methods allows the kinetics of a system to be fully resolved.

Compounds **6** and **7** were studied using several ferrocene-based mediators. (For a full list of mediators and their standard oxidation potentials, see the Supporting Information.) In past studies using redox catalysis, our experiments were conducted at γ = 1, and the rate limiting step and kinetic parameters were obtained by monitoring i_p/i_{pd} as a function of sweep rate--an approach that minimizes the consumption of expensive starting materials.[44] Unfortunately, for **6** and **7**, catalysis was only observed at low sweep rates. As the sweep rate was increased, two distinct waves were observed: the first attributable to catalysis, and the second arising from the direct oxidation of the substrate at the electrode surface. Figure 2 illustrates this phenomenon for **6** (with 4-cyanophenylferrocene as mediator). This observation provided an early clue that the ring opening of the radical cations generated from **6** and **7** might be slower than expected. As noted above, redox catalysis requires a fast follow up chemical reaction to drive the electron transfer. The observation of the second oxidation wave, attributable to the direct oxidation of substrate at high scan rates, meant that this requirement for k_o was not met. A costlier, more material intensive approach was needed to circumvent this problem--monitoring i_p/i_{pd} as a function of γ at low sweep rates.

Figure 3 shows the results for the mediated oxidation of **6** by two mediators, 4-cyanophenylferrocene (E^o = 0.145 V) and 2-nitrophenylferrocene (E^o = 0.143 V). Theoretical working curves were generated by modeling the reaction mechanism using digital simulation software, with k_{obs} adjusted to obtain the best fit to the experimental data. With k_{obs} in hand, the results from redox catalysis can be reconciled with those from the direct electrochemistry experiments above through Eqs. 4, 11 and 12, allowing k_o and E^o_A to be solved. With 4-cyanophenylferrocene as mediator, we find E^o_A = 0.299 V and k_o = 3.1 x 10^2 s^{-1}. These results were further validated with 2-nitrophenylferrocene yielding E^o_A = 0.301 V and k_o = 3.8 x 10^2 s^{-1}.

$$\boldsymbol{k_{obs} = k_o\left(\frac{k_{et}}{k_{-et}}\right) = k_o K_{et}} \quad \textbf{(11)}$$

$$\boldsymbol{K_{et} = \frac{k_{et}}{k_{-et}} exp\left(\frac{F}{RT}\left(E^0_A - E^0_M\right)\right)} \quad \textbf{(12)}$$

Indirect electrochemistry was also utilized to study **7**. Only one mediator (2,4-dinitrophenylferrocene, E^o = 0.280 V) was suitable because of a lack of available mediators in the desired potential range. The results are provided in the Supporting Information. Analysis of the results as described above yielded E^o_A = 0.366 V and k_o = 4.1 x 10^2 s^{-1}.

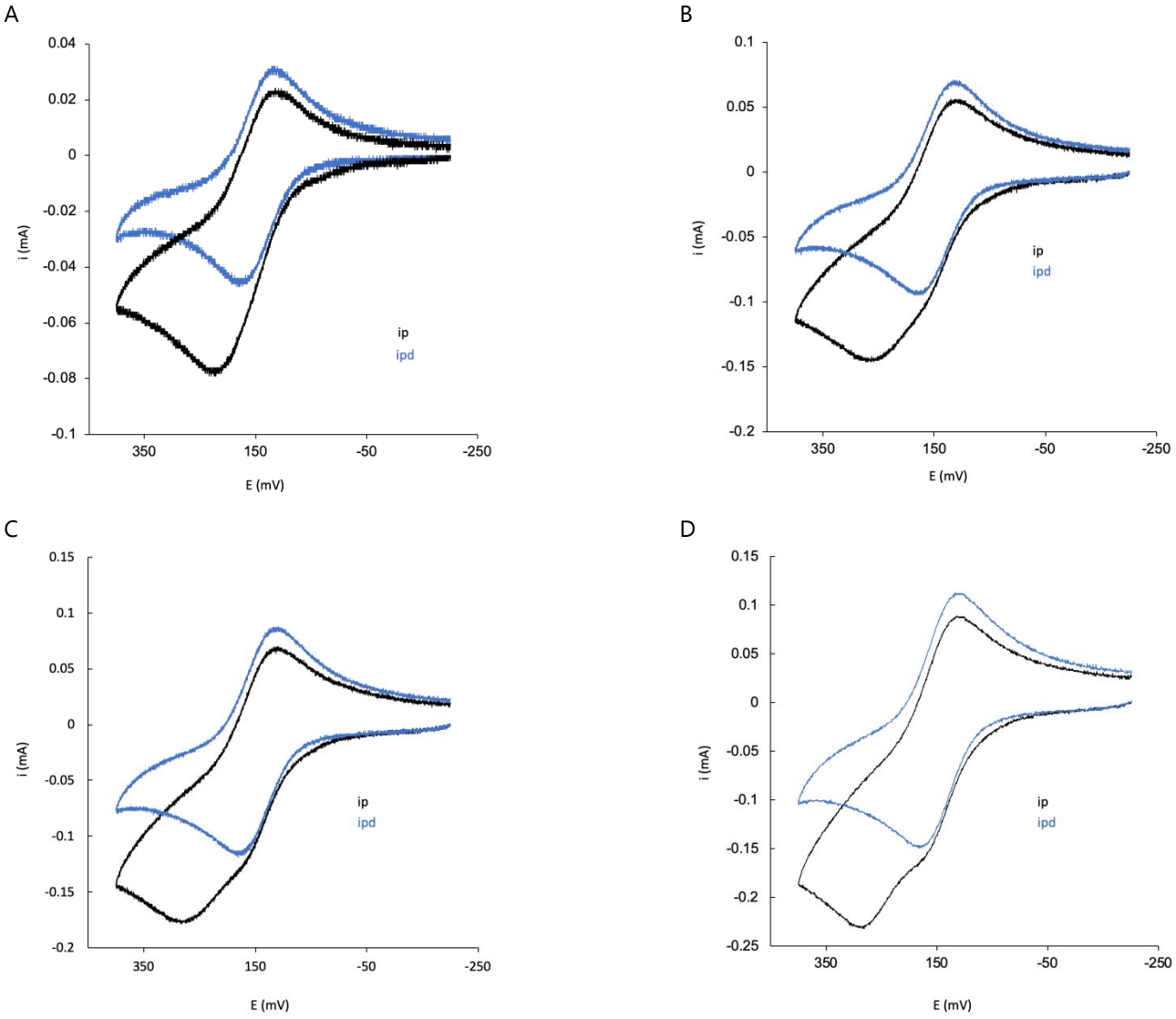


Figure 2. Mediated oxidation of 6 by 4-cyanophenylferrocene (0.1 M $LiClO_4$, 0.5 M CH_3OH/CH_3CN, γ = 1): A: 100 mV/s; B: 400 mV/s; C: 600 mV/s; D: 1000 mV/s

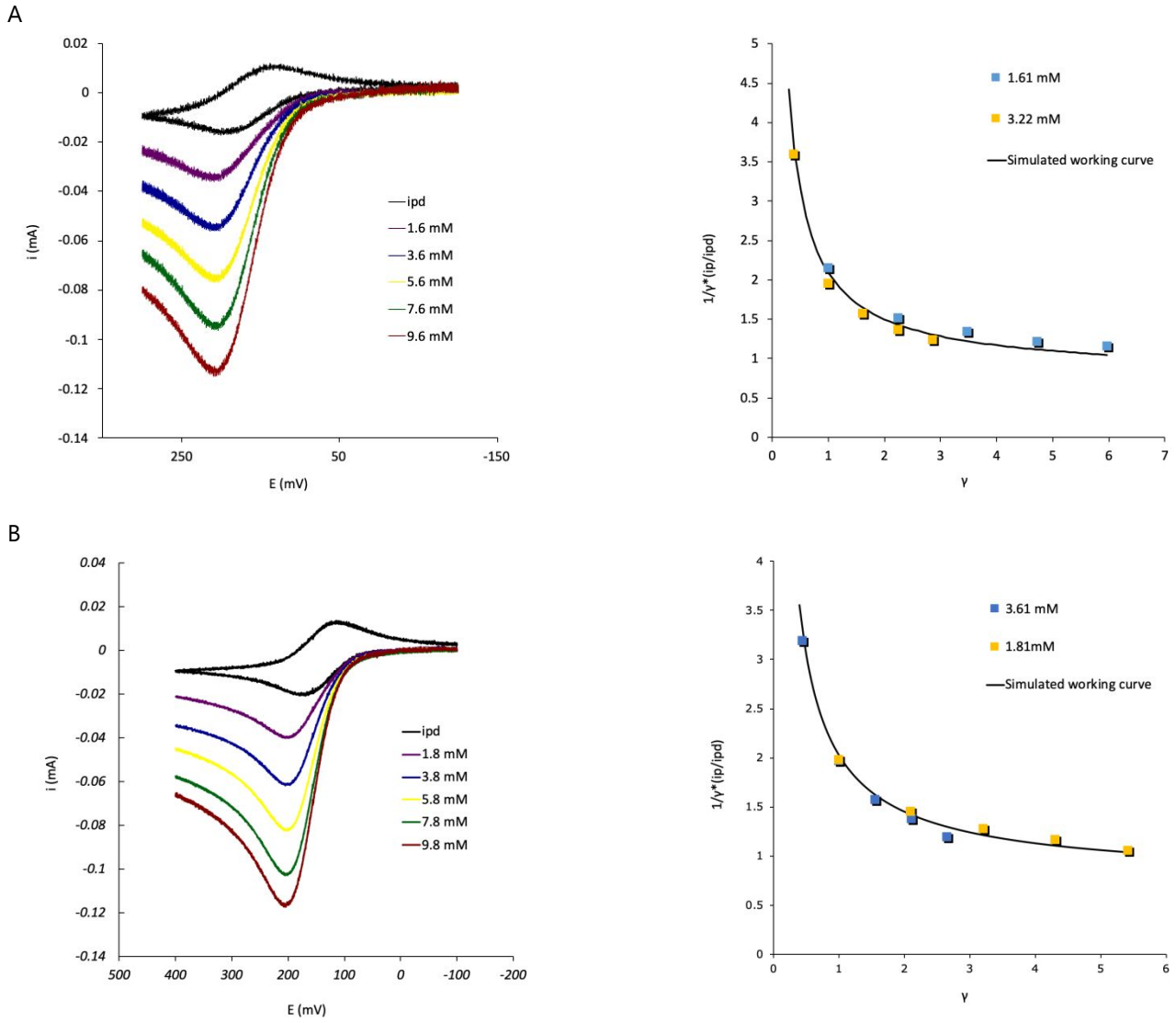


Figure 3. Mediated oxidation of 6 using ferrocene-based mediators (CH_3CN, 0.5 M CH_3OH, 0.5 M $^nBu_4NBF_4$, ν = 25 mV/s) A: 1.6 mM 6; 4-cyanophenylferrocene; (i_p/i_{pd})/γ vs. γ compared to theoretical working curve for k_{obs} = 1.1 x 10^5 s^{-1}; B: 1.8 mM 6; 2-nitrophenylferrocene; (i_p/i_{pd})/γ vs. γ compared to theoretical working curve for k_{obs} = 9.7 x 10^4 s^{-1}

Finally, the indirect electrochemistry of **8** was studied with two mediators, ferrocene carboxylic acid (E^o = 0.264 V) and 4-cyanoferrocene (E^o = 0.145 V). For **8**, the more economical approach of examining i_p/i_{pd} as a function of sweep rate and mediator concentration at constant γ was feasible. As can be shown through Eqs. 8 - 10, at constant γ, i_p/i_{pd} is a function of log([M]/ν) when electron transfer is rate determining, or log(1/ν) when the chemical step is rate limiting. For the mediated oxidation of **8** by both of these mediators, plots of i_p/i_{pd} vs. log(1/ν) at different mediator concentrations resulted in three distinct lines, while for plots of i_p/i_{pd} vs. log([M]/ν) the data converged onto a single curve, unambiguously demonstrating a concentration dependence and revealing the rate limiting step to be electron transfer (Figure 4).[44] By fitting the experimental data to the working curves, the rate constant for electron transfer between the mediator and **8** (k_{et}) can be extracted. Because the electron transfer event is thermodynamically unfavorable, and assuming that we are operating in the Marcus counter-diffusion control region where back electron transfer (k_{-et}) is diffusion-controlled, through Eq. 12 we can solve for the oxidation potential of the substrate (E^o_A). Based upon the results obtained with ferrocene carboxylic acid as mediator, for **8** E^o = 0.527 V. The results for 4-(cyanophenyl)ferrocene were in excellent agreement, with E^o = 0.533 V. Giving confidence in our assumptions and the estimate of E^o for

8, these oxidation potentials were also compared to a model compound, 4-chloro-*N*,*N*-dimethylaniline, which exhibited a reversible cyclic voltammogram and an oxidation potential of 0.514 V .

Recalling that the direct electrochemistry of **8** was under mixed kinetic control and that Eq. 7 was applicable, we now have enough information to solve for the rate constant for ring opening of $\mathbf{8}^{\bullet+}$; k_o = 1.7 x 10^8 s^{-1}.

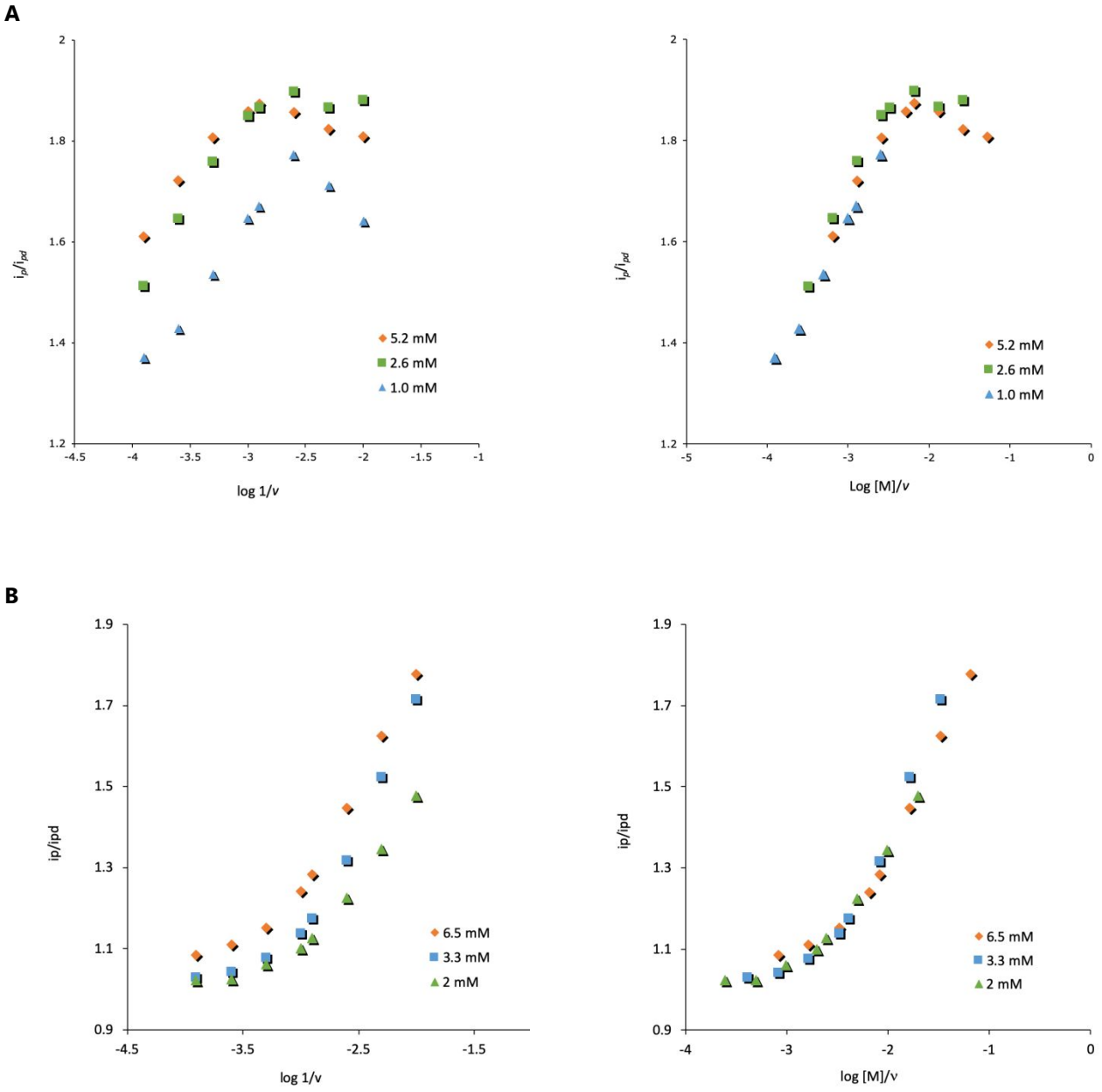


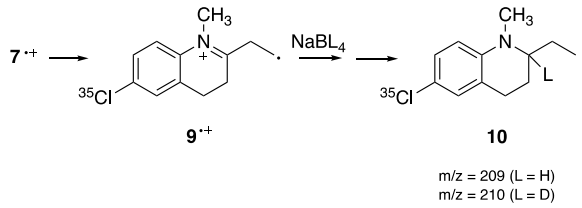
Figure 4. Plots of i_p/i_{pd} *vs*. log(1/ν) and log([M]/ν) for the mediated oxidation of 8 by A: ferrocene carboxylic acid and B: 4-cyanoferrocene (0.1 M $LiClO_4$, 0.5 M CH_3OH/CH_3CN, γ = 1.00, ν = 100 - 8000 mV/s)

Product studies

To verify that the measured rate constants for the chemical step of these oxidations were actually arising from cyclopropane ring opening, product studies were performed on **7** and **8**. However, because ring opening of $\mathbf{7}^{\bullet+}$ and $\mathbf{8}^{\bullet+}$ generates a charged iminyl species, the workup procedure required a reducing agent ($NaBH_4$) or nucleophile to yield a neutral organic product. Constant current electrolysis was employed, and the reaction mixture was analyzed by GC/MS (electron impact

ionization). Invariably these experiments were characterized by electrode fouling and poor mass balances.

Constant-current electrolysis of **7** in CH_3CN/CH_3OH, followed by $NaBH_4$ workup gave rise to a compound (m/z = 209) which is assigned to **10**, in addition to unreacted starting material (m/z =207). (These assignments correspond to ^{35}Cl. The corresponding ^{37}Cl peaks were also observed with the expected intensities.) To confirm that that the $C{=}N^+$ bond was reduced by BH_4^- post-electrolysis, $NaBD_4$ was used in the workup and the 209 peak was replaced by a new peak at m/z = 210. These observations are entirely consistent with the proposed cyclopropane ring opening of $\mathbf{7}^{\bullet+} \rightarrow \mathbf{9}^{\bullet+}$ as shown in Scheme 5. Note: the reduction of the 1° radical portion of $\mathbf{9}^{\bullet+}$ to methyl likely involves H-atom abstraction from some component of the reaction mixture. Experiments conducted with deuterated solvents suggested that neither CH_3CN nor CH_3OH were the H-atom donors, making it likely that **9** or species derived therefrom were the H-atom donor(s).

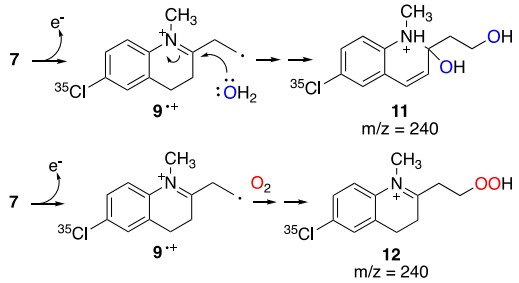


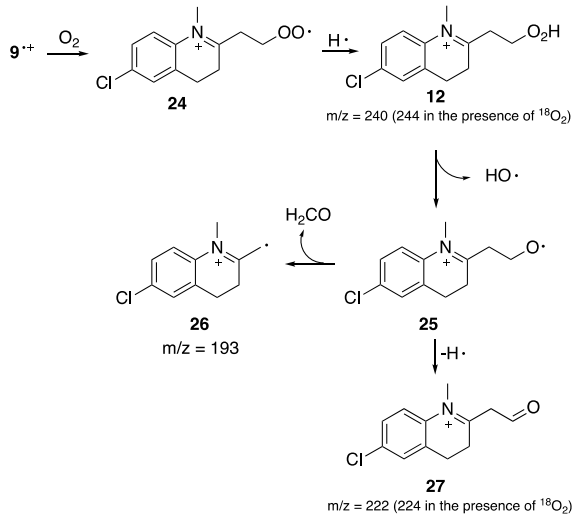
Scheme 5. Ring opening of $7^{\bullet+}$ and subsequent trapping by $NaBH_4$ or $NaBD_4$ to yield an isolable product (20)

Because of the issues associated with these product studies, the oxidation of **7** was examined further using EC-ESI/MS (Electrochemistry-ElectroSpray Ionization Mass Spectrometry). EC-ESI/MS is a novel technique that adds a new dimension to electrochemical investigations.[19] This method involves pumping a solution containing an electroactive species through an electrochemical (EC) flow cell that is coupled directly to an electrospray ionization mass spectrometer (ESI/MS). In addition to allowing product studies to be conducted "on the fly," by monitoring the MS ion intensity of the substrate or any reaction product as a function of potential, a "mass voltammogram" (plot of intensity of a given ion monitored by MS *vs*. the potential of the electrochemical cell) is obtained providing novel information that may be used to elucidate the mechanisms of electrochemical oxidations. (The electrochemical flow cell utilizes a pseudo reference electrode so the measured potentials are relative, not absolute, and thus differ from those recorded by cyclic voltammetry as described above).

The mass spectrum obtained for **7** at an electrochemical cell potential of 0 mV is shown in Fig. 5A. The peaks at m/z 208 (100%) and 210 correspond to $\mathbf{7H}^+$ (^{35}Cl and ^{37}Cl, respectively); a small amount of a $\mathbf{7H}^+/CH_3CN$ adduct is also detected (m/z = 249, 251). At an electrochemical cell potential of 300 mV, the peaks corresponding to $\mathbf{7H}^+$ vanish, and are replaced by two peaks at m/z = 240 (100%) and 242. The complete mass voltammogram obtained for **7**, monitoring the ^{35}Cl-containing ions (m/z = 208 and 240) as a function of electrochemical cell potential is shown in Figure 5C. Collision induced dissociation of the ion at m/z 240 leads to peaks at m/z = 222 and 193 (Figure 6A).

Two possible structures were considered for the ion at m/z = 240, **11** which we reasoned might arise from nucleophilic trapping of a cationic intermediate(s) by water (Eq. 13, see the Supporting Information for a proposed mechanism), or **12** via arising from trapping of a paramagnetic intermediate by O_2 (Eq. 14).





Scheme 6. Proposed structures and fragmentations of products arising from ring opening ($7^{\bullet+} \rightarrow 9^{\bullet+}$), and subsequent reaction of $9^{\bullet+}$ with O_2

To differentiate between these two pathways, the EC-ESI/MS experiments were conducted in the presence of $H_2{}^{18}O$ or $^{18}O_2$. If the m/z = 240 peak resulted from

nucleophilic trapping of the distonic radical cation by water via the mechanism provided in the Supporting Information, then with $H_2{}^{18}O$ the m/z ion at 240 would shift to 244, and its collision induced dissociation spectrum would show the following changes: 222 → 224, and 193 → 195. However, in the presence of $H_2{}^{18}O$, at an electrochemical cell potential of 300 mV, the total ion chromatogram did not show any new peaks, and the observed collision induced mass fragmentation of the m/z = 240 (^{35}Cl) ion was unchanged in the presence of $H_2{}^{18}O$.

In contrast, at an electrochemical cell potential of 300 mV the total ion chromatogram of **7** in the presence of $^{18}O_2$ enriched oxygen exhibited significant changes. The base peak was now at m/z = 242, and new peaks at m/z = 244 and 246 appeared. CID of the newly formed base peak (m/z = 244) is shown in Fig. 6C. All these observations are consistent with O_2 trapping of the radical portion of distonic radical cation $\mathbf{9}^{\bullet+}$ via the mechanism shown in Scheme 6.

Constant-current electrolysis of **8** was straight forward, and gave rise to 4-chloro-*N*-methyl aniline (**15**), via the mechanism proposed in Scheme 7. Aldehyde **16** was presumably lost during workup. This was confirmed via treatment of the electrolysis mixture with $NaBH_4$, after which a small amount of $PhCH_2CH_2CH_2OH$ was detected.

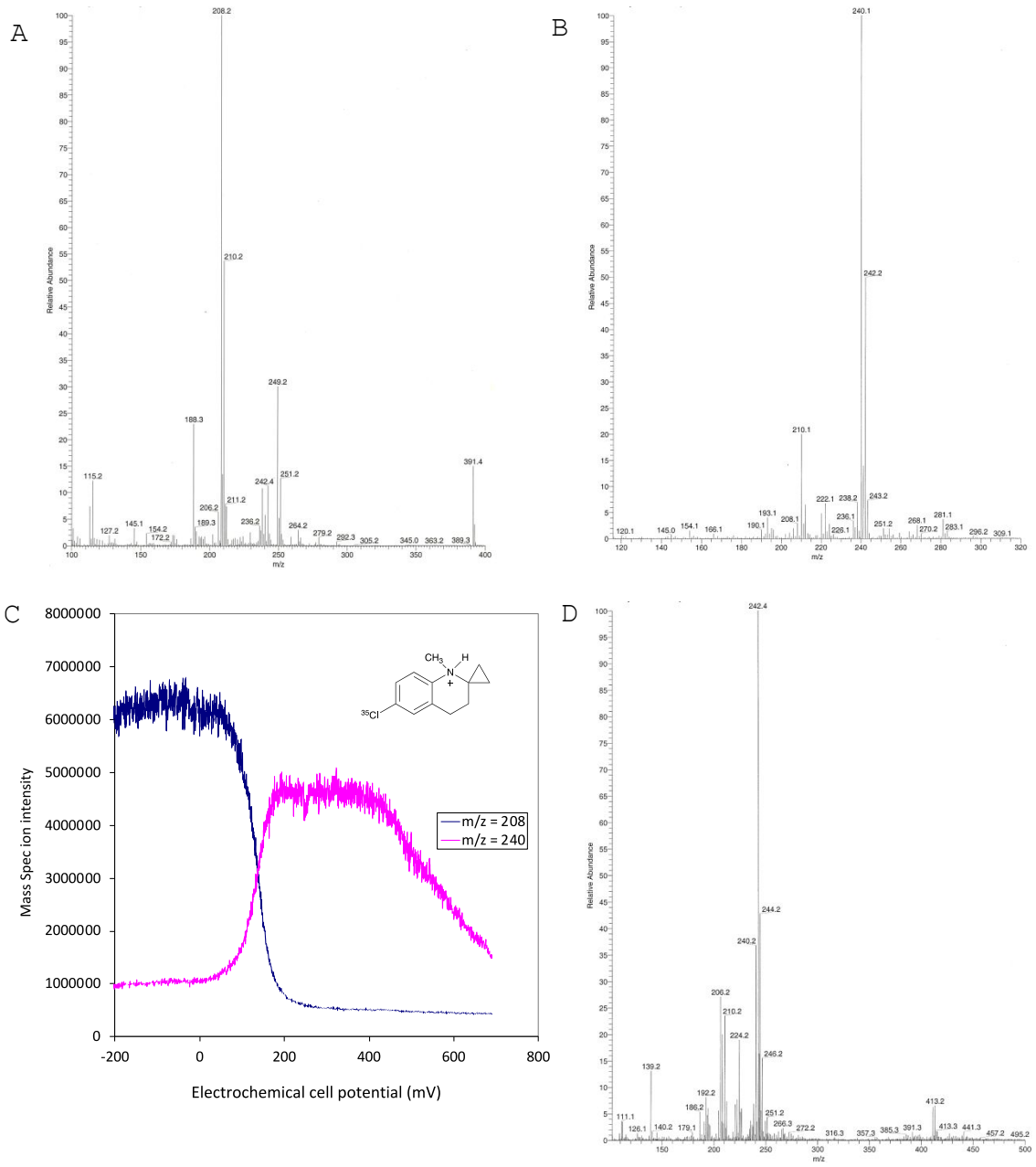
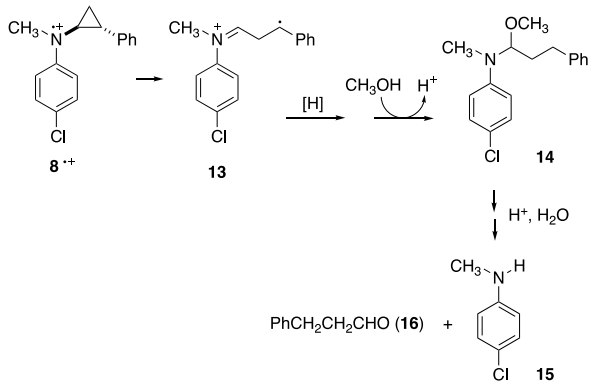


Figure 5. Total ion chromatogram (Q1) of 7 at an electrochemical cell potential of (A) 0 mV and (B) 300 mV. (C) Mass voltammogram of 7. Mass spec ion intensity of the m/z 208 and 240 ions are depicted as a function of the electrochemical cell potential. (D) Total ion chromatogram of 7 at an electrochemical cell potential of 300 mV and in the presence of $^{18}O_2$. (Conditions: 70% CH_3CN/29% H_2O; 1% HCO_2H)

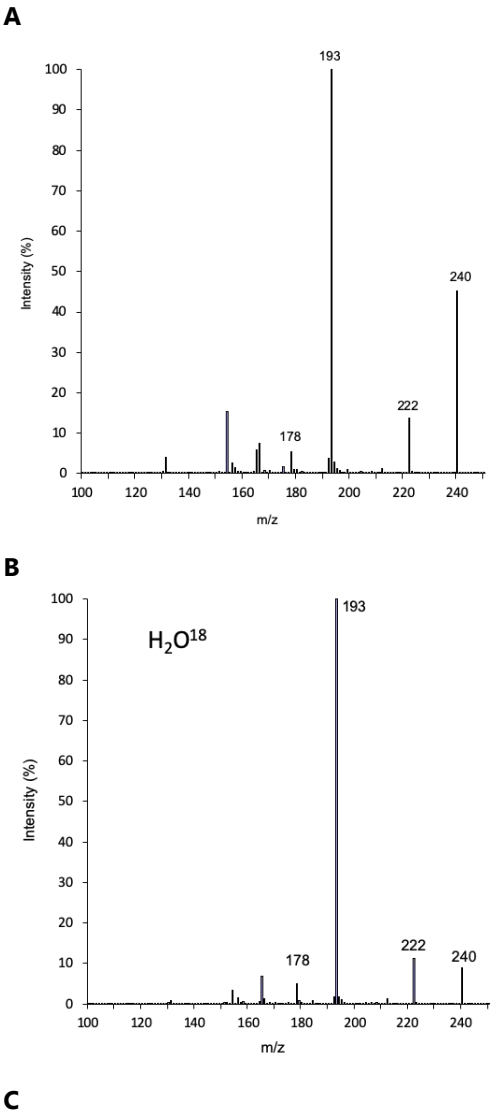


Scheme 7. Products of and proposed mechanism for the preparative scale electrochemical oxidation of 8

Discussion

The oxidation potentials of compounds **5** → **8**, and rate constants for ring opening of the corresponding anilinyl radical cations are summarized in Table 2. Given the assumptions made in the electrochemical treatment and analysis, some comment about the quality of these numbers is appropriate. Through Eqs. 4 and 7, it can be seen that the values for E^o and k_o are linked, *e.g.*, a roughly 30 mV variation in E^o corresponds to an order of magnitude variation in the derived rate constant. To probe the viability of our derived E^os further, the oxidation potentials of a series of substituted *N,N*-dimethyl anilines (*p*-X-$C_6H_4NMe_2$, with X = CH_3O, CH_3, H, Cl) were measured in our lab under identical conditions. These, and the values for compounds **5** → **8** were then compared to their calculated (Spartan 18: B3LYP/6-31G* with the CPCM solvent model)[45] adiabatic ionization potentials, taken as the energy difference between the neutral and radical cation.[46] An excellent correlation is observed for all these compounds (Figure 7), suggesting the experimentally derived values are reasonable and valid.

Rate constants for ring opening differed by several orders of magnitude in the order **8**$^{\bullet+}$ >> **5**$^{\bullet+}$ > **6**$^{\bullet+}$ ≈ **7**$^{\bullet+}$, with the quinoline derivatives being the slowest. "Cyclization," fusing the cyclopropyl into 6-membered ring to force the *N*-cyclopropyl group into more of a bisected conformation, had the *opposite* effect expected if stereoelectronic factors were responsible for the sluggish ring opening of **5**$^{\bullet+}$. Thus, the likely culprit is resonance stabilization of the ring-closed radical cation.



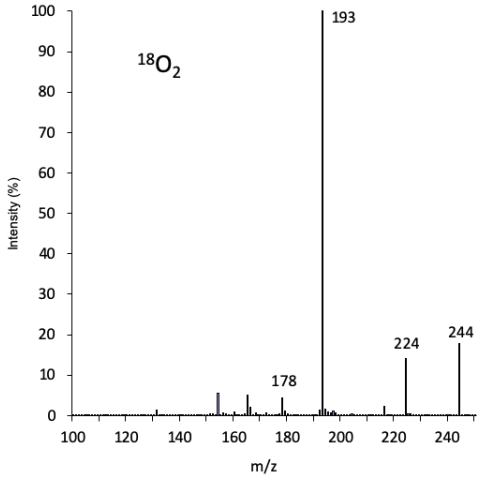


Figure 6. Fragmentation observed for the m/z = 240 peak a) original, b) in the presence of H_2O^{18}, and c) of the newly observed m/z = 244 peak in the presence of $^{18}O_2$.

Table 2. Oxidation potentials of compounds 5 → 8 and kinetic data pertaining to the ring opening of their corresponding radical cations.

Compound	E^o (V)	k_o (s^{-1})		$\Delta G^{\neq}_{exp}$ (kcal/mol)[1]	$\Delta G^{\neq}_{th}$ (kcal/mol)[2]
5	0.528	$4.1\ 10^4$	x	11	10.2
6	0.300	$3.5\ 10^2$	x	14	11.1
7	0.366	$4.1\ 10^2$	x	14	11.7
8	0.530	$1.7\ 10^8$	x	6.2	1.5

[1]Experimental: From the observed rate constant at 298 K, calculated using the Eyring equation.

[2]Theory: DFT calculations performed at the PBEPBE-D3/6-311+G(d,p) level.

And of course, the large rate constant observed for ring opening of **8**$^{\bullet+}$ clearly shows that the loss of resonance stabilization of the ring-closed form can be offset in the transition state by radical-stabilizing groups on the cyclopropane ring. The rate constant for the rearrangement of **8**$^{\bullet+}$ approaches that of the cyclopropylcarbinyl → homoallyl neutral radical rearrangement, and as such, compounds such as **8** emerge as superb probes for single electron transfer.

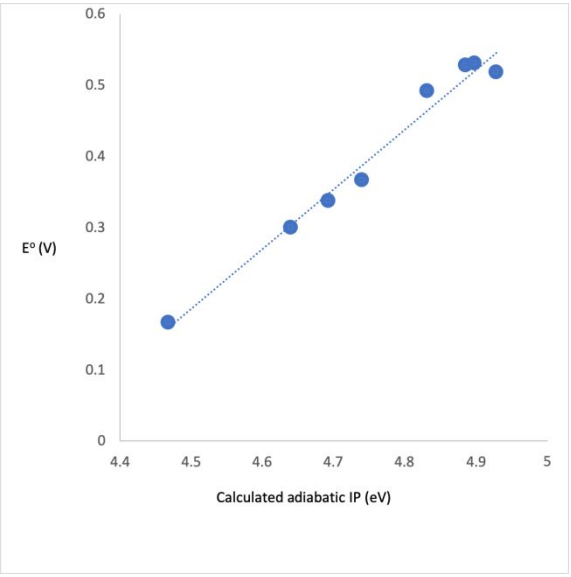


Figure 7. Experimental oxidation potentials for compounds 5 → 8 and several *p*-substituted *N*,*N*-dimethylanilines *vs*. their calculated adiabatic ionization potentials (B3LYP/6-31G* with the CPCM solvent model.)

To further understand the interplay between structure and reactivity, density functional theory (DFT) computations were performed at the PBEPBE-D3/6-311+G(d,p) level using the Gaussian 09 suite of programs[47] (see the Supporting Information more detail.) Consistent with experiment, compared to **5**$^{\bullet+}$, the calculations show that the presence of the radical-stabilizing phenyl group affixed to the cyclopropyl ring in **8**$^{\bullet+}$ resulted in a much lower barrier for ring opening, whereas tethering the cyclopropyl ring and aryl group through a two carbon linker as in quinoline derivatives **6**$^{\bullet+}$ and **7**$^{\bullet+}$ led a higher calculated barrier. The four lowest energy cyclopropyl ring opening transition states for these radical cations (**TS5** → **TS8**) were located and are depicted in Figure 8. Notably, the computed Gibbs free energy activation barriers ($\Delta G^{\neq}$) were in general agreement with the observed experimental values for **5**$^{\bullet+}$ → **7**$^{\bullet+}$, though the barriers were consistently underestimated; the calculated barrier for **8**$^{\bullet+}$ was significantly lower than the experimental value (Table 2).

Further inspection of **TS5** → **TS8** revealed the lengths of the rupturing C···C bonds spanned distances of 1.90 - 2.12 Å, with **TS8** having the shortest, consistent with an early transition state resembling the reactant (Figure 8A). This makes sense given greater radical stabilization by the additional phenyl ring attached to the cyclopropyl group. Along with this variation in bond breaking distances was a noticeable "gearing" of the Ar-N-C dihedral angle ($Ø_{C(1)\text{-}C(2)\text{-}N\text{-}C(3)}$) from 44.9° in **TS5** to 34.0° in **TS8**, with comparably smaller dihedral angles of ~27.0° in **TS6** and **TS7**, respectively (Figure 8A, far right-hand side). With this gearing was reduced electronic communication between the nitrogen atom and aryl ring systems, as supported by natural bond orbital (NBO) second order perturbation theory analysis. For instance, as seen from Figure 8A (right-hand side), in **TS5** an $n \rightarrow \pi^*$ donor-acceptor interaction of 5.6 kcal mol $^{-1}$ was present *vs.* values nearly doubling that of 9.3 kcal mol^{-1} and 9.6 kcal mol^{-1} in **TS6** and **TS7**.

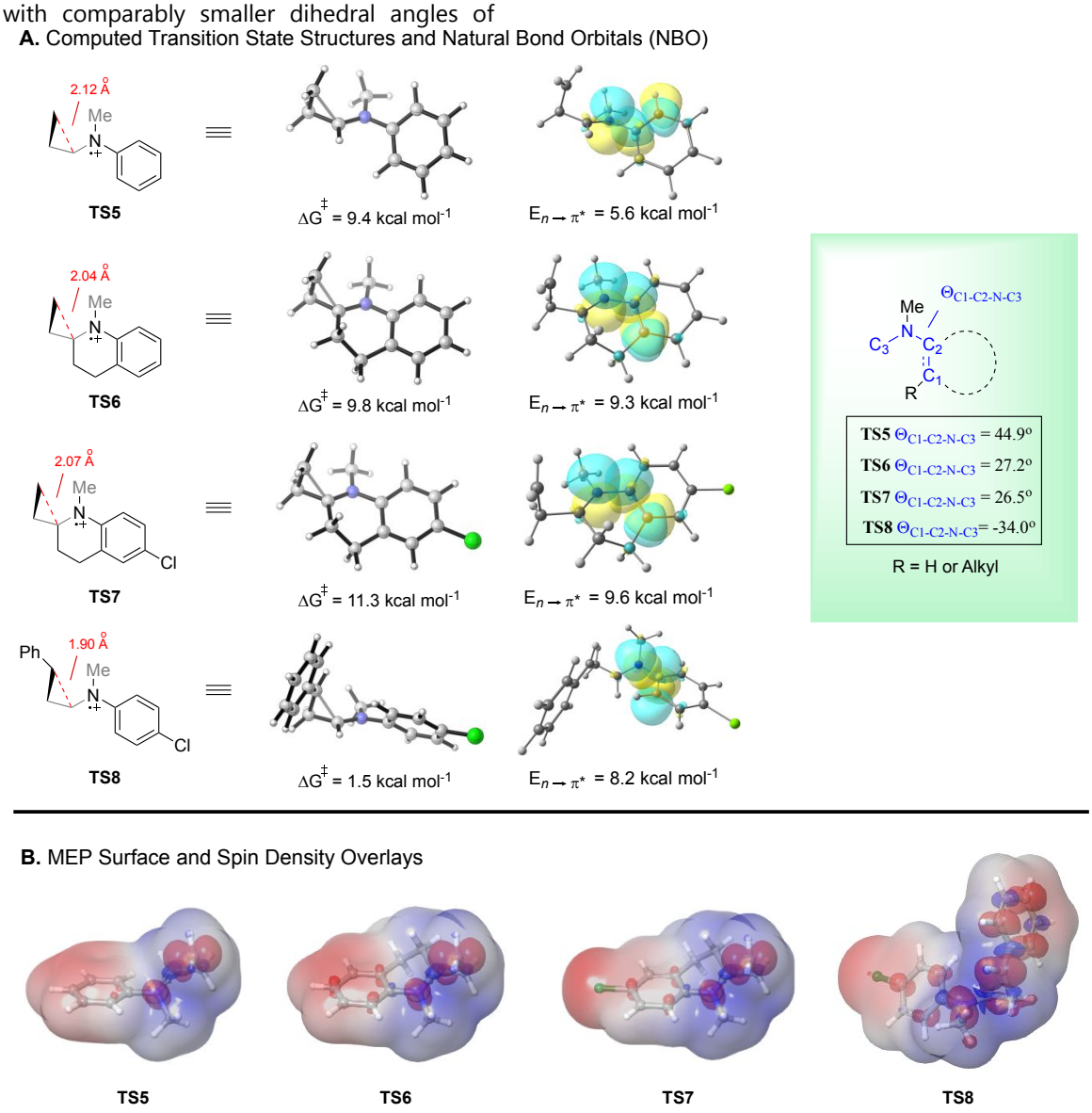


Figure 8. (A) ChemDraw and computed structures of TS5 → TS8 with corresponding Gibbs free energies of activation ($\Delta G^{\neq}$) in kcal mol^{-1} (left-hand side) with respective natural bond order (NBO) $n \rightarrow \pi^*$ donor–acceptor interactions (right-hand side). (B) Molecular electrostatic potential (MEP) surfaces of TS5 - TS8 with superimposed spin orbital density.

In line with this picture of nitrogen-aryl conjugation, was a marginal loss of positive charge (Mulliken) at nitrogen in **TS5** (+0.531) relative to **TS6** and **TS7** (+0.567 and +0.575, respectively). As for **TS8**, certainly a more complex case, the analogous donor-acceptor interaction had a value of 8.2 kcal/mol and the charge at nitrogen was +0.697.

Graphically, a more global view of this variation in charge is evident from the molecular electrostatic potential (MEP) surfaces in Figure 8B, with the spin densities superimposed for comparison. Clear from these overlays is an interesting relationship between spin and charge. Consider, *e.g.*, the overlaid charge-and-spin densities of transition state **TS5** → **TS7**, in which greater negative charge resides on the aryl ring systems at the expense of decreased electron density at nitrogen and the opening cyclopropyl ring bearing the majority of localized spin. At the extreme, however, **8**$^{\bullet+}$ is the most reactive owing to the presence of a cyclopropyl adjoined phenyl group allowing for further delocalization of spin into the adjacent aryl π-system. This stabilizing effect is evident from the overlaid charge-and-spin of **TS8** depicted in Figure 8B, displaying significant accumulation of spin into the phenyl π-system. Taken together it is clear from these models that there exists an interrelation between localization of spin and charge in these systems that to a degree is regulated by aryl-nitrogen conjugation.

Finally, for **6** and **7**, "cyclization" also lowered the oxidation potential of these compounds. A possible explanation is that the cyclopropyl group is more of an π-electron donating group than other alkyl groups as gauged by the Hammett σ^+ substituent constants: For CH_3 → $C(CH_3)_3$, σ^+ = -.26 → -.31. while for *c*-C_3H_5, σ^+ = -0.41.[48] Locking the cyclopropyl group into the bisected conformation would maximize its electron donating nature, stabilizing the ring-closed radical cation.)[30, 32-34]

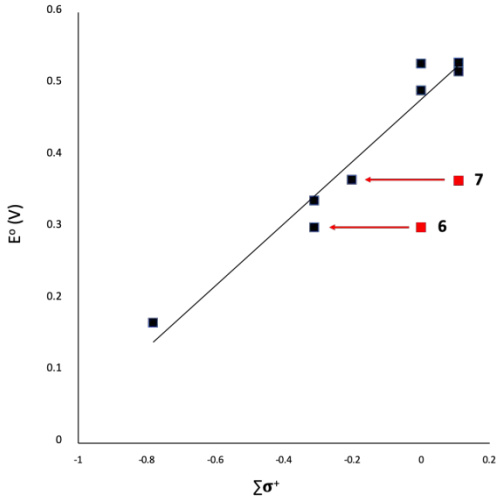


Figure 9. Experimental oxidation potentials for compounds 5 → 8 and several *p*-substituted *N*,*N*-dimethylanilines *vs*. Hammett σ^+ substituent constants. Adjusting $\sum\sigma^+$ for 6 and 7 to account for the added ortho substituent brings these points in line with the other aniline derivatives.

However, we believe the more likely explanation is that "cyclization" effectively introduces an alkyl (electron donating) substituent to the ortho position. Figure 9 shows a Hammett plot comparing the oxidation potentials of compounds **5** → **8**, and those of several other *N*,*N*-dimethyl anilines vs. the σ^+ substituent constant. Compounds **6** and **7** clearly fall off the line. However, adjusting the $\sum\sigma^+$ values for **6** and **7** to account for this *ortho* substitution, assuming that σ^+ for the ortho alkyl group (CH_2) introduced by cyclization is the same as for an alkyl group in the para position (CH_2CH_3), brought these points back onto the line without any need to adjust for the *N*-cyclopropyl substituent. (ρ^+ = -7.4 from a plot of $FE^o/(2.303RT)$ *vs*. σ^+.)

Conclusion

The experimental and computational results described herein clearly illustrate the interplay between structure and reactivity in the design of *N*-cyclopropyamines as probes for radical cation intermediates in oxidative processes. Because radical cations derived from *N*-cyclopropylanilines in particular are intrinsically stabilized by resonance interactions, rate constants for cyclopropyl ring opening are extremely low because this stabilization is lost in the transition state. As such, compounds **5** → **7** are poor probes for single electron transfer because ring opening would not be competitive with other processes such as radical cation deprotonation. In contrast, the results for **8** demonstrate that the resonance stabilization afforded **8**$^{\bullet+}$ in the ring-closed form can be amply compensated in the transition state for ring opening by the incorporation of a radical-stabilizing phenyl substituent on the cyclopropyl group. As such, compounds such as **8** are expected to be outstanding probes for single electron transfer. (However, the rate of ring opening is still several orders of magnitude slower than the corresponding phenyl-substituted cyclopropylcarbinyl radical.)[49]

ASSOCIATED CONTENT

Supporting Information

Material and methods, synthesis of **6** → **8** and the substituted ferrocenes, list of E^os for various ferrocenes, representative cyclic voltammograms and plots pertaining to the LSV and HRC studies of **6** → **8**, detailed analysis and proposed pathways for the EC-ESI/MS analysis of **7**, and structural data pertaining to the DFT calculations. (PDF)

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* jtanko@vt.edu

Notes

The authors declare no competing financial interest.

Present Addresses

[†]Chemistry Program, Division of Natural Sciences, University of Guam, UOG Station, Mangilao, Guam, 96923, USA

[‡]Division of Natural Sciences, Bennington College, One College Drive, Bennington, VT 05201, USA

[§]Montreat College, Montreat, NC 28757, USA

[⊥]Department of Chemistry, Brock University, St. Catharines, ON, L2S 3A1, CANADA

Author Contributions

All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

We thank Dr. Mehdi Ashraf-Khorassani for technical assistance with the EC/ESI-MS experiments. Funding for this work came from the National Science Foundation (CHE-0548129), Department of Chemistry and the College of Science at Virginia Tech.

REFERENCES

1. Loeppky, R. N.; Singh, S. P.; Elomari, S.; Hastings, R.; Theiss, T. E., Evidence for radical cations in linked mechanisms of N,N-dialkyl aromatic amine nitration and nitrosative dealkylation. *J. Am. Chem. Soc.* **1998,** *120*, 5193 - 5202.
2. Loeppky, R. N.; Elomari, S., N-Alkyl-N-cyclopropylanilines as mechanistic probes in the nitrosation of N,N-dialkyl aromatic amines. *J. Org. Chem.* **2000,** *65*, 96 - 103.
3. Wimalasena, K.; Wickman, H. B.; Mahindaratne, M. P. D., Autocatalytic radical ring opening of N-cyclopropyl-N-phenylamines under aerobic conditions - exclusive formation of the unknown oxygen adducts, N-(1,2-dioxolan-3-yl)-N-phenylamines. *Eur. J. Org. Chem.* **2001**, 3811 - 3817.
4. Blackburn, A.; Bowles, D. M.; Curran, T. T.; Kim, H., Air oxidation of N-cyclopropylanilines. *Synthetic Communications* **2012,** *42*, 1855 - 1863.
5. Shearer, J.; Zhang, C. X.; Zakharov, L. N.; Rheingold, A. L.; Karlin, K. D., Substrate oxidation by copper-dioxygen adducts: mechanistic considerations. *J. Am. Chem. Soc.* **2005,** *127*, 5469 - 5483.
6. Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N., Intermolecular [3+2] cycloaddition of cyclopropylamines with olefins by visible-light photocatalysis. *Angew. Chem. Int. Ed.* **2012,** *51*, 222 - 226.
7. Silverman, R. B., Radical ideas about monoamine oxidase. *Acc. Chem. Res.* **1995,** *28*, 335 - 342.
8. Franot, C.; Mabic, S.; Castagnoli, N., Chemical model studies on the monoamine oxidase-B catalyzed oxidation of 4-substituted 1-cyclopropyl-1,2,3,6-tetrahydropyridines. *Bioorg. Med. Chem.* **1998,** *6*, 283 - 291.
9. Rimoldi, J. M.; Wang, Y.-X.; Nimkar, S. K.; Kuttab, S. H.; Anderson, A. H.; Burch, H.; Castagnoli, N., Probing the mechanism of bioactivation of MPTP type analogs by monoamine oxidase B: Structure-activity studies on substituted 4-phenoxy-, 4-phenyl-, and 4-thiophenoxy-1-cyclopropyl-1,2,3,6-tetrahydropyridines. *Chem. Res. Toxicol.* **1995,** *8*, 703 - 710.
10. Hanzlik, R. P.; Tullman, R. H., Suicidal inactivation of cytochrome p-450 by cyclopropylamines. Evidence for cation-radical intermedites. *J. Am. Chem. Soc.* **1982,** *104*, 2048 - 2050.
11. Bhakta, M.; Hollenberg, P. F.; Wimalasena, K., Evidence for a hydrogen abstraction mechanism in P450-catalyzed N-dealkylations. *Chem. Commun.* **2005**, 265 - 267.
12. Totah, R. A.; Hanzlik, R. P., Detection of aminium ion intermediates: N-Cyclopropyl versus N-carboxymethyl groups as reporters. *J. Am. Chem. Soc.* **2001,** *123*, 10107 - 10108.
13. Chen, H.; de Groot, M. J.; Vermeulen, N. P. E.; Hanzlik, R. P., Oxidative N-dealkylation of p-cyclopropyl-N,N-dimethylaniline. A substituent effect on a radical-clock reaction rationalized by ab initio calculations on radical cation intermediates. *J. Org. Chem.* **1997,** *62*, 8227 - 8230.
14. Shaffer, C. L.; Morton, M. D.; Hanzlik, R. P., Enzymatic N-dealkylation of an N-cyclopropylamine: An unusual fate for the cyclopropyl group. *J. Am. Chem. Soc.* **2001,** *123*, 349 - 350.
15. Cerny, M. A.; Hanzlik, R. P., Cytochrome P450-catalyzed oxidation of N-benzyl-N-cyclopropylamine generates both cyclopropanone hydrate and 3-hydroxypropionaldehyde via hydrogen abstraction, not single electron transfer. *J. Am. Chem. Soc.* **2006,** *128*, 3346 - 3354.
16. Bhakta, M. N.; Wimalasena, K., Microsomal P450-catalyzed N-dealkylation of N,N-dialkylanilines: Evidence for a Cα-H abstraction mechanism. *J. Am. Chem. Soc.* **2002,** *124*, 1844 - 1845.
17. Bhakta, M. N.; Wimalasena, K., A mechanistic comparison between cytochrome P450- and chloroperoxidase-catalyzed N-dealkylation of N,N-dialkyl anilines. *Eur. J. Org. Chem.* **2005**, 4801 - 4805.
18. Guengerich, F. P.; Willard, R. J.; Shea, J. P.; Richards, L. E.; Macdonald, T. L., Mechanism-based inactivation of cytochrome P-450 by heteroatom-substituted cyclopropanes and formation of ring-opened products. *J. Am. Chem. Soc.* **1984,** *106* (6446 - 6447).
19. Jurva, U.; Bissel, P.; Isin, E. M.; Igarashi, K.; Kuttab, S.; Castagnoli, N., Model electrochemical-mass spectrometric studies of the cytochrom P450-catalyzed oxidations of cyclic tertiary allylamines. *J. Am. Chem. Soc.* **2005,** *127*, 12368 - 12377.
20. Roberts, K. M.; Jones, J. P., Anilinic N-oxides support cytochrome P450-mediated N-dealkylation through hydrogen-atom transfer. *Chem. Eur. J.* **2010,** *16*, 8096 - 8107.
21. Li, D.; Wang, Y.-X.; Yang, C.; Han, K., Theoretical study of N-dealkylation of N-cyclopropyl-N-methylaniline catalyzed by cytochrome P450: instight into the origin of regioselectivity. *Dalton Trans.* **2009**, 291 - 297.
22. Shaffer, C. L.; Harriman, S.; Koen, Y. M.; Hanzlik, R. P., Formation of cyclopropanone during cytochrome P450-catalyzed N-dealkylation of a cyclopropylamne. *J. Am. Chem. Soc.* **2002,** *124*, 8268 - 8274.

23. Bhakta, M.; Hollenberg, P. F.; Wimalasena, K., P450/NADPH/O2- and P450/PhIO-catalyzed N-dealkylations are mechanistically distinct. *J. Am. Chem. Soc.* **2005,** *127*, 1376 - 1377.

24. Shaffer, C. L.; Morton, M. D.; Hanzlik, R. P., N-Dealkylation of an N-cyclopropylamine by horseradish peroxidase. Fate of the cyclopropyl group. *J. Am. Chem. Soc.* **2001,** *123*, 8502 - 8508.

25. Totah, R. A.; Hanzlik, R. P., Oxidative and nonoxidative decarboxylation of N-alkyl-N-phenylglycines by horseradish peroxidase. Mechanistic switching by varying hydrogen peroxide, oxygen, and solvent deuterium. *Biochemistry* **2004,** *43*, 7907 - 7914.

26. Chen, Z.-W.; Zhao, G.; Martinovic, S.; Jorns, M. S.; Mathews, F. S., Structure of the sodium borohydride-reduced N-(cyclopropyl)glycine adduct of the flavoenzyme monomeric sarcosine oxidase. *Biochemistry* **2005,** *44*, 15444 - 15450.

27. Qin, X.-Z.; Williams, F., ESR studies on the radical cation mechanism of the ring opening of cyclopropylamines. *J. Am. Chem. Soc.* **1987,** *109*, 595 - 597.

28. Wang, Y.-X.; Luttrull, D. K.; Dinnocenzo, J. P.; Goodman, J. L.; Farid, S.; Gould, I. R., Associative return electron transfer. A bond-coupled electron transfer in the photoreactions of cyclopropylamines. *Photochem. Photobiol. Sci.* **2003,** *2*, 1169 - 1176.

29. Bouchoux, G.; Alcaraz, C.; Dutuit, O.; Nguyen, M. T., Unimolecular chemistry of the gaseous cyclopropylamine radical cation. *J. Am. Chem. Soc.* **1998,** *120*, 152 - 160.

30. Cooksy, A. L.; King, H. F.; Richardson, W. H., Molecular orbital calculations of ring opening of the isoelectronic cyclopropylcarbinyl radical, cyclopropoxy radical, and cyclopropylaminium radical cation series of radical clocks. *J. Org. Chem.* **2003,** *68*, 9441 - 9452.

31. Li, X.; Grimm, M. L.; Igarashi, K.; Castagnoli, N.; Tanko, J. M., The first calibration of an aminiumyl radical ion clock: Why N-cyclopropylanilines may be poor mechanistic probes for single electron transfer. *Chem. Commun.* **2007**, 2648 - 2650.

32. Bauld, N. L.; McDermed, J. D.; Hudson, C. E.; Rim, Y. S.; Zoeller, J.; Gordon, R. D.; Hyde, J. S., Conformation analysis of cyclopropyl groups attached to trigonal carbon in organic radicals. *J. Am. Chem. Soc.* **1969,** *91*, 6666 - 6676.

33. de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E., Radical cations of trialkylamines: ESR spectra and structures. *J. Org. Chem.* **1999,** *64*, 6951 - 6959.

34. Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J. M.; Hudlicky, T., Use of cyclopropanes and their derivatives in organic synthesis. *Chem. Rev.* **1989,** *89*, 165 - 198.

35. Yang, H.; Wipf, D. O.; Bard, A. J., Application of rapid scan cyclic voltammetry to a study of the oxidation and dimerization of N,N-dimethylanilne in acetonitrile. *J. Electroanal. Chem.* **1992,** *331*, 913 - 924.

36. Andrieux, C. P.; Savéant, J. M., Electrochemical Reactions. In *Investigations of Rates and Mechanisms of Reactions, Part II.*, Bernasconi, C., Ed. Wiley: New York, 1986; pp 305 - 390.

37. Rao, V. R.; Hixson, S. S., Arylcyclopropane photochemistry. Electron-transfer-mediated photochemical addition of methanol to arylcyclopropanes. *J. Am. Chem. Soc.* **1979,** *101*, 6458 - 6459.

38. Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, W. P.; Todd, W. P.; Heinrich, T., Three-electron SN2 reactions of arylcyclopropane cation radicals. 1. Mechanism. *J. Am. Chem. Soc.* **1997,** *119*, 987 - 993.

39. Dinnocenzo, J. P.; Zuilhof, W. P.; Lieberman, D. R.; Simpson, T. R.; McKechney, M. W., Three-electron SN2 reactions of arylcyclopropane cation radicals. 2. Steric and electronic effects of substitution. *J. Am. Chem. Soc.* **1997,** *119*, 994 - 1004.

40. Nadjo, L.; Savéant, J. M., Linear sweep voltammetery: Kinetic control by charge transfer and/or secondary chemical reacitons. *Electroanal. Chem.* **1973,** *48*, 113 - 145.

41. Costentin, C.; Robert, M.; Savéant, J. M., Fragmentation of aryl halide *J. Am. Chem. Soc.* **2004,** *126*, 16051 - 16057.

42. Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; M'Halla, F.; Savéant, J. M., Homogeneous redox catalysis of electrochemical reactions. Part V. Cyclic voltammetry. *J. Electroanal. Chem.* **1980,** *113*, 19 - 40.

43. Savéant, J. M.; Su, K. B., Homogeneous redox catalysis of multielectron electrochemical reactions. Part I. Competition between heterogeneous and homogeneous electron transfer. *J. Electroanal. Chem.* **1985,** *196*, 1 - 22.

44. Stevenson, J. P.; Jackson, W. F.; Tanko, J. M., Cyclopropylcarbinyl-type ring openings. Reconciling the chemistry of neutral radicals and radical anions. *J. Am. Chem. Soc.* **2002,** *124*, 4271 - 4281.

45. *Spartan '18*, Wavefunction, Inc.: Irvine, CA.

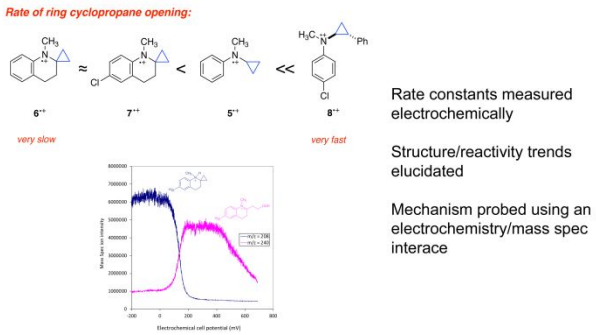
46. Speelman, A. L.; Gillmore, J. G., Efficient computational methods for accurately predicting reduction potentials of organic molecules. *J. Phys. Chem. A* **2008,** *112*, 5684 - 5690.

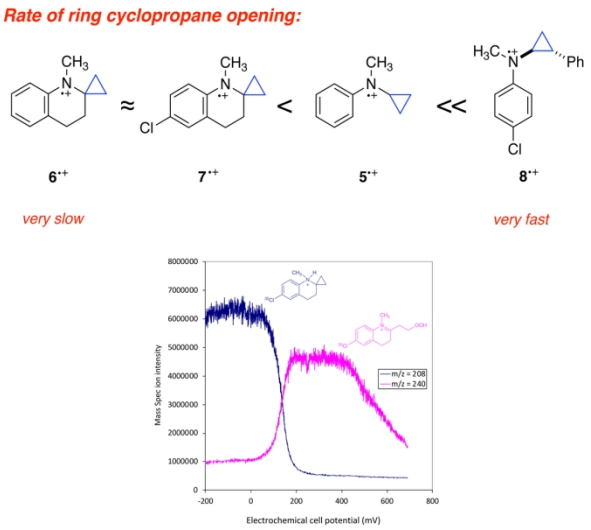
47. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; J. A. Montgomery, J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09* Gaussian, Inc.: Wallingford CT, 2009.

48. Hansch, C.; Leo, A.; Taft, R. W., A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991,** *91*, 165 - 195. 1. Loeppky, R. N.; Singh, S. P.; Elomari, S.; Hastings, R.; Theiss, T. E., Evidence for radical cations in linked mechanisms of N,N-dialkyl aromatic amine nitration and nitrosative dealkylation. *J. Am. Chem. Soc.* **1998,** *120*, 5193 - 5202.

49. Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R., Picosecond radical kinetics. Ring openings of phenyl substituted cyclopropylcarbinyl radicals. *J. Am. Chem. Soc.* **1992,** *114*, 10915 - 10921.

Table of Contents artwork





Rate constants measured electrochemically

Structure/reactivity trends elucidated

Mechanism probed using an electrochemistry/mass spec interace

82x44mm (600 x 600 DPI)