

Supplementary Information for

**The First Calibration of an Aminiumyl Radical Ion Clock:
Why *N*-Cyclopropylanilines May Be Poor Mechanistic Probes
for Single Electron Transfer**

Xiangzhong Li, Michelle Grimm, Neal Castagnoli, Jr., Kazuo Igarashi, and J. M. Tanko

Department of Chemistry

Virginia Polytechnic Institute and State University

Blacksburg, VA 24061

I. Laser flash photolysis results

Table S1. Absorption maxima and apparent lifetimes of radical cations generated from **4** \rightarrow **7**

Species	λ_{\max} (nm)	t (ms)
4 ^{•+}	460, 480	0.72
5 ^{•+}	460	0.93
6 ^{•+}	480	0.58
7 ^{•+}	470 - 490	0.21

II. Direct and indirect electrochemistry results

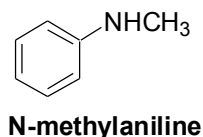
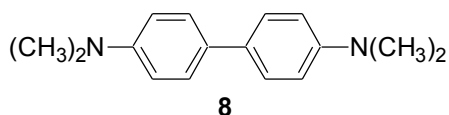
Table S2. Linear sweep voltammetry results for the direct oxidation of *N,N*-dimethylaniline (**4**) and *N*-cyclopropyl-*N*-methylaniline (**6**)

Compound	$\eta E_p/\eta \log(n)^a$	$\eta E_p/\eta \log[A]^a$	$\eta E_p/\eta \log[CH_3OH]^a$
4	18.4	-20.0	0.7
	(19.7) ^b	(-19.7) ^b	(0.0) ^b
6	31.7	0.7	0.1
	(29.6) ^c	(0.0) ^c	(0.0) ^c

^amV/decade. ^bTheoretical response for $-d[A^{•+}]/dt = k[A^{•+}]^2$ (references 1-3). ^cTheoretical response for $-d[A^{•+}]/dt = k[A^{•+}]$ (references 1-3)

A. *N,N*-dimethylaniline (**4**)

1. Consistent with previous electrochemical studies,^{4,5} the radical cation derived from *N,N*-dimethylaniline (**4**^{•+}) undergoes bimolecular decay, $-d[A^{•+}]/dt = k_D [4^{•+}]^2$ (Table S2); neither the neutral amine nor methanol are involved in the rate determining step.⁵
2. The major product of the electrochemical oxidation (preparative scale electrolysis, followed by quenching with NaBH₄) is the expected dimeric product, *N,N,N',N'*-tetramethylbenzidine (**8**);^{4,6} a small amount of *N*-methylaniline is also detected:



3. The estimate of the oxidation potential of **4** (+0.414 V vs. 0.1 M Ag⁺/Ag) is based upon the peak potential data and Eq. 1^{1,2} ($k_D = 6.3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$;⁵ R, T, n, and F have their usual meanings; C_o is the bulk concentration of substrate).

$$E_p = E_{ox}^o + 0.502 \frac{RT}{nF} - \frac{RT}{3nF} \left(\ln \frac{2k_D RTC_o}{3nF\eta} \right) \quad (1)$$

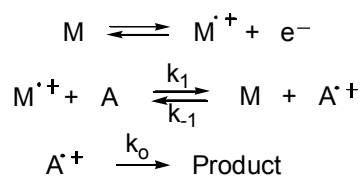
B. N-cyclopropyl-N-methylaniline (**6**)

1. The radical cation generated from **6**^{•+} undergoes first order decay, $-d[\mathbf{6}^{\bullet+}]/dt = k [\mathbf{6}^{\bullet+}]$ (Table S2).
2. With a first order rate law established, a linear relationship between the peak potential (E_p) and $\log(v)$ is expected (Figure S1) in accordance with Eq. 2,^{1,2} where E_A^o is the oxidation potential of the substrate and k_o is the rate constant for ring opening.

$$E_p = E_A^o + \frac{0.78RT}{nF} - \frac{2.303RT}{2nF} \log\left(\frac{kRT}{nF}\right) \log\left(\frac{1}{v}\right) \quad (2)$$

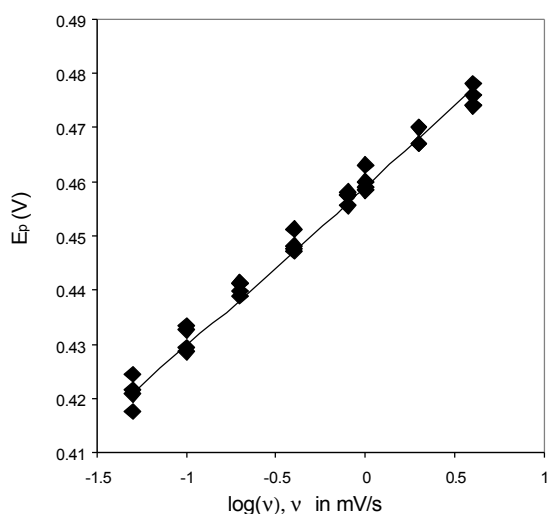
3. Indirect electrochemistry:^{1,7-10} Consider the reactions depicted in Scheme S1. Rather than the substrate **A**, an electron-transfer mediator or catalyst **M** is oxidized at the electrode surface. In order for this to occur, the mediator must be more easily oxidized than the substrate, and the oxidation must be reversible. Oxidation of the substrate occurs in solution (homogeneous) via electron transfer from the oxidized form of the mediator (**M**^{•+}). Effects of substrate addition on this reversible electron transfer are manifested experimentally by an increase in peak current and a loss of reversibility for the cyclic voltammogram of the **M**/**M**^{•+} couple if catalysis is occurring; the experimental observable is the current ratio i_p/i_{pd} , where i_{pd} and i_p are the peak currents in the absence and presence of substrate. Kinetic control may be governed by either the homogeneous electron transfer step (k_1) or the chemical step (k_o) and is easily diagnosed by examining the effect of concentration (at constant $[\mathbf{M}]/[\mathbf{A}]$) on the peak current.

Scheme S1



Three mediators were used for the oxidation of **6**: Ferrocenecarboxaldehyde (+0.309 V), benzoylferrocene (+0.289 V), and ferrocene carboxylic acid (+0.264 V); all potentials are

Figure S1. Variation of peak potential with sweep rate for the direct oxidation of N-cyclopropyl-N-methylaniline (**6**) at various concentrations of substrate and methanol



reported vs. 0.1 M Ag⁺/Ag reference. For each mediator, the chemical step was determined to be rate-limiting, with the electron transfer step as a rapid pre-equilibrium (based upon the fact that i_p/i_{pd} did not vary with substrate concentration at constant $[M]/[A]$; the results are summarized in Figure 2 of the manuscript). Under these conditions, the composite rate constant $k_{obs} = k_o k_1/k_{-1} = k_o K_1$ can be determined by fitting of the i_p/i_{pd} vs. $\log(1/v)$ data to theoretical working curves.^{1,7,11,12}

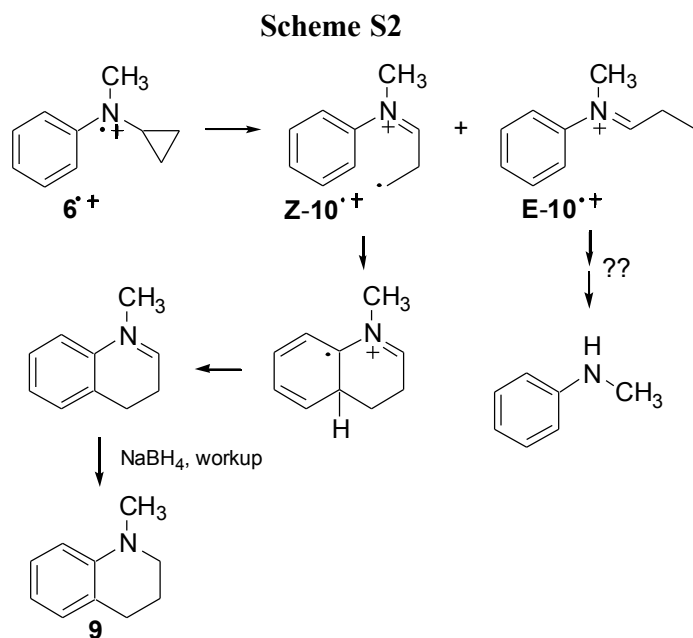
Recognizing that K_1 is related to the difference in the oxidation potentials of the mediator and substrate leads to Eq. 3.

$$k_{obs} = k_o \exp\left(\frac{F(E_M^o - E_A^o)}{RT}\right) \quad (3)$$

There are only two unknowns associated with Eqs. 2 and 3: The rate constant for ring opening (k_o), and the oxidation potential of the substrate E_A^o . Reconciliation of these equations and the data in Figures S1 and 2 (manuscript) leads to $E_A^o = +0.528$ V and $k_o = 4.1 \times 10^4$ s⁻¹. (The solid lines in Figures 1 and 2 are simulated based upon these values).

- Formation of **9** is consistent with ring opening of **6**^{•+} to the distonic radical cation (**Z-10**^{•+}) followed by radical cyclization as shown in Scheme S1. The same oxidation product was observed by Hanzlik, *et al.* in horseradish peroxidase incubation mixtures of

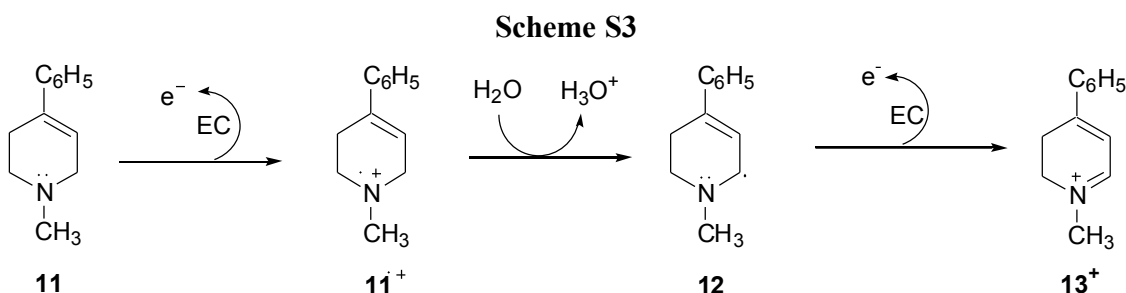
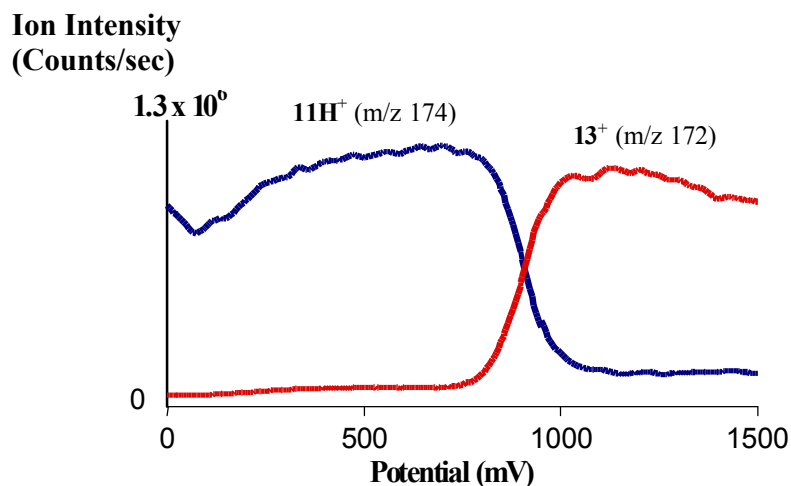
6.^{13,14} The immediate fate of **E-10**^{•+}, which cannot cyclize to a stable product, is not certain although it seems likely that further oxidation and hydrolysis will give *N*-methylaniline. No dimeric products of any kind were detected, consistent with the kinetic results described above which revealed overall first order decay of **6**^{•+}.



III. EC-MS Studies on *N,N*-Dimethylaniline and *N*-Cyclopropyl-*N*-methylaniline

As background information, consider the mass voltammogram of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP (**11**)] shown in Figure S2.¹⁵ The initial oxidation of **11** occurs approximately at 750 mV. The only major oxidation product detected in the full mass spectrum throughout the experiment (0 to 1500 mV) is the corresponding dihydropyridinium species **13**⁺. Scheme S3 rationalizes the oxidation pathway observed with MPTP. The aminyl radical cation **11**^{•+} formed from MPTP undergoes α -carbon deprotonation to yield the α -carbon radical **12** that forms regioselectively, presumably due to its allylic character. A second 1-electron oxidation occurs to yield the dihydropyridinium product **13**⁺.

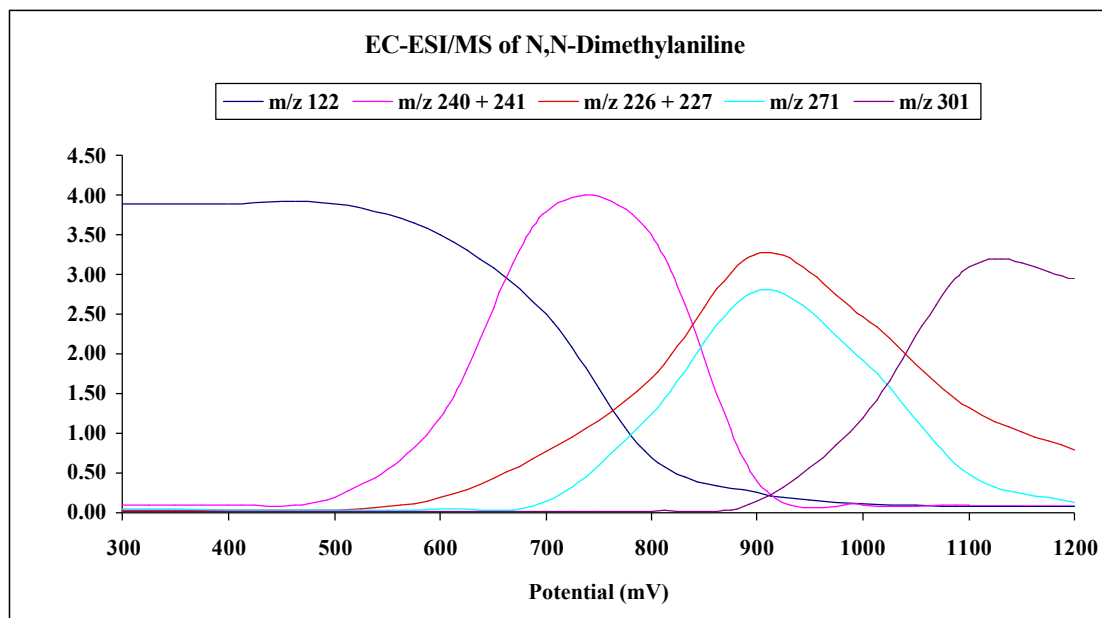
Figure S2. The mass voltammogram obtained with MPTP (**11**, 18 μM in cell) under the following conditions: Direct infusion of sample through the unheated cell in 70% methanol:30% water:0.7% formic acid at a flow rate of 50 $\mu\text{L}/\text{min}$.



The EC-ESI/MS studies reported here were conducted using the ESI source on the Sciex 365 mass spectrometer. The mobile phase was 70% methanol : 30% water with a final concentration of 0.7 % formic acid. The flow rate was 50 $\mu\text{L}/\text{min}$ and the cell was not heated. The concentration of the substrate in the electrochemical cell was 18 μM .¹⁵

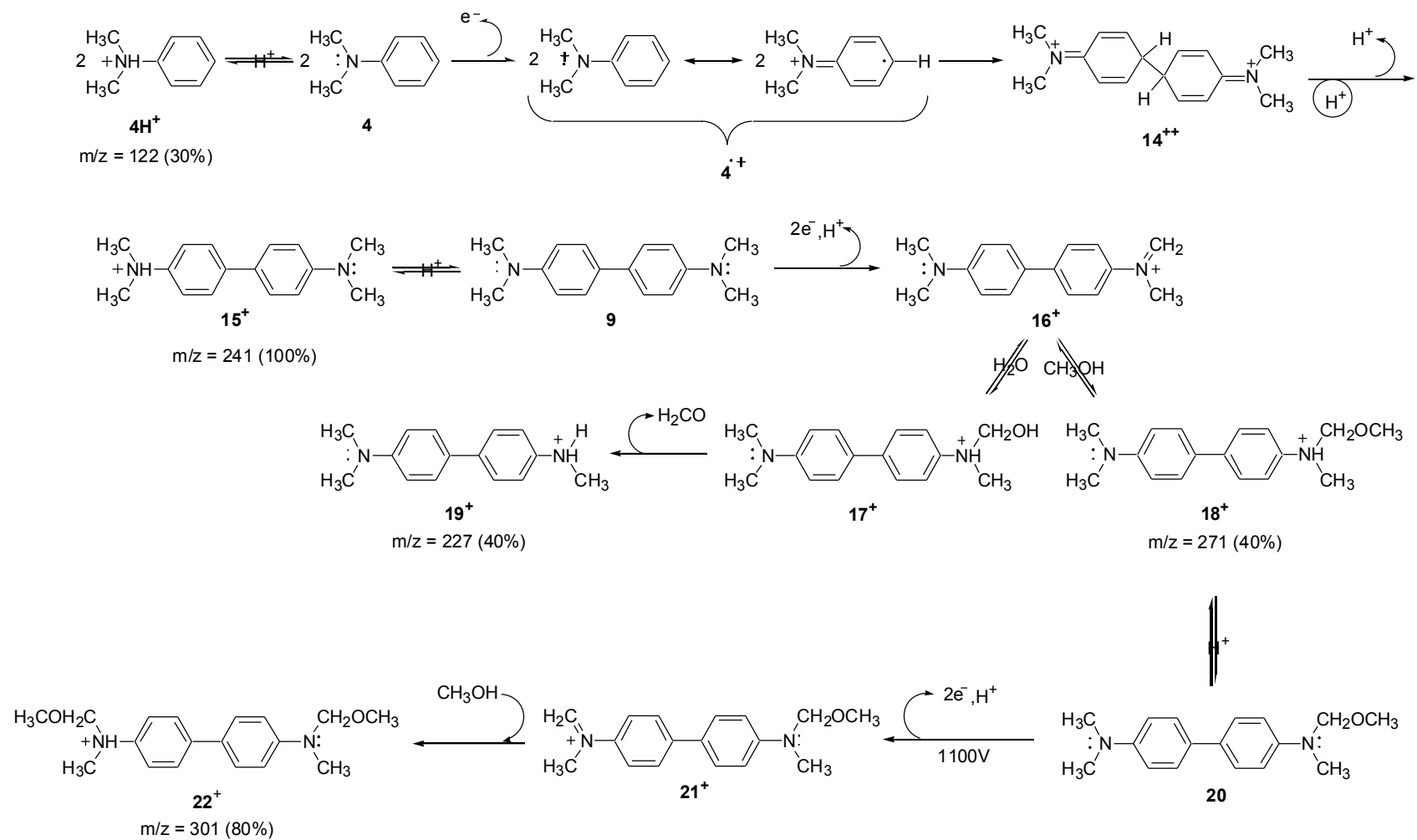
***N,N*-Dimethylaniline (4).** The mass voltammogram obtained with *N,N*-dimethylaniline (Figure S3) shows the initial oxidation of **4** occurring at approximately 600 mV, about 150 mV below the initial oxidation potential of MPTP. The greater ease of oxidation of **4** compared to MPTP may reflect the greater resonance stabilization of the aniliny radical cation **4⁺** vs. the *N*-methylaminyl radical cation **11⁺** formed from MPTP.

Figure S3. The mass voltammogram obtained with *N,N*-dimethylaniline (**4**, 18 μM in cell). For clarity, the ion intensity for the monomeric species 4H^+ at m/z 122 is recorded at 50% of the actual value. The ion intensity for the species at m/z 241 is a sum of the currents observed at both m/z 240 (about 10% of total) and m/z 241 (about 90% of total) since the m/z 240 ion current is due to the in source fragmentation of MH^+ 241. Additionally, a background current (approximately 5% of total) has been subtracted from the plot for 6H^+ at m/z 241.

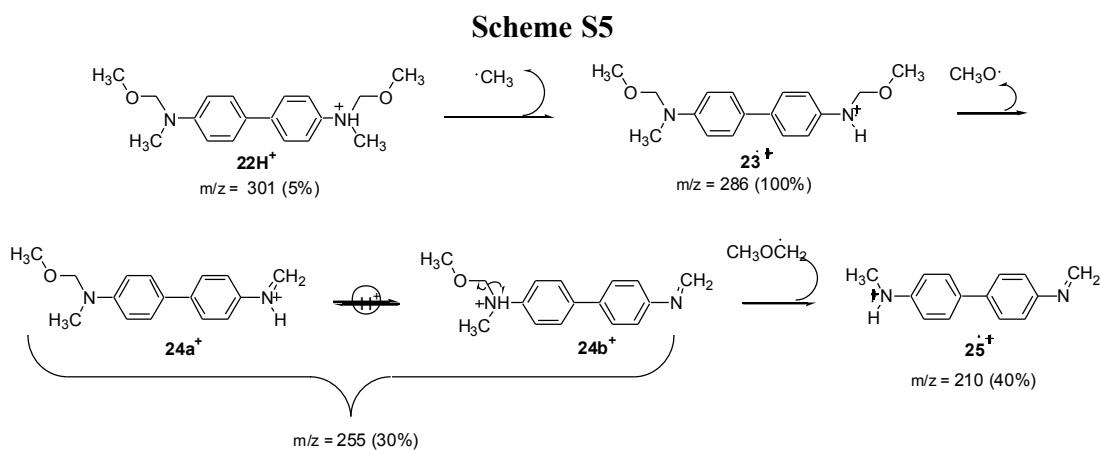


Four principal oxidation products, observed at m/z 227, 240, 271 and 301, are generated from *N,N*-dimethylaniline. Scheme S4 describes pathways that rationalize the formation of these products. Initial 1-electron oxidation of **4** generates the resonance stabilized aniliny radical cation $4^{\bullet+}$. This intermediate undergoes rapid dimerization to form the *biscationic* species 5^{++} (m/z 121) which is not detected. Mono-deprotonation of 14^{++} together with a proton transfer produces the tetramethylbenzidinium product 15^+ , the dominant ion at 750 mV that replaces 4H^+ . The product ion spectra (PIS) of a synthetic sample of 15^+ was identical to that obtained with the EC-generated compound. A second 2-electron oxidation of the free base **9** results in the methylene iminium intermediate 16^+ (m/z 239) which is not detected. This intermediate is converted rapidly to the methanol addition product 18^+ (m/z 271). Although a synthetic standard of 18^+ was not prepared, this pathway was confirmed by observing the shift in mass from m/z 271 to m/z 274 (18^+-d_3) when the mobile phase was made up with CD_3OD . Intermediate 16^+ also hydrates to give 17^+ which undergoes rapid deformylation to yield 19^+ (m/z 227).

Scheme S4



At higher potentials, one also observes an ion at m/z 301. Several structures may be proposed for this species, all of which involve an additional 2-electron oxidation of the *N*-methoxymethylaniline **20** followed by addition of a mole of methanol to the resulting methylene iminium intermediate. The mass shift to m/z 305 with CD_3OD confirms the empirical composition of the product. The pathway shown in Scheme S4 accounts for this transformation. One of the methyl groups of the dimethylamino substituent of **20** is oxidized to the corresponding iminium species **21**⁺. Methoxylation of **21**⁺ gives the *N,N'*-bismethoxymethyl product **22**⁺. Evidence to support the proposed regiochemical outcome was obtained from the PIS of the m/z 301 species (Scheme S5). Three principal fragment ions at m/z 286, 255 and 210 are present in the spectrum. Formation of these fragment ions can be accommodated by (a) loss of $\cdot\text{CH}_3$ from **22H**⁺ to give the radical cation **23**⁺ at m/z 286. Subsequent loss of $\cdot\text{OCH}_3$ leads to the equilibrium pair of the iminium (**24a**⁺)-aminium (**24b**⁺) species at m/z 255. Finally loss of $\cdot\text{CH}_2\text{OCH}_3$ generates **25**⁺ at m/z 210. The *N,N*-bismethoxymethyl isomer (not shown) would not be expected to fragment in this manner.

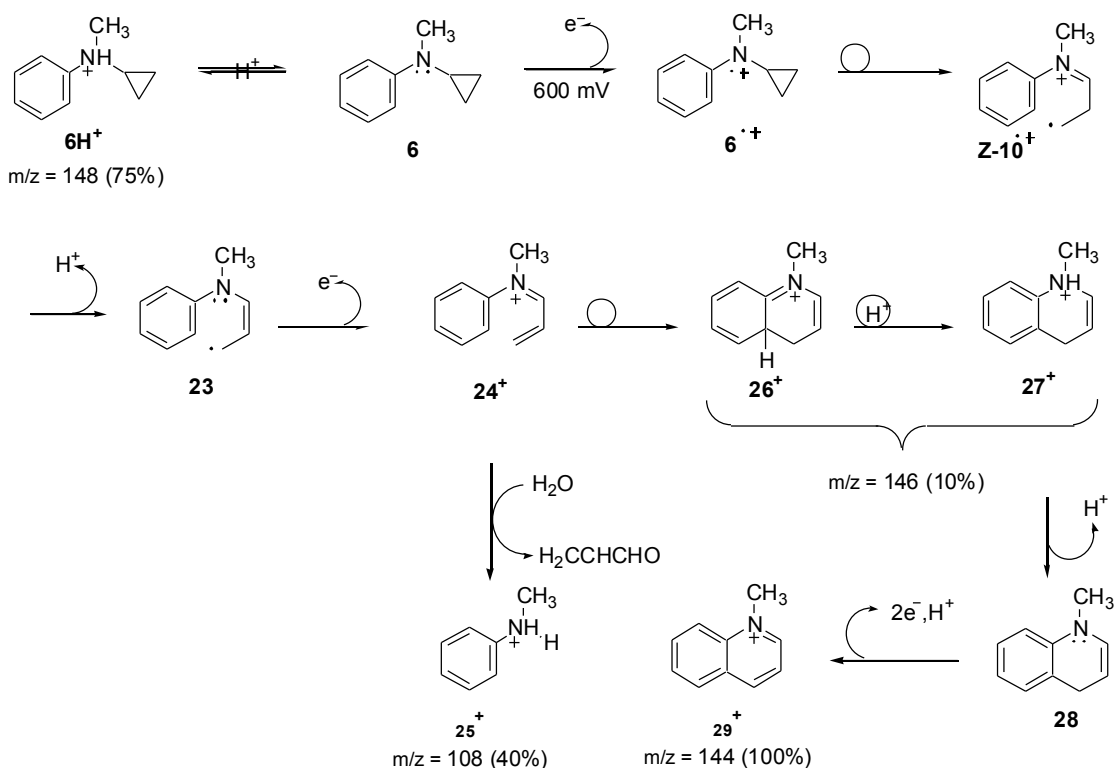


ESI mass spectral analysis demonstrates that synthetic *N,N,N',N'*-tetramethylbenzidine (**9**) undergoes in source fragmentation (loss of H^+) to give a weak signal corresponding to the radical cation **9**⁺ at m/z 240. Figure S2 therefore shows the plot of the sum of these two ion currents which is a more accurate representation of the voltage dependent formation of **9**. A similar phenomenon is observed with the *N,N,N'*-trimethyl product **19**—i.e., a low yield of an ion at m/z 226 follows the curve of ion at m/z 227. The plot in Figure S2 is the sum of these two ion counts as well. Finally, it should be noted that low

intensity signals at m/z 240 and 241 (a total of about 0.25×10^5 counts) are present in the mass voltammogram of **4** between 0 mV and 500 mV. These background signals have been subtracted from the ion intensity plot of m/z 240 + 241.

N-Cyclopropyl-N-methylaniline (6). The principal ions generated in the mass voltammogram of **6** (Figure 1 in manuscript) are observed at m/z 108, 144, 146 and 148. The proposed pathways leading to these products (Scheme S6) start with opening of the cyclopropyl ring of **6**⁺ to give the distonic radical cation **Z-10**⁺. Proton loss from **Z-10**⁺ leads to the allylic, α -carbon radical **23** that loses a second electron to form the eniminium intermediate **24**⁺. Cyclization of **24**⁺ to **26**⁺ followed by proton rearrangement gives the dihydroquinolinium intermediate **27**⁺ that, via free base **28**, undergoes, a second 2-electron oxidation to yield the stable quinolinium product **29**⁺. Comparison of the PIS obtained with the ion at m/z 144 at a collision induced dissociation voltage of 35 V [m/z 144 (100%), 128 (50%) 115 (20%), 103 (50%) and 94 (10%)] with that of synthetic **29** [m/z 144 (100%), 128 (60%) 115 (10%), 103 (35%) and 94 (20%)] confirmed this assignment. An alternative fate of **25**⁺ results in the formation of the hydrolysis product **25**⁺ (MH⁺ at m/z 108).

Scheme S6



IV. References

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