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Reaction of benzophenone triplet with aliphatic amines. What a potent neurotoxin can tell us about the reaction mechanism

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ABSTRACT

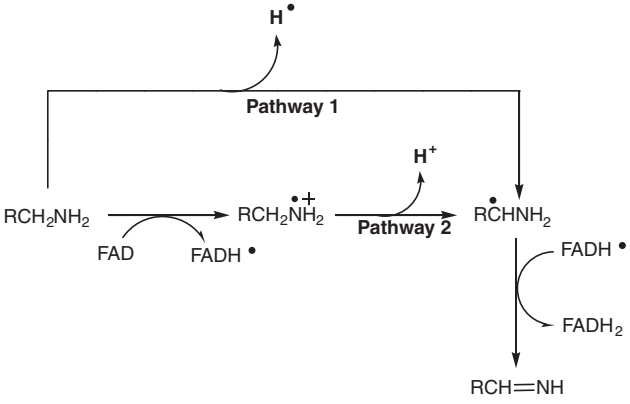
A photochemical model study of benzophenone triplet (^{3}BP) with the MAO-B substrate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP (**1**)] and two of it's derivatives, 1-cyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine (**2**) and (±)-[*trans*-2-phenylcyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine (**3**) were performed. Literature precedent and calculations reported herein suggest that the barrier to ring opening for aminyl radical cations derived from *N*-cyclopropyl derivatives of tertiary amines (such as MPTP) will be low. The LFP results reported herein demonstrate that pathways for the reaction of ^{3}BP with **1**, **2**, and **3** are very similar. In each instance, disappearance of ^{3}BP is accompanied solely by appearance of bands corresponding to the diphenylhydroxylmethyl radical and neutral radical derived from MPTP and it's two derivatives **2** and **3**. These results suggest that the reaction between benzophenone triplet and tertiary aliphatic amines proceed via a simple hydrogen atom transfer reaction. Additionally these model examinations provide evidence that oxidations of *N*-cyclopropyl derivatives of MPTP catalyzed by MAO-B may not be consistent with a pure SET pathway.

1. Introduction

Monoamine oxidase (MAO) A and B are flavoenzymes that catalyze the oxidation of various monoaminergic neurotransmitters, including serotonin and dopamine,[1] as well as some xenobiotics.[2] MAO-A selectively catalyzes the oxidation of serotonin; the B form is the principal enzyme that catalyzes the oxidation of dopamine.[3] MAO-B has gained additional attention since it catalyzes the bioactivation of certain tetrahydropyridinyl derivatives to neurotoxic metabolites that mediate the degradation of dopaminergic neurons in the substantia nigra resulting in a parkinsonian syndrome closely resembling idiopathic Parkinson's disease.[4]

Model studies have led to several proposals to account for the catalytic activity of MAO-B. A polar pathway involving the addition of the aminyl substrate across the 4a–5 double bond of the covalently bound FAD co-factor followed by an intramolecular redox reaction has been proposed by Mariano[5,6] and, more recently, Edmondson.[7] Two radical-based pathways also have been considered. Silverman has been a strong proponent of the single electron transfer (SET) mechanism[1,8] and Castagnoli has presented evidence consistent with a hydrogen atom transfer (HAT) mechanism[2,9] (Scheme 1).

Scheme 1 outlines the differences between the SET and HAT proposals. Although these two pathways can account for some of the behavior of substrates and inhibitors, it is our view that neither of these radical-based mechanisms nor the polar pathway account for all of the available experimental evidence. Since our interests are linked to the MAO-catalyzed metabolic activation of cyclic tertiary allylamines, the discussion that follows will focus on the radical pathways since nucleophilic addition of tertiary amines across the 4a–5 double bond (the polar pathway) should be sterically prohibited. The present manuscript describes the results of our attempts to provide evidence to help distinguish the potential contributions of the SET and HAT mechanisms using photochemically activated benzophenone as the electron or hydrogen atom



Scheme 1. Proposed pathways for MAO oxidations.

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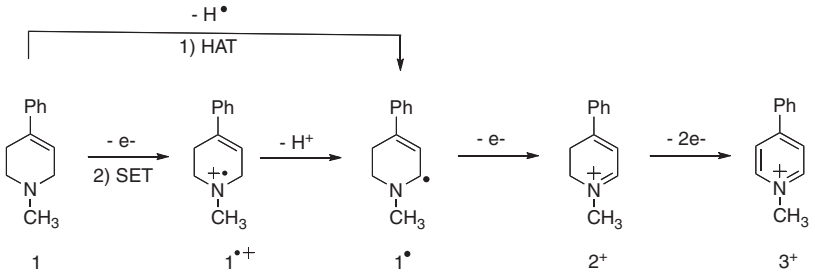


Scheme 2. The MAO-B catalyzed bioactivation of MPTP (**1**) to MPDP$^+$ (**2**$^+$) and MPP$^+$ (**3**$^+$).

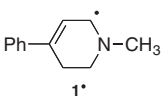
acceptor and various tetrahydropyridinyl derivatives that are known MAO-B substrates and/or for which independent documentation of the fate of electrochemically mediated 1-electron oxidations is available.

Over the past 30 years much focus has been given to 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine [MPTP (**1**)], a compound known to induce an irreversible parkinsonian disorder in humans and animal models.[10,11] Subsequent biochemical studies led to the discovery that MPTP is oxidatively metabolized in the brain to give the dihydropyridiniumyl species MPDP$^+$ (**2**) that subsequently undergoes a two electron oxidation to give the toxic pyridiniumyl product MPP$^+$ (**3**) (Scheme 2).[9] MPP$^+$ is thought to mediate the degeneration of dopaminergic neurons.[4] Mechanistic details of this important bioactivation pathway remain poorly understood. What is known is that the initial 2-electron oxidation is catalyzed efficiently by MAO-B.

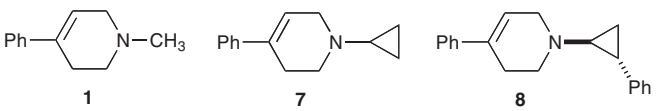
Benzophenone is a common photosensitizer; its chemistry with aromatic amines has been well characterized. Although the products of the reaction give the *appearance* of a hydrogen atom transfer process, laser flash photolysis (LFP) experiments have shown that the reaction of benzophenone triplet (**4**) with aromatic amines proceeds by a single electron transfer, generating a solvent separated ion pair (SSIP) consisting of benzophenone radical anion [(**4**$^{\bullet-}$) λ_{max} = 715 nm] and an aminyl radical cation (**5**$^{\bullet+}$).[12,13] This caged-pair subsequently reacts via proton transfer, with the aminyl radical cation acting as an acid and the benzophenone radical anion as a base, generating diphenylmethanol radical [(**6**) λ_{max} = 545 nm] and the neutral aminyl radical (**5**$^{\bullet}$) (Scheme 3).

Similarly, ^{3}BP reacts readily with aliphatic amines with a reactivity order 3° > 2° > 1°.[9] Rate constants for tertiary and secondary amines are on the order of diffusion controlled, while primary amines are on the order of 10^7 M^{-1} s^{-1}.[14] Although the reaction is also a formal hydrogen atom transfer process, the details of the mechanism remain ambiguous. Assuming electron transfer occurs, proton transfer between the initially produced **4**$^{\bullet-}$/**5**$^{\bullet+}$ caged pair may occur too rapidly for these species to be detected. Also, unlike aromatic amines, spectroscopic characterization of the initially formed $R_3N^{\bullet+}$ is difficult because these species absorb weakly and thus are invisible by UV. Consequently, both hydrogen atom transfer and single electron transfer mechanisms have been suggested for the reactions of benzophenone triplet and aliphatic amines. Achieving an unambiguous assignment of the reaction mechanism has proven problematic.

Recently, we reported rate constants for the reaction of *t*-butoxyl radical (^{t}BuO$^{\bullet}$) with the potent neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[15,16] In this study, ^{t}BuO$^{\bullet}$ was generated by the photolysis of di-*t*-butyl peroxide (DTBPO). This method was employed to measure the absolute rate constants for hydrogen atom abstractions from MPTP by ^{t}BuO**.**, generated by laser flash photolysis (LFP), in order to gain insight into the radical-based chemistry of MPTP. Unlike the radicals derived from HAT in simple aliphatic amines,[17,18] the MPTP derived radical (**1**$^{\bullet}$) gave rise to a transient species (λ_{max} = 385 nm) that could be easily monitored. The strongly absorbing species was assigned to the α-allylic MPTP radical based on isotopic labeling studies. The observed rate constant for the formation of the MPTP derived radical was determined to be 2.27×10^8 M^{-1} s^{-1}.[15,16]

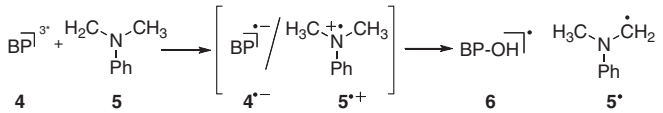


In principle, hydrogen atom abstraction can occur at each of the carbons alpha to nitrogen in MPTP, as was demonstrated for hydrogen abstractions by *t*-butoxyl radical.[15] However, only neutral radical **1**$^{\bullet}$ possesses a suitable chromophore that can be readily monitored at 385 nm. Accordingly, it was envisioned that this radical would provide a unique spectroscopic handle to study the mechanism of the reaction between benzophenone triplet and aliphatic amines. This manuscript describes the photochemical investigation of reaction of ^{3}BP with 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) (**1**) and two of its derivatives; 1-cyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine [*N*-cyclopropyl MPTP] (**7**) and (±)-[*trans*-2-phenylcyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine] [*N*-cyclopropylphenyl MPTP] (**8**).

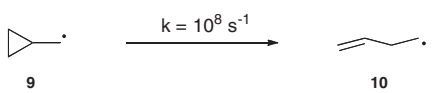


The *N*-cyclopropyl MPTP derivatives provide a unique way to probe the mechanism of these benzophenone triplet-mediated oxidations because in direct analogy to the cyclopropylcarbinyl→homoallyl neutral radical rearrangement (Scheme 4),[19] the derived radical cations (if produced) are expected to undergo instantaneous ring opening. Moreover, because the barrier to this ring opening is exceedingly small (vide infra), this process should be competitive with deprotonation of the aminyl radical cation.

Literature precedent suggests that **7**$^{\bullet+}$ and **8**$^{\bullet+}$ will have little or no barrier to ring opening. Indeed, 1-electron oxidation of **8** may



Scheme 3. Reaction of benzophenone triplet (^{3}BP) with aromatic amines.



Scheme 4. Ring opening of the cyclopropylcarbinyl neutral radical.

occur via a dissociative electron transfer (DET) reaction, wherein electron transfer and ring opening occur simultaneously.[20] Electron paramagnetic resonance (EPR) examinations of the radical cation generated from *N*-cyclopropylamine (**11**) support this statement.[19] EPR experiments in a solid matrix have provided evidence for the distonic radical cation (ring-opened) structure based upon hyperfine coupling constants and have shown that the aminyl radical cation ring-opens to the distonic radical cation rapidly upon electron removal.[21,22] Subsequent molecular orbital calculations at the MP2 and other levels of theory have suggested that the removal of an electron from *N*-cyclopropylamine occurs simultaneously with ring opening; the only stable structure is the distonic radical ion, which collapses to a more stable aminopropenyl ion.[23,24]

Studies on MPTP and the cyclopropyl analogs **7** and **8** by online coupling of electrochemistry and mass spectrometry (EC–ESI-MS) have been reported.[25] The technique involves passing a substrate solution through a porous graphite electrode and varying the potential from 0 to 1500 mV. The concentrations of substrates and products resulting from 1-electron oxidation are then monitored via LC–MS. Experiments conducted with compound **1** showed evidence for electron transfer to generate the aminyl radical cation **1**$^{\bullet+}$ followed by subsequent deprotonation at the allylic position to yield **1**$^{\bullet}$. On the other hand, the analogous reactions with compounds **7** and **8** were consistent with rapid ring opening of the aminyl radical cations to give corresponding distonic radical cation. No dihydropyridinium products corresponding to electron transfer followed by allylic α-carbon deprotonation were detected. These experiments were further probed by computational analysis at the UHF level of theory. No global minima corresponding to the ring closed aminyl radical cations **8**$^{\bullet+}$ were ever obtained indicating that the electron transfer and ring opening proceed by a concerted process.

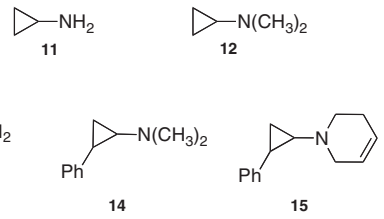
Dinnocenzo and co-workers[26] studied the fate of a series of structurally-related *N*-(2-phenylcyclopropyl) aminyl radical cations (**11**$^{\bullet+}$ and **12**$^{\bullet+}$) by nanosecond laser flash photolysis. Ring opening of the radical cation was estimated to be exothermic by −26 kcal/mol. It was suggested that ring opening and electron transfer were occurring in a concerted fashion and that *N*-(2-phenylcyclopropyl) aminyl radical cations have virtually no barrier for ring opening (Scheme 5).

Literature precedent as well as higher order molecular orbital calculations suggest that the barrier for ring opening of tertiary amine radical cations such as *N*-(2-phenylcyclopropyl) derivative (**3**) to be virtually nonexistent. Due to the unique chromophore derived from **3**, laser flash photolysis can be used to spectroscopically observe a reactive intermediate that is generated from excitation, be it radical or radical ion. Herein we report: (1) computational analysis of ring opening reactions of relevant cyclopropyl amines, and (2) the results of model studies on the photochemically-mediated oxidation of MPTP and two of its derivatives that are designed to evaluate the HAT versus the SET pathways.

2. Results and discussion

2.1. Calculations

The ring opening of radical cations derived from: *N*-cyclopropylamine (**11**), *N*,*N*-dimethylaminocyclopropane (**12**), 2-phenylcyclopropylamine (**13**), *N*,*N*-dimethyl-*N*-(2-phenyl-cyclopropyl)amine, and (**14**) 1-cyclopropylphenyl-1,2,3,6-tetrahydropyridine (**15**) were examined computationally. As noted, calculations pertaining to the ring opening chemistry of **11**$^{\bullet+}$ have been previously reported,[21–24] thereby allowing us to validate the computational methods before examining the chemistry of compounds **12**$^{\bullet+}$→**15**$^{\bullet+}$. The following are the specific issues to be addressed: will a tertiary aminyl radical cation such as **12**$^{\bullet+}$ be more stable than primary radical **11**$^{\bullet+}$ and thus have a barrier to ring opening? Will phenyl substitution on the cyclopropyl group lower or eliminate the barrier to ring opening, if indeed such a barrier exists?



2.1.1. *N*-Cyclopropylaminyl radical cation (11$^{\bullet+}$)

Consistent with published results,[21–24] an energy profile (plot of energy vs C–C bond length) of **11**$^{\bullet+}$ at the UHF/6-31G* level of theory suggest that the ring-closed form of **11**$^{\bullet+}$ does not exist at a potential energy minimum. Attempts to minimize the energy of the cyclopropyl ring-closed from of **11**$^{\bullet+}$ led to a minimized structure corresponding to the distonic (ring-opened) radical cation. Similar results were obtained at the UMP2/6-31G* and UMP4SDTQ/6-311G** levels of theory/basis sets. Geometry optimization led exclusively to the ring-opened form. These results confirm that there is no barrier associated with the ring-opening of **11**$^{\bullet+}$. Because these results correspond with previously published studies,[21–24] it can be said with confidence that these computational methods can also be utilized to examine **12**$^{\bullet+}$→**15**$^{\bullet+}$.

2.1.2. *N*,*N*-Dimethyl-*N*-cyclopropylaminyl radical cation (12$^{\bullet+}$)

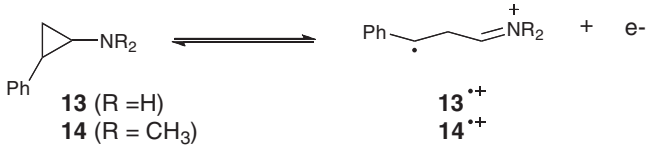
Energy profiles on **12**$^{\bullet+}$ at the UHF/6-31G*, UMP2/6-31G*, and, UMP4SDTQ/6-31G** levels all reveal (a) the ring-closed and ring-opened forms of **12**$^{\bullet+}$ reside at potential energy minima (no imaginary frequencies) and (b) that there is small barrier to the ring opening reaction. A transition state for ring opening was successfully located, characterized by one imaginary frequency corresponding to C–C bond cleavage. In the case of UHF/6-31G*, the energy of activation for the ring opening pathway was found to be 4.7 kcal/mol. Ring opening was exothermic by ca. −7.5 kcal/mol.

2.1.3. *N*-(2-Phenylcyclopropyl)aminyl radical cation (13$^{\bullet+}$)

As was the case for **11**$^{\bullet+}$, calculations at the UHF/6-31G* level of theory revealed that ring-opening of **13**$^{\bullet+}$ occurs with essential no barrier, consistent with the results of Dinnocenzo and co-workers. The interaction between C1 and C3 is purely repulsive. Similar results were obtained at UMP2/G-31G*, and UMP4STDQ/6-31G** levels of theory, further confirming that the ring closed form of **13**$^{\bullet+}$ does not exist at a potential energy minimum, and that no barrier to ring opening exists.

2.1.4. *N*,*N*-Dimethyl-*N*-(2-phenylcyclopropyl)aminyl radical cation (14$^{\bullet+}$)

Geometry optimizations at UHF/6-31G* revealed a stable ring-opened form and a stable ring-closed form of the radical cation with no imaginary frequencies for either. ΔE° for ring opening was found to be −27.0 kcal/mol, consistent with the results of Dinnocenzo and co-workers.[26] Curiously, an energy profile of the cyclopropyl ring opening reaction (Fig. 1) did not reveal either a



Scheme 5. Ring opening of *N*-(2-phenylcyclopropyl) aminyl radical cations.

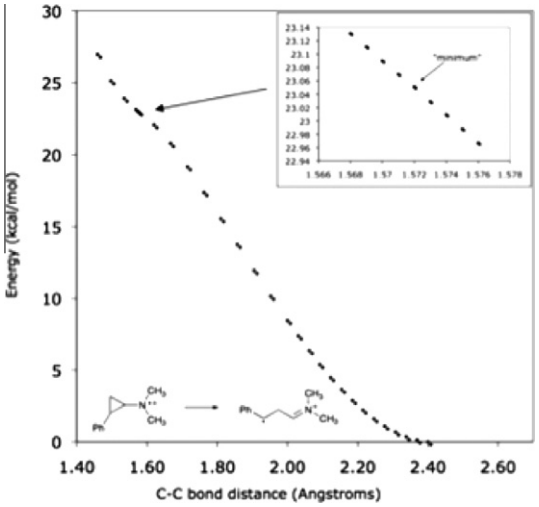


Figure 1. Reaction coordinate diagram for the ring opening of **14**$^{\cdot+}$ calculated at the UHF/6-31G* level of theory.

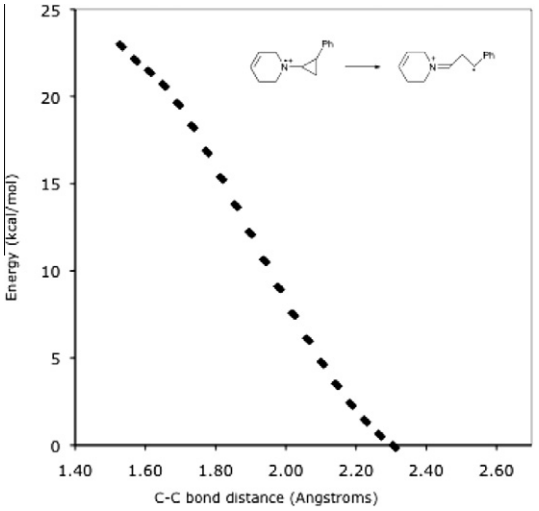


Figure 3. Reaction coordinate diagram for the ring opening of **15**$^{\cdot+}$ calculated at the UHF/6-31G* level of theory.

minimum for the ring-closed form of **14**$^{\cdot+}$ or a transition state for ring opening. Similarly, geometry optimization calculations at the UMP2 level of theory using the 6-31G* basis set also found both the ring-opened and ring-closed form of **14**$^{\cdot+}$. Again, the barrier to ring opening was nonexistent. (Unfortunately, the limitations of the computational system used in this study prevented us from probing this problem further as energy profiles at UMP2/6-31G* and UMP4STDQ/6-31G** levels of theory were unsuccessful).

Careful inspection of the profile for **14**$^{\cdot+}$, varying the C–C bond length in very small increments (0.001 Å) in the vicinity of the ring-closed minimum proved informative. Variation of the C–C bond length is accompanied by a simultaneous rotation of one of the methyl groups as depicted in Figure 2. Thus, a simple, two-dimensional reaction coordinate diagrams such as in Figure 1 does not depict the full dynamics of the system, explaining why no minimum appears in this plot. All attempts to locate a transition state for ring opening failed, and as the calculations pertain to 0 K, we conclude that there is no significant barrier to ring opening of **14**$^{\cdot+}$ at room temperature.

Because of the anomaly with rotation of the methyl groups in **14**$^{\cdot+}$, ring opening of cyclic aminyl radical cation **15**$^{\cdot+}$ was reexamined as a model for the ring opening of the radical cation generated from *trans*-2-phenylcyclopropyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (**8**). No minimum corresponding to a cyclopropane ring-closed structure could be located at any level of theory. The reaction coordinate diagram (Fig. 3) is unambiguous in showing that the interaction between C1 and C3 is purely repulsive, consistent with earlier observations.[20] Accordingly, it appears quite reasonable to assume that ring-opening of **8**$^{\cdot+}$ is barrier-free.

2.1.5. Comparison of 11$^{\cdot+}$ and 12$^{\cdot+}$

Computationally, we observed that **11**$^{\cdot+}$ exhibits no stable ring closed form and opens spontaneously with the transfer of an electron, consistent with earlier reports on this system. On the other hand, **12**$^{\cdot+}$ can lose an electron and remain a stable ring-closed radical cation. A barrier to ring-opening exists, thus a transition state exists. A chemical reason for this is that the electron donating character of the methyl groups on **12**$^{\cdot+}$ can stabilize the radical cation in the ring-closed form.

2.1.6. Comparison of 12$^{\cdot+}$ and 14$^{\cdot+}$

Computational analysis of **12**$^{\cdot+}$ clearly reveals a barrier to ring opening. Conversely, ring opening of **14**$^{\cdot+}$ is highly exothermic (ΔE° = −27 kcal/mol) with no significant barrier to ring opening, consistent with the report of Dinnocenzo and co-workers.[26] One electron oxidation of **8** and **14** likely occurs via a concerted dissociative electron transfer reaction. This process is driven by the fact that the ring-opened form is stabilized by the formation of a benzylic radical (Scheme 6). For **12**$^{\cdot+}$, no such stabilization exists resulting in a 4.71 kcal/mol barrier for the ring opening pathway.

2.2. Laser flash photolysis (LFP)

The transient absorption spectra for the reaction of ^{3}BP with MPTP (**1**) in benzene are presented in Figure 4; virtually identical results were obtained in acetonitrile. The key features of these spectra are that for MPTP, the data suggest that the decay of benzophenone triplet [**4**^{3*} (λ_{max} = 520)] [12] is accompanied by the formation of two new species at λ_{max} = 545[12] and 385 nm.[16] These two species are the diphenylhydroxylmethyl radical [**6** (545 nm)] and MPTP$_{-H^{\cdot}}$ [**1**$^{\cdot}$ (385 nm)], which are formed either by in-cage proton abstraction in the caged ion pair, or direct hydrogen atom abstraction (Scheme 7). The spectra showed no indication that the benzophenone radical anion [**4**$^{\cdot-}$ (λ_{max} = 650 nm)] was formed.

In order to probe further the mechanism of this system, and to differentiate between the direct HAT and SET pathways, an analogous LFP study was conducted on the corresponding *N*-cyclopropyl MPTP derivatives **7** and **8**. In the case of MPTP, either hydrogen atom abstraction, or SET followed by in-cage deprotonation, would result in the formation of **1**$^{\cdot}$. However in the case of the two cyclopropyl derivatives, if SET is occurring, cyclopropyl ring opening is expected to compete with deprotonation because there is little (in the case of **7**$^{\cdot+}$) or no (in the case of **8**$^{\cdot+}$) barrier to ring opening

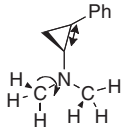


Figure 2. Depiction of how variation on C–C bond length of **14**$^{\cdot+}$ is accompanied by simultaneous rotation of the *N*-methyl group.

Scheme 6. Resonance stabilization of the distonic radical cation derived from **8**$^{\cdot+}$ and **14**$^{\cdot+}$.

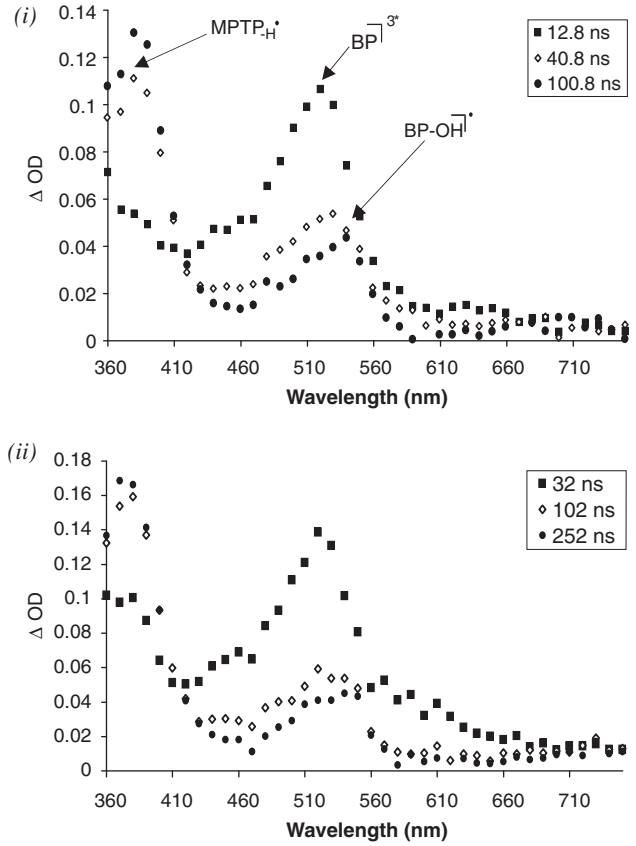
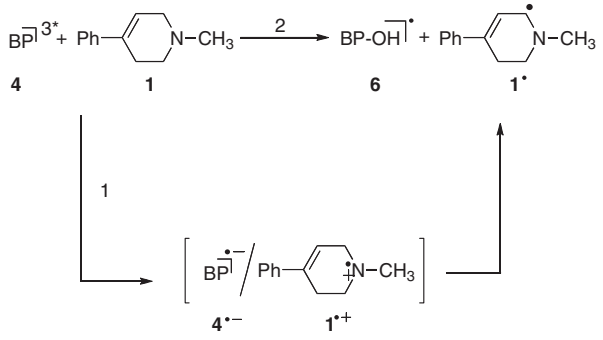


Figure 4. Transient absorption spectra of (*i*) MPTP (**1**) in CH_3CN and (*ii*) *N*-cyclopropylphenyl MPTP (**8**) in CH_3CN.



Scheme 7. Reaction pathways for ^{3}BP with MPTP (1) SET and (2) HAT.

(vide supra). Electron transfer from **8** is likely to be concerted with ring opening. This system is an ultrasensitive probe for single electron transfer—competitive with events such as deprotonation which may be occurring within the lifetime of a caged-radical ion pair.

For each, the reaction of ^{3}BP produced only species absorbing at 540 nm, corresponding to diphenylmethanol radical (**6**) and 380 nm corresponding to the hydrogen atom abstraction product. In examining the chemistry of these compounds, using benzophenone triplet as a sensitizer it has been inferred that the 'hydrogen atom abstraction' is the only observable process.

These experiments were also conducted in the presence of 0.5 M lithium perchlorate, which has been shown to aid in the separation of the contact ion pair to facilitate the diffusion of the contact ion pair forming a solvent separated ion pair.[27] Lithium cation will complex with benzophenone radical anion, which can be monitored at λ_{max} = 650 nm on a nanosecond time regime. Examination of all three compounds showed no evidence of benzophenone radical anion in the presence of lithium perchlorate. In the case of the *N*-cyclopropyl derivatives, the MPTP derived radical absorption band (**7**$^{\bullet}$) should be diminished and the band corresponding to the benzophenone radical anion should be visible in the absorption spectra, making the reasonable assumption that ring opening is competitive with deprotonation. In the case of compound **8**, the molecule is expected to undergo a concerted dissociative electron transfer reaction, and therefore neither the band at 385 nm (corresponding to the MPTP derived radical (**8**$^{\bullet}$)) or band at 545 nm (corresponding to **6**$^{\bullet}$) are expected to be present. Because both of these bands are observed, it can be surmised that an electron transfer process is not occurring in this system. These results are fully consistent with the proposal that these oxidations of MPTP and its derivatives by benzophenone occur by a HAT process.

Rate constants for the reaction of benzophenone triplet with **1** and **7** were examined by varying the concentration of MPTP derivatives and monitoring the growth of the MPTP radical species on a nanosecond time regime as described previously.[14] For both substrates, the rate constants were on the order of diffusion controlled and not significantly affected by added electrolyte (Table 1).

3. Conclusions

Literature precedent and the calculations reported herein suggest for tertiary amines (such as these MPTP derivatives) that the barrier to ring opening of the corresponding radical cations is anticipated to be low for the *N*-cyclopropyl derivative (e.g., **7**$^{\bullet+}$)[21–24] and nonexistent for the *N*-(2-phenylcyclopropyl) derivative (e.g., **8**$^{\bullet+}$).[20,26] These systems are thus expected to be ultrasensitive probes for single electron transfer. The LFP results reported herein demonstrate that for the reaction of ^{3}BP with **1**, **7**, and **8**, the intermediates formed are very similar. In each instance, disappearance of ^{3}BP is accompanied solely by appearance of bands corresponding to the diphenylhydroxylmethyl radical and neutral radical derived from MPTP and its derivatives. In principle, this is consistent with either an apparent hydrogen abstraction from the MPTP derivative, or deprotonation within the radical ion pair formed by single electron transfer. However, the results obtained for **7**, and especially for **8** do not support an electron transfer pathway. Electron transfer from **8** is expected to lead immediately to the cyclopropyl ring-opened product. If this were occurring, the observations would be drastically different: (a) Bands corresponding to either the diphenylhydroxymethyl radical (λ_{max} = 540 nm) or neutral radical derived from the MPTP derivative (λ_{max} = 380) would *not* be observed because the ring opening would beat out deprotonation, and (b) a band corresponding to the benzophenone radical anion (λ_{max} = 650 nm) *would* be observed. Accordingly, these results suggest that the reaction between benzophenone triplet and tertiary aliphatic amines proceed via a hydrogen atom transfer reaction. Additionally these models provide evidence that oxidations of N-cyclopropyl derivatives of MPTP catalyzed by MAO-B may not proceed by a pure SET pathway.

Table 1
Rate constants for the reaction of ^{3}BP with **1** and **2**

Substrate	Solvent	k_{obs} (M^{-1} s^{-1}) ($\times 10^9$)
1	Benzene	2.12
1	Acetonitrile	8.34
1	Acetonitrile/$LiOCl_4$	5.83
7	Benzene	2.19
7	Acetonitrile	5.47
7	Acetonitrile/$LiOCl_4$	6.37

4. Experimental section

4.1. Materials

All solvents and fine chemicals used in this study were obtained from Aldrich and used as received unless otherwise noted. Benzophenone was recrystallized in methanol prior to use. Syntheses of MPTP and derivatives have been described previously;[20,28] these compounds were stored as their oxalate salts. For sample preparation, the oxalate salts were suspended in saturated potassium carbonate and extracted using ethyl acetate to render the free base prior to use. Solution concentrations were calculated using the mass of the free base. Caution: MPTP is a known neurotoxin and should be handled in a well-ventilated hood and proper personal protective equipment should be worn while working with this material. Procedures for the safe handling of MPTP have been documented.[29]

4.2. Apparatus

Steady-state UV/vis spectra were recorded on a Hewlett–Packard diode array UV/visible spectrophotometer (HP 8452A). Laser flash photolysis (LFP) experiments were conducted using an Applied Photophysics LKS.60 spectrometer using the third harmonic of a Continuum Surelite I-10 Nd:YAG laser (4–6 ns pulse, 355 nm). Absorption spectra were monitored by a Hewlett–Packard Infinium digital oscilloscope and analyzed with an Applied Photophysics SpectraKinetic Workstation software package (v. 4.59). Experiments were preformed with a jacketed cell holder connected to a VWR Scientific Products (PolyScience) variable temperature circulating bath (model 1150-A) thermally equilibrated to 25C.

4.3. Laser flash photolysis (LFP)

Sample solutions were prepared in benzene or acetonitrile and deoxygenated with argon prior to use. (Steady-state UV/visible spectra were recorded to ensure that benzophenone was the only species absorbing at the excitation wavelength). In most LFP experiments, 1:1 concentrations of the MPTP derivatives and benzophenone (4.5 mM) were examined in acetonitrile with varying concentrations of lithium perchlorate.

4.4. Calculations

Density functional theory calculations were performed using the Titan[30] molecular modeling software and/or GAUSSIAN 03.[31]

4.5. Calculations. (Experimental)

Initial calculations for all four compounds (**11**–**15**) included the structure of the radical cation in the ring-closed form, transition state, and ring-opened form of each of the compounds were isolated at the AM1 level of theory. Structural results were imported from the AM1 level calculations, followed by geometry optimization and frequency calculations at the UHF level of theory with the 6-31G* basis set. The results (structural coordinates) from this calculation were taken to a higher energy level, and once again geometry optimization and frequency calculations were performed at the UMP2 level of theory with the 6-31G* basis set. Finally, the energies of the structures that were determined at UMP2 were calculated once more at the UMP4SDTQ level of theory with the 6-311G** basis set.

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Supplementary data

Supplementary data (reaction coordinate diagrams for ring opening of $\mathbf{12}^{\cdot+}$ and $\mathbf{13}^{\cdot+}$, transient absorption spectra for and MPTP and *N*-cyclopropylphenyl MPTP as well as concentration profiles of MPTP and *N*-cyclopropyl MPTP in benzene and acetonitrile) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.01.002.

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