Generation of *N*,*N*-Di(4-bromophenyl)nitrenium Ion Under Acidic Conditions: Search for a Nitrenium Dication

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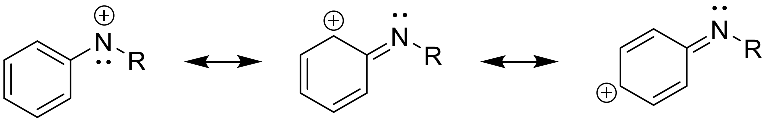
ABSTRACT: The behavior of the *N*,*N*-di(4-bromophenyl)nitrenium ion under acidic aqueous conditions was examined via laser flash photolysis experiments. A long-lived species forms and can be assigned as the cation radical or the dication. This species is unreactive towards nucleophiles and reactive towards strong electron donors, consistent with a cation radical. Mechanistic analysis indicates its formation is through a separate pathway than that of the nitrenium ion, suggestive of a triplet mechanism.

Introduction

Nitrenium ions are reactive intermediates characterized by a dicoordinate nitrogen atom having a lone pair of electrons and bearing a formal positive charge. These species are isoelectronic other reactive intermediates such as nitrenes, carbenes, and carbenium ions.[1-3] In general such species behave as strong electrophiles, reacting rapidly with weak nucleophiles such as water or rearranging to form stable iminium ions. Due to their role in DNA damaging reactions, the arylnitrenium ions have been extensively characterized.[4-8] In general, it has been shown that there is significant delocalization of positive charge from the nitrenium ion center into the aromatic ring as illustrated in Scheme 1. For this reason, it is possible to form a nitrenium dication through protonation of the nitrogen lone pair.

Scheme 1. Delocalization of positive charge in arylnitrenium ions

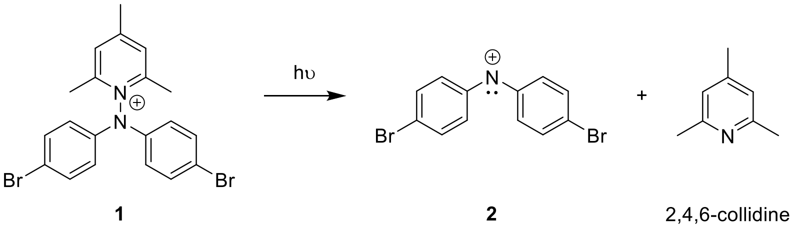


Indeed McClelland et al. found evidence for such a species by laser flash photolysis (LFP) experiments on arylazides in acidic media.[9] In these studies, the dication was not directly detected. However, its formation was inferred on the basis of the pH dependence of nitrenium ion (i.e. the monocation) decay kinetics.

The diarylnitrenium ions (i.e. the series where both N substituents are aromatic rings) have been studied to a somewhat lesser extent than the monoaryls. As might be expected, the additional aromatic ring provides additional pi-donation to the nitrenium ion center, further stabilizing the nitrenium ions toward reactions with nucleophiles. For example, *N,N*-di(4-chlorophenyl)nitrenium ion reacts with methanol with a rate constant of 1.1×10^5 $M^{-1}s^{-1}$.[10] In contrast, a comparable monoaryl system, N-methyl-N-(4-chlorophenyl)nitrenium ion reacts methanol ca. 6000 fold faster (7.0×10^8 $M^{-1}s^{-1}$).[11] The increased delocalization of positive charge in the diaryl series suggests that N-protonation might be even more favorable that it is in the monoaryl series.

Earlier studies[10, 12] demonstrated that *N,N*-di(4-bromophenyl)nitrenium ion **2** can be formed by photolysis of *N*-(4,4'-dibromodiphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate **1**. The latter was shown to cleave the N—N bond to heterolytically, generating nitrenium ion **2** and 2,4,6-collidine, as outlined in Scheme 2. The nitrenium ion was identified by absorptions bands at 450 nm and 690 nm. In many cases also observed was a longer-lived, overlapping signal at 720 nm. The long-lived species was attributed to the cation radical. However, there were several unresolved issues associated with the formation of the longer-lived species. First, nitrenium ion **2** is calculated to have a singlet ground state. Cation radicals are normally understood to arise from H atom transfer to triplet state nitrenium ions. Second, addition of strong acids appears to enhance the formation of this long-lived species. The latter observation raises the possibility that the long-lived 720 nm species might be the dication. In fact, several transient Raman peaks detected in this process are consistent with the theoretically predicted spectrum for the dication.[13]

Scheme 2. Photolysis of *N*-(4,4'-dibromodiphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate **1** to generate nitrenium ion **2**



These ambiguities encouraged us to reexamine the long-lived species formed from in the photolysis of **1.** Specifically, the formation and decay kinetics of both the nitrenium ion and the long lived species are studied by LFP as a function pH, added traps, etc. The results, described below, show: (1) Formation of the long-lived 720 nm peak increases at lower pH, but there is no corresponding acceleration in the decay of the singlet nitrenium ion, indicating that the 720 nm species is not formed from protonation of the singlet nitrenium ion. (2) The 720 nm species lives for >500 μs in water and does not react at an observable rate with any added nucleophiles. These experiments support the original assignment of the 720 nm signal to the radical cation, rather than the nitrenium dication. (3) Calculated electronic spectra (TD-DFT) are more consistent with the cation radical than the ground state of the dication. These observations lead us to re-affirm the original assignment. An alternative excited state pathway for formation of **3** is proposed.

Methods

General Procedures: UV-Vis spectra were collected on a Shimadzu UV-1800 spectrometer using UVProbe 2.43 software. Samples were scanned using a fast scanning speed and a sampling interval of 1.0 nm. Each sample was blanked with the solvent used in solvating the compound. Kinetic decay curves were fitted using MATLAB software. All ^{1}H NMR spectra were obtained on a Bruker 400 MHz instrument.

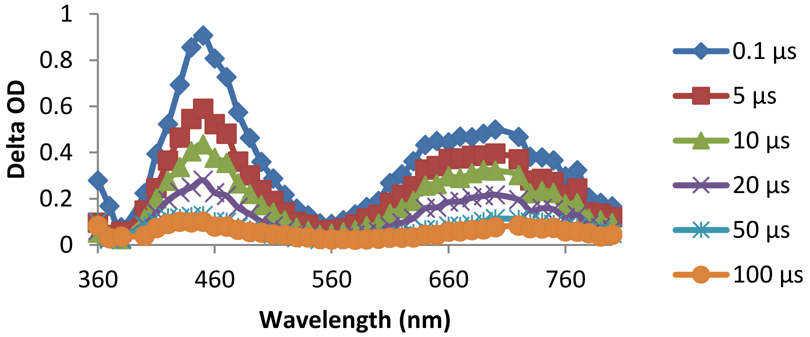
Laser Flash Photolysis Studies: Laser flash photolysis studies were conducted using a Nd:YAG laser (355 nm output) supplied by Continuum with pulses 4-6 ns in duration as the excitation source. The probe beam was a 350 W Xe arc lamp which passed through a monochromator to a PMT detector. Samples were prepared such that the absorption at 355 nm was between 1.0 and 2.0. When obtaining a full spectrum, a fresh supply of the substrate into the cuvette was attained by setting up a nitrogen purged flow cell which connects the cuvette to the stock solution via a double-headed needle. The photolyzate was then drained from the cuvette into a waste vessel. This setup prevents accumulation of photoproducts and avoids the depletion of the substrate throughout the duration of the experiment.

Synthesis: *N*-(4,4'-dibromodiphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate was synthesized according to a literature procedure.[10]

Calculations: Geometry optimizations and frequency calculations were carried out using the Gaussian09 suite of programs.[14] Structures were optimized using (U)M06-2X/6-311G++(d,p).

Results and Discussion

LFP Generation of Nitrenium Ion 2 at Varying pH. Figure 1 (top) shows transient absorption spectra resulting from pulsed laser (355 nm, 50 mJ/pulse, 7 ns) photolysis of pyridinium ion **1** is aqueous solution. At neutral pH the spectrum shows maxima at 450 and 680 nm. At this acidity, both signals decay with a first order lifetime of 13.5 μs and little, if any, long-lived signals remain following their decay. These signals are consistent with previous reports[10] and are therefore assigned to the singlet nitrenium ion **2**. Under acidic conditions (pH 1.76) the same experiment provides the same nitrenium ion signals, but in this case following their decay, long-lived signals at 720 nm and 350 nm are observed. The latter peak overlaps with the long wavelength band of the nitrenium ion **2**, but is sharper and can be distinguished by its longer lifetime. In fact, this signal persists for over 500 μs, and consequently it is not possible to provide a specific lifetime given the constraints of the experimental set up. The 720 nm transient has been observed in other experiments involving LFP of **1** and has been attributed to radical cation **3**.[10] Indeed, this absorption maximum is consistent with other reports where **3** has been generated by other routes.[10]



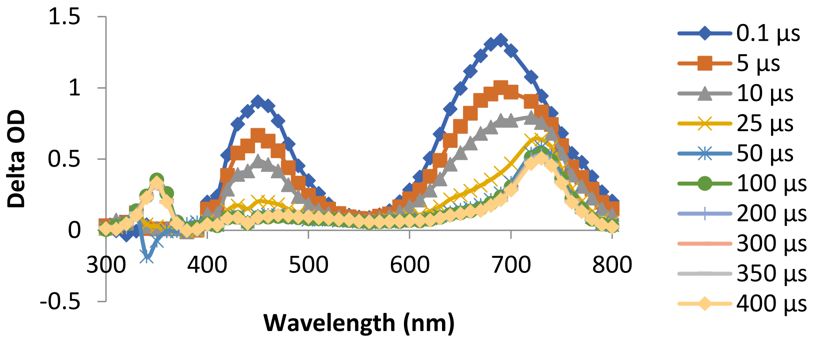
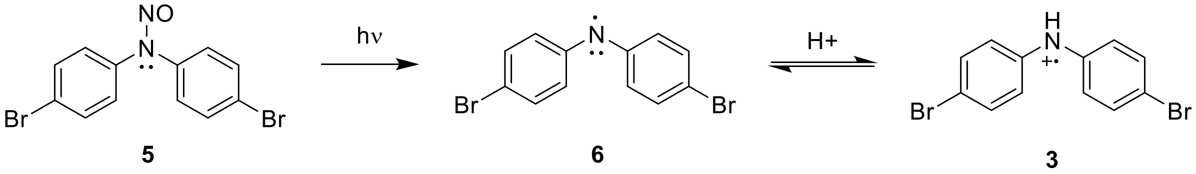


Figure 1. Transient absorption spectrum from 355 nm pulsed photolysis of **1**. Top: in 9:1 water: acetonitrile, Bottom: in pH 1.76 water

To further verify this assignment, we also generated **3** by LFP using an alternate route. Lusztyk and coworkers demonstrated that various arylamine cation radicals can be generated through photolysis of the corresponding *N*-nitrosamines under acidic conditions.[15] Using this methodology, cation radical **3** was generated as outlined in Scheme 3 and the resulting transient spectrum is shown in Figure 2. A broad signal at 700 nm is observed immediately following the laser pulse. As this decays, a longer-lived and sharper signal at 720 nm remains. This behavior is consistent with Lusztyk's report. The initial broad peak corresponds to the neutral radical **6**. This species is replaced by **3** as the neutral radical acquires a proton.

Scheme 3. Generation of cation radical **3** via photolysis of nitrosamine **5**



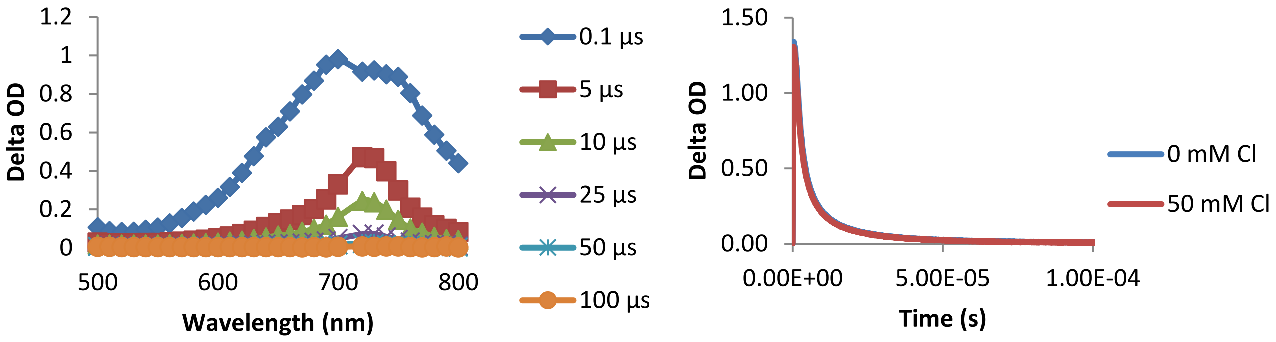
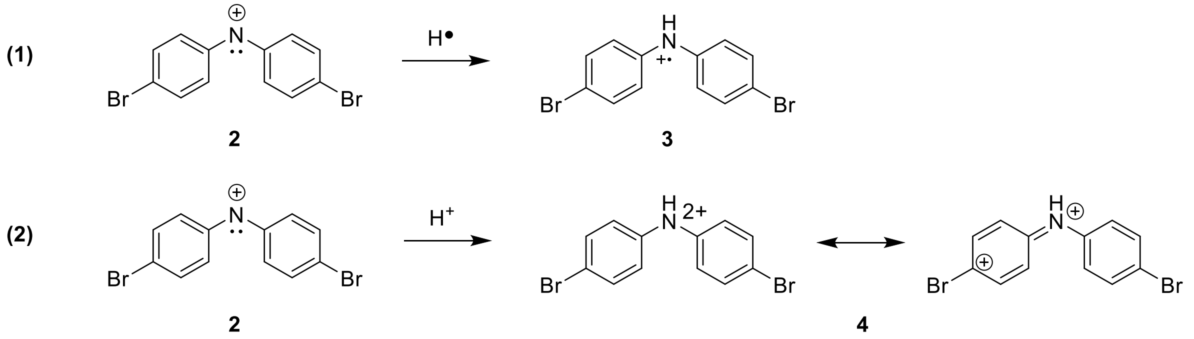


Figure 2. Left: Transient absorption spectrum from 355 nm pulsed photolysis of **5** in 1:1 acetonitrile: pH 1.90 water. Right: Waveforms taken at 720 nm in the presence and absence of tetrabutylammonium chloride

These experiments as well, as the earlier reports, show that the long-lived 720 nm signal is an excellent match for the cation radical **3**. However, the observation that the 720 nm species forms in aqueous solution leaves unresolved the mechanism for its formation. The cation radical **3** would be derived from nitrenium ion **2** through a net H atom transfer (Scheme 4, Eq. 1). Water has a very high homolytic bond strength of 119.3 kcal/mol[16] and does not, generally, serve as a source of H atoms. Moreover, the observation that formation of the 720 nm species is enhanced under acidic conditions leaves open the possibility that this species may be the dication **4** derived from protonation of the nitrenium ion (Scheme 4, Eq. 2). In that case, the rate of protonation should increase with the concentration of hydronium ion, or decrease with pH.

Scheme 4: Possible identities of the 720 nm species and routes to their generation



To test for this, LFP was used to determine the decay rate constant for **2** aqueous solution at varying values of pH. The results, diagrammed in Figure 3, show that this is not the case. Specifically, there is a <20% variance in the decay rate constant for the nitrenium ion **2** over the pH range of 5.9 to 1.7. However, the yield of the long-lived 720 nm intermediate (evaluated by comparing the initial signal to the persistent signal at 720 nm, ΔA) increases substantially in over the range of pH 4 to pH 2. Regardless of the identity of the 720 nm, this experiment shows that it cannot arise from direct protonation of the singlet nitrenium ion **2**.

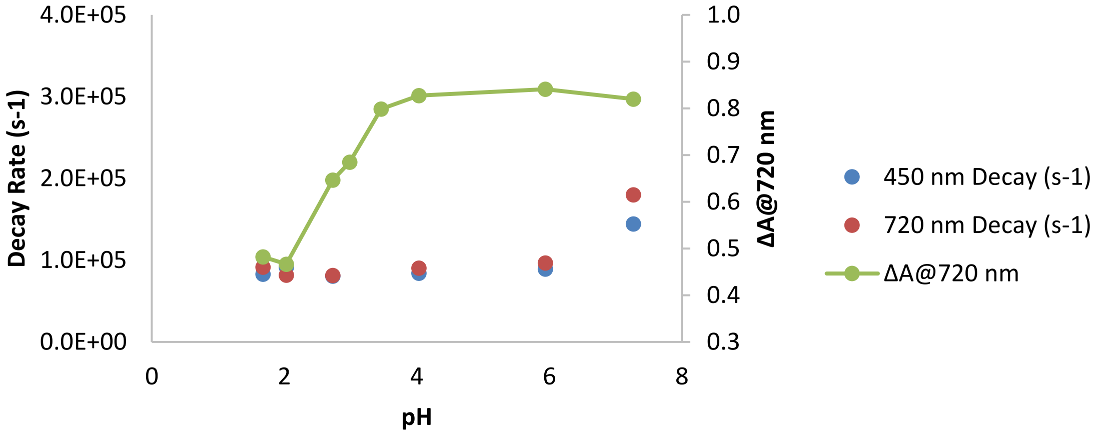


Figure 3. First order decay rates of **2** at 450 nm (●) and 720 nm (●) in buffered water at varying pH. Change in initial vs. final absorbance at 720 nm (●)

DFT Calculations. Geometries of the singlet and triplet nitrenium ions (**2**), the corresponding singlet and triplet dications (**4**) and the cation radical (**3**) were optimized using DFT ((U)M06-

2X/6-311G++(d,p)),[14] and the electronic absorption spectra were calculated using TD-DFT.[14] The reported structures were all determined to be local minima on the PES through frequency calculations. Singlet-Triplet energy splittings include corrections for zero point vibrational energy (negative values indicate a singlet ground state). These results are summarized in Figure 4,which shows the geometries, and Table 1, which shows the energetic and structural predictions.

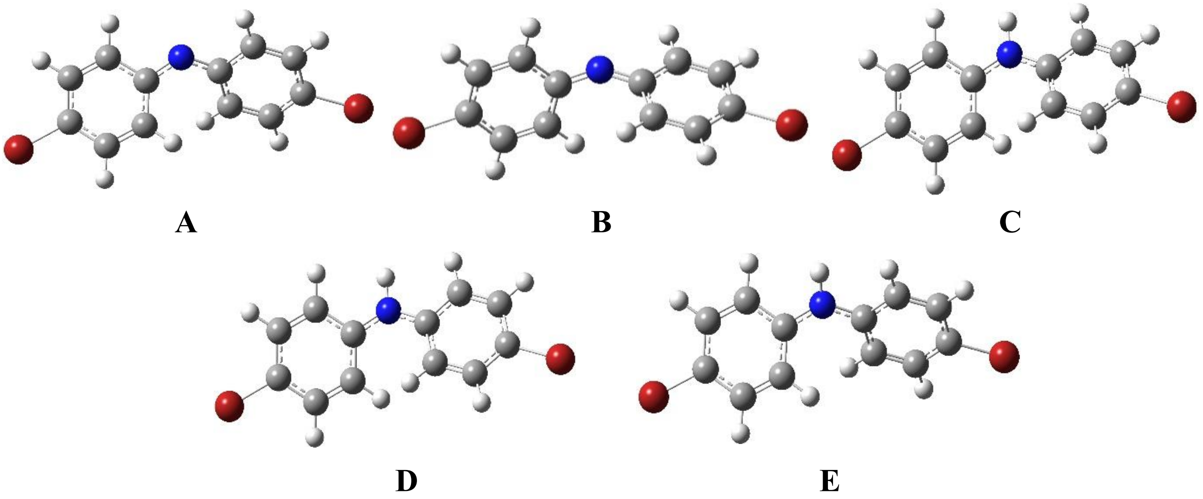


Figure 4. DFT calculated geometries of singlet **2** (A) , triplet **2** (B) , radical cation **3** (C), singlet dication **4** (D), and triplet dication **4** (E)

Table 1. Calculated (TD-(U)M062X) electronic spectra various intermediates considered in this study

Structure	**Calculated (λ_{max})**	**ΔE_{st} (kcal/mol)**
2 (Singlet)	400, 662	-11.3
2 (Triplet)	302, 480	
3	303, 763	
4 (Singlet)	571	-6.8
4 (Triplet)	321, 674	

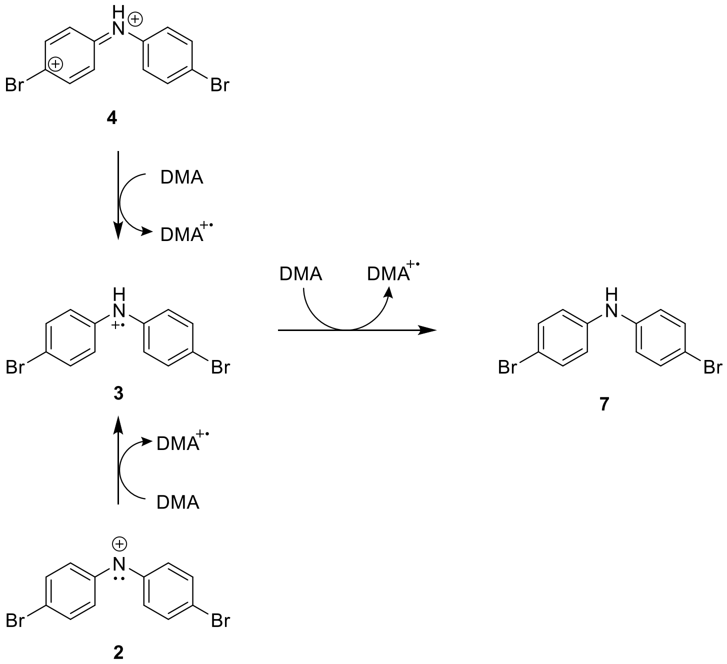
Table 1 lists the calculated UV-Vis absorption bands for the singlet and triplet states of nitrenium ion **2,** the cation radical **3** as well as the singlet and triplet states of the dication **4.** Calculated spectra for the nitrenium ion show good qualitative agreement with the experimental. Two strong bands in the low wavelength and high wavelength visible region are predicted and observed. There are some quantitative disagreements, however. The low wavelength band in particular is predicted to be 50 nm lower than what is observed. An earlier calculation using a different functional (B3LYP) showed similar features. In that case the high wavelength feature showed the larger discrepancy.[10] Two of the calculated spectra show reasonable agreement with the long-lived intermediate. Both the cation radical **3** and the triplet state dication **4** are expected to have both UV as well as high wavelength visible absorption bands. However, the triplet state **4** is also predicted to lie about 7 kcal/mol above the singlet. In general, DFT calculated singlet-triplet energy splitting tend to overestimate the stability of triplets. Therefore, the calculated value is more likely to be less favorable to the singlet than the real value. The observed lifetime of >500 μs would not be consistent with an excited triplet dication.

Reactivity of the Long-Lived Intermediate. One significant challenge in evaluating the potential assignment of a nitrenium dication is the paucity of experimental data on their reactivity. Intuitively, one would expect the increased positive charge density ought to make these species more reactive than the Consistent with this expectation, McClelland et al. inferred that the dication of 4-biphenlylylnitrenium ion reacts with water and other nucleophiles approximately 50 times faster than the corresponding monocations.[9]

To confirm that this long-lived species is **3** as previously assigned, an electron donor was added in order to quench the signal. The parent amine **7** has an oxidation potential of +0.585 V[17] so in order for electron transfer to be exergonic, the electron donor must have a lower oxidation potential. N,N-dimethylaniline (DMA), which has an oxidation potential of +0.53 V vs. SCE[18], was selected and a transient absorption spectrum with the addition of DMA was obtained, as shown in Figure 5. Tetrabutylammonium chloride was also added in sufficient concentration to suppress any direct reaction between DMA and **2**.

Addition of DMA accelerates the decay of the 720 nm species, and a new band at 470 nm grows in at approximately the same rate. The band at 470 nm agrees with the previously reported spectrum for cation radical of DMA.[19] Pseudo-first order analysis of the quenching of the long-lived species by DMA provides a second order rate constant of 5.00×10^6 $M^{-1}s^{-1}$. This value is significantly slower than the diffusion limit. However, at the acidity necessary to produce the long–lived species, the DMA trap is mainly in its non-reactive conjugate acid form (pKa =5.1).[20]

Scheme 5. Electron transfer pathways



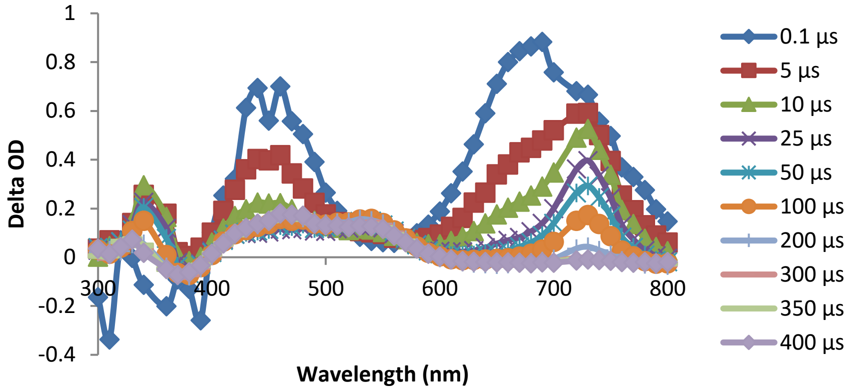


Figure 3. Transient absorption spectrum from 355 nm pulsed photolysis of **1** in pH 1.9 water in the presence of 0.947 mM N,N-dimethylaniline and 2.03 mM tetrabutylammonium chloride

Also examined was the reaction of the long-lived species toward electron donors with higher oxidation potentials, 1,4-dimethoxybenzene (E_{ox} = 1.34 V vs. SCE[21]) and 1,3,5-trimethoxybenzene (E_{ox} = 1.49 V vs. SCE[21]). Neither of these electron donors showed any reactivity toward the long-lived intermediate. In both cases, no change in lifetime was observed when the donor concentrations varied from 0 mM to 1 mM. In summary, the behavior of the long-lived intermediate toward nucleophiles and electron donors corresponds is entirely consistent with the long-lived intermediate being the cation radical, and inconsistent with any reasonable expectations for a nitrenium ion dication.

Interestingly, as displayed in Figure 6, as the pH changes there is no change in the initial absorption at 450 nm where only **2** absorbs. This indicates that **3** is not formed from the same excited state intermediate that gives rise to **2**.

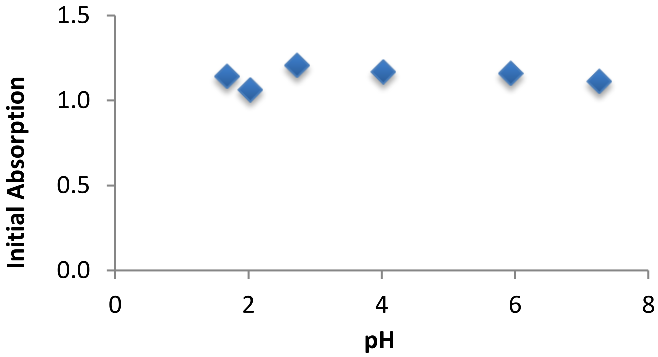
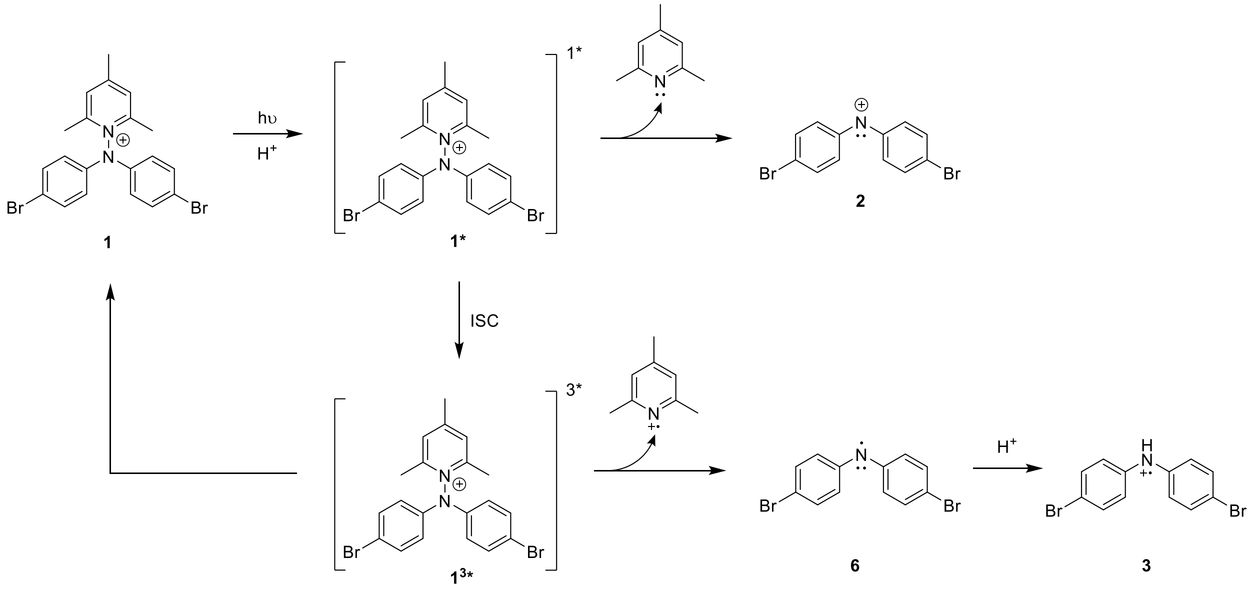


Figure 6. Initial absorption at 450 nm as a function of pH

The experiments described above make it clear that the long-lived intermediate in these experiments is cation radical **3.** However, the mechanism for its formation remains to be addressed. Three observations are relevant to this issue. First, significant formation of **3** is only observed at pH <3. On the other hand, neither the lifetime, nor the initial yield of the singlet **2** is changed at these acidities. Therefore, the formation of **3** occurs neither directly from singlet **2**, nor does it occur at the expense of singlet **2.** Scheme 6 shows what can be inferred about the initial photophysical processes in the photolysis of pyridinium ion **1**. Initial excitation creates the singlet excited state of **1.** The latter partitions between heterolysis, forming the observed singlet **2** along with collidine, and intersystem crossing, creating the triplet state of **1.** The latter is not detected in these experiments, but we postulate that this state either relaxes to ground state **1** or undergoes acid-promoted formation of **3**. The specific steps involved in the latter process are not known at this time. It is possible that triplet dication **4** forms transiently before being reduced by one electron. Alternatively, homolysis of the N–N bond could occur either from a protonated triplet state or via concerted proton transfer and N–N homolysis. Several subtle, but distinct shifts can be detected in the UV-vis and ^{1}H NMR spectrum of **1** at low pH, compared with neutral conditions. (See SI). Future ultrafast studies of the early events in this process could help distinguish these possibilities. Finally, it is noted that the behavior reported here applies to photolysis of **1** in aqueous solution (90%) at 355 nm. There remains a possibility that the dication might be formed under different solvent conditions or via higher excited states.

Scheme 6. Proposed pathway for formation of **3** under acidic conditions



Conclusions

The above experiments revisit an earlier report that during the photolysis of N-(4,4’-dibromodiphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate at low pH, the formation of a long-lived species is observed. Using laser flash photolysis, it is confirmed that this species is indeed the cation radical as previously assigned. Quenching experiments indicate that this species is unreactive towards nucleophiles but it is reactive towards strong electron donors, consistent with a cation radical. Mechanistic analysis demonstrates that pH does not affect the behavior of the nitrenium ion consistent with formation the cation radical via a pathway parallel to nitrenium generation. This pathway is likely through the triplet state of N-(4,4’-dibromodiphenylamino)-2,4,6-trimethylpyridinium tetrafluoroborate, which undergoes homolytic cleavage of the N—N bond and subsequent protonation to generate the cation radical.

AUTHOR INFORMATION

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REFERENCES

1. Falvey, D. E., Nitrenium Ions. In *Reactive Intermediate Chemistry*, Moss, R. A.; Platz, M. S.; Jones Jr., M., Eds. 2003; pp 593-650.

2. Falvey, D. E., Electronic Properties of Nitrenium Ions. In *Nitrenes and Nitrenium Ions*, Falvey, D. E.; Gudmundsdottir, A. D., Eds. 2013; pp 191-216.

3. McClelland, R. A., Flash photolysis generation and reactivities of carbenium ions and nitrenium ions. *Tetrahedron* **1996,** *52* (20), 6823-6858.

4. Novak, M.; Kennedy, S. A., Selective Trapping of N-Acetyl-N-(4-biphenylyl)nitrenium and N-Acetyl-N-(2-fluorenyl)nitrenium Ions by 2'-Deoxyguanosine in Aqueous Solution. *Journal of the American Chemical Society* **1995,** *117* (1), 574-575.

5. Novak, M.; Kennedy, S. A., Inhibitory effect of DNA structure on the efficiency of reaction of guanosine moieties with a nitrenium ion. *Journal of Physical Organic Chemistry* **1998,** *11* (1), 71-76.

6. McClelland, R. A.; Ahmad, A.; Dicks, A. P.; Licence, V. E., Spectroscopic Characterization of the Initial C8 Intermediate in the Reaction of the 2-Fluorenylnitrenium Ion with 2‘-Deoxyguanosine. *Journal of the American Chemical Society* **1999,** *121* (14), 3303-3310.

7. McClelland, R. A.; Gadosy, T. A.; Ren, D., 1997 Alfred Bader Award Lecture Reactivities of arylnitrenium ions with guanine derivatives and other nucleophiles. *Canadian Journal of Chemistry* **1998,** *76* (10), 1327-1337.

8. McClelland, R. A.; Kahley, M. J.; Davidse, P. A., Reactivity of the 4-biphenylyl and 2-fluorenylnitrenium ions with heterocyclic and carbon nucleophiles. *Journal of physical organic chemistry* **1996,** *9* (6), 355-360.

9. McClelland, R. A.; Kahley, M. J.; Davidse, P. A.; Hadzialic, G., Acid−Base Properties of Arylnitrenium Ions. *Journal of the American Chemical Society* **1996,** *118* (20), 4794-4803.

10. Thomas, S. I.; Falvey, D. E., N,N-Di(4-halophenyl)nitrenium Ions: Nucleophilic Trapping, Aromatic Substitution, and Hydrogen Atom Transfer. *The Journal of Organic Chemistry* **2007,** *72* (13), 4626-4634.

11. Kung, A. C.; Chiapperino, D.; Falvey, D. E., Photochemically generated arylnitrenium ions: substituent effects on reactivity studied by laser flash photolysis. *Photochemical & Photobiological Sciences* **2003,** *2* (11), 1205-1208.

12. Du, L.; Lan, X.; Yan, Z.; Zhu, R.; Phillips, D. L., Time-Resolved Spectroscopic Study of N , N -Di(4-bromo)nitrenium Ions in Selected Solutions. *Molecules* **2018,** *23* (12), 3182.

13. Du, L.; Yan, Z.; Bai, X.; Liang, R.; Phillips, D. L., Time-Resolved Spectroscopic Study of N,N –Di(4–bromo)nitrenium Ions in Acidic Aqueous Solution. *International Journal of Molecular Sciences* **2019,** *20* (21), 5512.

14. 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.; Montgomery, J. A., Jr.; 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, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09 Rev. D.01*, Wallingford, CT, 2009.

15. Wagner, B. D.; Ruel, G.; Lusztyk, J., Absolute Kinetics of Aminium Radical Reactions with Olefins in Acetonitrile Solution1. *Journal of the American Chemical Society* **1996,** *118* (1), 13-19.

16. Berkowitz, J.; Ellison, G. B.; Gutman, D., Three methods to measure RH bond energies. *The Journal of Physical Chemistry* **1994,** *98* (11), 2744-2765.

17. Bordwell, F. G.; Zhang, X. M.; Cheng, J. P., Bond dissociation energies of the nitrogen-hydrogen bonds in anilines and in the corresponding radical anions. Equilibrium acidities of aniline radical cations. *The Journal of Organic Chemistry* **1993,** *58* (23), 6410-6416.

18. Zweig, A.; Lancaster, J. E.; Neglia, M. T.; Jura, W. H., Cumulative Influence of Dimethylamino Groups on the -System Properties of Aromatic Hydrocarbons. *Journal of the American Chemical Society* **1964,** *86* (19), 4130-4136.

19. Shida, T., *Electronic Absorption Spectra of Radical Ions*. Elsevier: 1988.

20. Fickling, M. M.; Fischer, A.; Mann, B. R.; Packer, J.; Vaughan, J., Hammett substituent constants for electron-withdrawing substituents: Dissociation of phenols, anilinium ions and dimethylanilinium ions. *Journal of the American Chemical Society* **1959,** *81* (16), 4226-4230.

21. Zweig, A.; Hodgson, W. G.; Jura, W. H., The oxidation of methoxybenzenes. *Journal of the American Chemical Society* **1964,** *86* (19), 4124-4129.