Communications to the Editor

Electron-Deficient Strong Bases. Generation of the 4-Biphenylyl- and 2-Fluorenylnitrenium Ions by Nitrene Protonation in Water

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Aryl azide irradiation results in a singlet arylnitrene, an unstable species that rapidly reacts by several routes, the principal ones being ring expansion to a didehydroazepine and intersystem crossing to a triplet.[1] A nitrene is also the conjugate base of a nitrenium ion, and this raises the possibility of trapping this species by protonation as a route for effecting photochemical entry into these cations.[2] The paucity of photochemical reactions that produce nitrenium ions[2a,3] is a principal reason that these ions have seen limited study using flash photolysis methods. Knowledge of the reactivity of nitrenium ions is important since these electrophiles are proposed to be the DNA-binding intermediates responsible for the carcinogenicity of aromatic amines such as 4-aminobiphenyl and 2-aminofluorene.[4] We have recently reported lifetimes of the *N*-acetyl analogs of the nitrenium ions derived from these two amines, the ions being generated in aqueous solution by photoheterolysis of precursors with various leaving groups.[5] However, the high solvolytic reactivity of the derivatives lacking the *N*-acetyl group precludes their use, and we therefore turned to the azides as possible precursors. To our surprise, these produce excellent yields of nitrenium ions without the need for added acids, that is, with water as proton donor. These experiments place an upper limit on the aqueous acidity constants for N−H deprotonation of the nitrenium ions, showing that these are very weak acids. In analogy with nucleophilic carbenes,[6] the 4-biphenyl- and 2-fluorenylnitrenes are remarkably strong bases despite their formal electron-deficient character.

The nitrenium ion presence is best seen through product analysis in the biphenyl system. Novak and co-workers have examined this nitrenium ion (**1**), as formed in the ionization of a hydroxylamine derivative with pivalate as leaving group.[7] Two stable products were observed, the cyclohexadienone **2** in 91% yield and 6% of material retaining pivalate attributable to ion pair collapse.

In our experiments, azide **3** (50 μM) was irradiated at 300 nm for 30−90 s in 20% acetonitrile: water, at pH 3.5−7 using dilute (2−5 mM) acetate or phosphate buffer. These irradiations resulted in 30−90% loss of **3**; **2** was quantitatively analyzed after 20 h and accounted for 84 ± 3% of the reacted **3**, the yield independent of conversion.[8] As was also reported by Novak,[7] there was no peak for **2** in the HPLC immediately after reaction, but a peak for a precursor could be observed. This decayed as **2** formed, and is likely due to the imine **4**,[7] the initial product of water addition to the para position in **1**. Several other small peaks were present in the HPLC; we presume these are products arising from typical nitrene reactions.

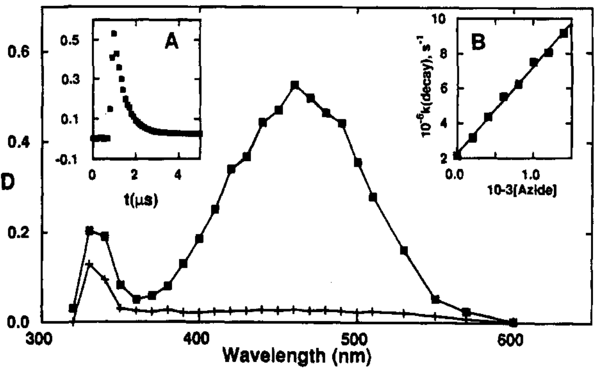
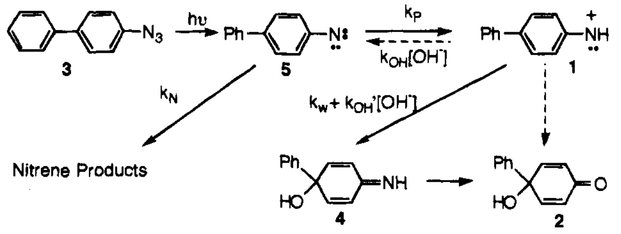


Figure 1. Transient spectra of the 4-biphenylylnitrenium ion **1** obtained by 248 nm irradiation of 50 μM 4-azidobiphenyl in 1:1 acetate buffer (2 mM) in 20% acetonitrile:water. The initial spectrum (■) was obtained immediately after the laser pulse, and the second spectrum (+) after 5 μs. Inset A shows the change in optical density at 460 nm as a function of time. Inset B shows the dependence of the exponential rate constant for decay at 460 nm as a function of the concentration of sodium azide. The permanent absorbance at 320−330 nm is attributed to an intermediate or product derived from nitrene chemistry. The precursor absorbs below 320 nm.

Scheme 1



Flash photolysis, at 248 or 308 nm, revealed a strong transient with λ_{max} at 460 nm (Figure 1), for which there is compelling evidence for assignment to the nitrenium ion **1**. (a) This is obviously consistent with **2** as the major product. In fact, in solutions with varying acetonitrile:water content, there is a direct correlation between the yield of **2** and the initial intensity of the 460 nm transient. In acetonitrile-rich solutions (>90%), **2** is not formed, and there is only a weak tailing absorbance above 400 nm. What is observed is a broad peak centered around 350 nm. Although we cannot conclusively assign this transient, such a peak is characteristic of a ring-expanded didehydroazepine.[1] (b) The spectrum is very similar to the one assigned to the *N*-acetyl analog generated by a completely different photoreaction.[5] (c) The transient decays with exponential kinetics and is quenched by nucleophiles but unaffected by oxygen. (d) The k_{Az}:k_w ratio measured by flash photolysis is (2.8 ± 0.2) × 10^3 M^{-1} (Table 1), in excellent agreement with Novak's value, (2.9 ± 0.2) × 10^3, obtained by the

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[1] (a) Schuster, G. B.; Platz, M. S. *Adv. Photochem.* **1992**, *17*, 69. (b) Marcinek, A.; Leyva, E.; Whitt, D.; Platz, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 8609.

[2] (a) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1270. (b) See also: Takeuchi, H.; Hirayama, S.; Mitani, M.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 521 and references therein.

[3] For examples, see: (a) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 227. (b) Anderson, G. B.; Falvey, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 9870, (c) Anderson, G. B.; Yang, L. L.-N.; Falvey, D. E. *J. Am. Chem. Soc.* **1193**, *115*, 7254. See also ref 2a.

[4] Miller, J. A. *Cancer Res.* **1970**, *30*, 559. Miller, E. C.; Miller, J. A. *Cancer* **1981**, *47*, 2327.

[5] Davidse, P. A.; Kahley, M. J.; McClelland, R. A.; Novak, M. *J. Am. Chem. Soc.* **1994**, *116*, 4513.

[6] Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.

[7] Novak, M.; Kahley, M. J.; Eiger, E.; Helmick, J. S.; Peters, H. E. *J. Am. Chem. Soc.* **1993**, *115*, 9453.

[8] To conclusively demonstrate that **2** forms on irradiation of **3**, a 500 MHz ^{1}H NMR spectrum was recorded after removal of solvent from an experiment where HPLC analysis showed an 82% yield with complete disappearance of **3**. The only significant peaks were ones identical to those obtained with the authentic sample of **2**.

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Table 1. Rate Constants for Decay of Nitrenium Ions at 20 °C in 5% Acetonitrile:Water, pH 4.5, Ionic Strength 0.5 M with $NaClO_4$

nitrenium	k_w, s^{-1}	k_{Az}, M^{-1} s^{-1}
N-acetyl-4-biphenylyl[a]	5.9×10^6	5.1×10^9
4-biphenylyl	1.8×10^6	5.0×10^9
N-acetyl-2-fluorenyl[a]	7.7×10^4	4.2×10^9
2-fluorenyl	3.4×10^4	4.0×10^9

[a] From ref 5.

competition kinetics method in the solvolysis of the pivalate.[7] This last comparison obviously also establishes that the species being observed with flash photolysis is a ground state intermediate.

A similar, longer-lived transient is observed with 2-azidofluorene, and we assign this to the 2-fluorenylnitrenium ion.[9] As seen from the comparisons in Table 1, 2-fluorenylnitrenium ions are a little less than 2 orders of magnitude longer lived in water than the 4-biphenylyl analogs. In each case, substitution of N−H by *N*-acetyl has only a small effect, as has been suggested by the competition kinetics studies.[7,10] The azide rate constants in the four cases are at or very close to the diffusion limit.[11]

The cations being observed in this study show behavior characteristic of singlet nitrenium ions.[3b,c] Their high yield implies that they arise from singlet nitrenes, and not by a circuitous route involving triplet protonation. Irradiation of aryl azides at ambient temperature normally results in low yields of products from triplet nitrene, the principal reaction of the singlet nitrene being ring expansion.[1] Moreover, protonation must be occurring with water as the acid, since very low concentrations of added acids were employed, and in the flash photolysis studies, a signal of the same intensity was observed with no added acid. Since the ions are fully present immediately after the 20 ns laser pulse, protonation must be occurring with a rate constant of $>5 \times 10^7$ s^{-1}. The microscopic reverse is deprotonation with hydroxide, and this reaction can have at most a rate constant of $\sim 10^{10}$ M^{-1} s^{-1}.[12] This means that the acid dissociation constants for these nitrenium ions are less than 10^{-12}.

There is, in fact, evidence that the values are less than 10^{-14}. Flash photolysis experiments in aqueous NaOH, carried out under identical conditions of substrate concentration and laser intensity, result in the same initial OD for the nitrenium ion, up to the point where the amount of transient being formed cannot be reliably measured since OH^- quenching results in decay within the laser pulse. This limit is reached at 0.1 M NaOH for biphenyl and 0.5 M NaOH for fluorenyl. The implication is that even in these solutions, there is little shift of the nitrenium:nitrene equilibrium toward nitrene. Equally revealing are the rate constants for hydroxide quenching, 8×10^7 and 6×10^6 M^{-1} s^{-1} for 4-biphenyl and 2-fluorenyl, respectively. In basic solution, the nitrenium ion can decay by two pathways, direct reaction with hydroxide (the k_{OH}' pathway of Scheme 1) and deprotonation to nitrene (the k_{OH} pathway), followed by some reaction of this species (k_N pathway). Thus, the above rate constants are equal to $k_{OH}' + k_{OH}/(1 + k_P/k_N)$, where k_P/k_N represents the partitioning of nitrene between reprotonation and other reactions. This ratio can be estimated in the biphenyl system from product data at neutral pH. Under these conditions, nitrenium ion does not deprotonate, so that products reflect the partitioning of the nitrene formed initially in the photolysis. The product **2**, the only product from free **1**,[7] can then be used as a marker of protonation, providing $k_P/k_N = 84:16$. This means that with the biphenyl system, the maximum that k_{OH} can be is 4×10^8 M^{-1} s^{-1}, this value pertaining to the situation where the products in the base come only from nitrene.[13] This is significantly below the value that would be expected for a diffusion-controlled proton transfer involving a cationic acid $N^+{-}H$ and hydroxide ion. Thus, the conclusion is that the microscopic reverse, the reaction of nitrene plus water, represents the thermodynamically favored direction; that is, singlet 4-biphenylnitrene is a strong base in water.

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(9) HPLC analysis immediately following irradiation shows the presence of a single major peak with retention time and stability similar to that of the initial peak assigned to the imine **4** with biphenyl. We assume that this is the fluorenyl analog. Unlike the biphenyl system, however, several new peaks appear. Novak has also observed that products from the 2-fluorenylnitrenium ion are more complex. (M. Novak, personal communication.)

(10) Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A. *J. Am. Chem. Soc.* **1994**, *116*, 11626.

(11) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009.

(12) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(13) HPLC analysis, in fact, indicates that products derived from nitrenium ion are still present. Thus, although **2** is unstable in base, the HPLC peak for its precursor is still present immediately after irradiation.