

Direct observation of 4-alkoxyphenylnitrenium ions upon irradiation of 4-alkoxyphenyl azides in aqueous solution

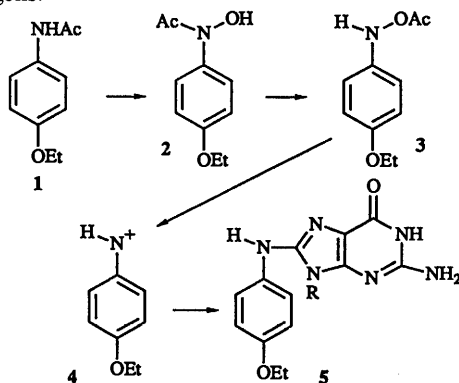
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Photolysis of 4-ethoxy- and 4-methoxy-phenyl azide in aqueous solution results in quantitative formation of 4-ethoxy- and 4-methoxy-phenylnitrenium ions which have lifetimes of $\sim 1 \mu\text{s}$.

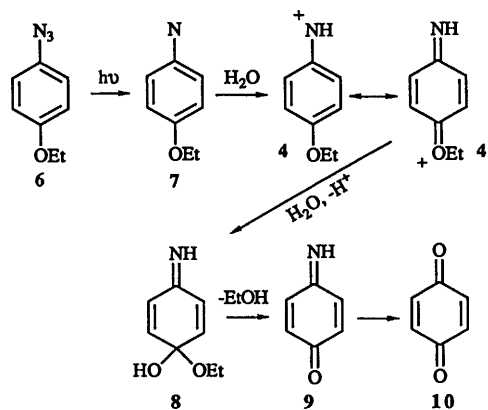
Phenacetin **1**, an analgetic and antipyretic drug introduced at the turn of the century, shows a number of side-effects that have resulted in its removal from the market. The compound is a carcinogen,¹ and in common with other aromatic amines and amides, metabolic *N*-oxidation is considered the first activation step in a pathway that leads through a nitrenium ion (**4**), to a DNA adduct.² Chemical studies have established the viability of such a model,³ demonstrating the *N*-O acyl transfer **2** \rightarrow **3**, and the reaction of **3** in the presence of deoxyguanosine to form an adduct **5** typical of those observed with arylamine carcinogens.



We have recently reported that nitrenium ions derived from 2-aminofluorene and 4-aminobiphenyl, two widely studied carcinogens, are formed in high yield on photolysis of the corresponding aryl azide in aqueous solution,⁴ with the two cations being observed with nanosecond laser flash photolysis (LFP). Arylnitrenium ions have not been spectroscopically characterized in super-acids⁵ but there have been several examples recently of their observation using the LFP technique.^{4,6} With the aryl azide as the photochemical precursor, the nitrenium ion arises from an initially formed singlet nitrene *via* simple protonation.⁷ Singlet arylnitrenes do undergo other rapid reactions⁸ but are sufficiently basic^{4,7} that protonation can compete even when the proton source is water.

In this paper we show that irradiation of 4-ethoxy- and 4-methoxy-phenyl azide in aqueous solution results in quantitative formation of the nitrenium ions, which can be observed as transient species with LFP. This represents the first spectroscopic detection of a nitrenium ion bearing a 4-alkoxy substituent, and provides the first direct information regarding the lifetime of such species in aqueous solutions.

As we have discussed previously,^{4,7} the occurrence of a pathway involving protonation of an arylnitrene is apparent in the products, since the nucleophilic adducts obtained from a nitrenium ion are different in nature from products associated with other reactions⁸ of arylnitrenes. In the case of nitrenium ions such as **4**, the reaction in water is expected to follow the course illustrated in Scheme 1,^{9,10} with benzoquinone as the



Scheme 1

final product, and two intermediates, the imine **9** and the initial water adduct **8**.

Indeed, 300 nm irradiation in water of 4-ethoxy- and 4-methoxy-phenyl azide ($10^{-4} \text{ mol dm}^{-3}$ in 0.01 mol dm^{-3} acetic acid: 0.01 mol dm^{-3} sodium acetate) for times corresponding to 20–50% conversion results in quantitative formation of benzoquinone (HPLC yield = $95 \pm 5\%$ based on reacted aryl azide). The imine precursor **9**, which has a half-life of 1–2 min at the pH of the experiment,¹¹ can be observed at early times, but there is no other product in the HPLC. This result implies that there is essentially complete trapping of the nitrene in water by protonation by the solvent. Consistent with the requirement for water, irradiation in acetonitrile results in no benzoquinone, with several as yet unidentified peaks appearing in the HPLC chromatogram.

Flash photolysis of the azides reveals a single transient whose absorption spectrum overlaps that of the precursor (Fig. 1). The decay follows excellent exponential kinetics, and azide ion is an effective quencher. Assignment of this transient as the 4-alkoxyphenylnitrenium ion is based on the product analysis, as discussed in the previous paragraph. The decay characteristics also point to a cation structure, and there is excellent corroborating evidence in the form of the $k_{Az}:k_w$ ratios. This takes the form of a comparison of the value of this ratio with one measured for a ground-state solvolysis reaction where there is no ambiguity over the formation of an intermediate arylnitrenium ion.^{4,6d} The comparison is shown in Table 1 and involves 4-ethoxyphenylnitrenium ions with *N*-H and *N*-acetyl groups, with the ratio for *N*-H from the LFP data and the ratio for *N*-acetyl by competition kinetics in a solvolysis experiment.¹⁰ These show a 4.5-fold difference in their $k_{Az}:k_w$ values. Flash photolysis data for biphenyl-4-yl cations have been obtained with both *N*-H and *N*-acetyl, and show a similar difference, a factor of 3.3. Thus, although there is not a comparison of LFP and competition kinetics data for the identical cation, these trends show that there is little doubt that the LFP data from the 4-ethoxyphenyl azide refer to the nitrenium ion.

In the course of preparing this manuscript, we became aware

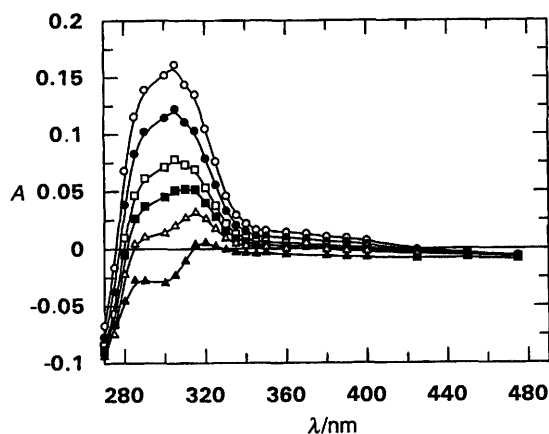


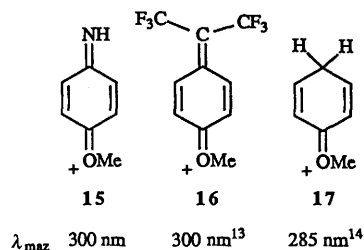
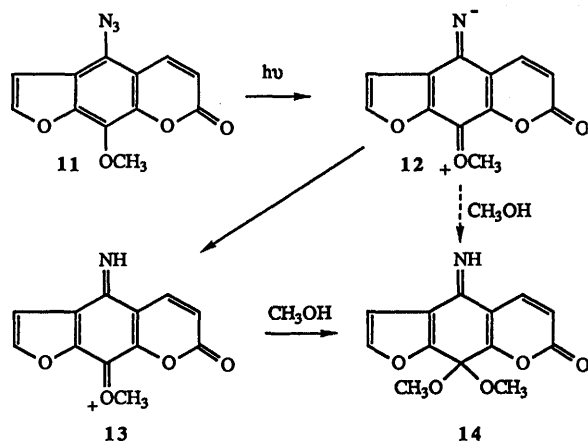
Fig. 1 Absorption spectra following 248 nm irradiation of 4-ethoxyphenyl azide in water (10^{-4} mol dm^{-3} substrate, 0.01 mol dm^{-3} acetic acid– 0.01 mol dm^{-3} sodium acetate). Spectra, in order of decreasing absorbance, were obtained at times 100, 157, 235, 300, 400 and 5000 ns after the laser flash. Absorbance changes followed single exponential kinetics with the same rate constant at each wavelength.

Table 1 Absolute rate constants^a for nitrenium ions reacting with water and azide

Nitrenium ion	$k_w/10^6 \text{ s}^{-1}$	$k_{\text{Az}}/10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$(k_{\text{Az}}:k_w)/\text{dm}^3 \text{ mol}^{-1}$
4-Methoxyphenyl ^b	1.9	2.9	1.5×10^3
4-Ethoxyphenyl ^b	1.2	3.0	2.5×10^3
<i>N</i> -Acetyl-4-ethoxyphenyl ^c	(5.5) ^d	(3.0) ^d	5.5×10^2 ^e
Biphenyl-4-yl ^{c,f}	1.8	5.0	2.8×10^3
<i>N</i> -Acetylbiphenyl-4-yl ^{c,g}	5.9	5.1	8.6×10^2

^a 20 °C and ionic strength 0.5 mol dm^{-3} with NaClO_4 . ^b 100% H_2O . ^c 5% CH_3CN –95% H_2O . ^d Assuming $k_{\text{Az}} = 3.0 \times 10^9$. ^e Ref. 10. Obtained in ground-state solvolysis by method of competition kinetics. ^f Ref. 4. ^g Ref. 7.

of a recent paper that shows that irradiation of 5-azido-8-methoxypsoralen (**11**) in alcohols and water gives high yields of nucleophilic adducts, such as **14** which is formed in 97% yield in methanol.¹² These products were proposed to arise from nucleophilic addition at the stage of the arylnitrene, writing the structure of that nitrene in its zwitterionic resonance form **12**. The precursor here is a 4-methoxyphenyl azide derivative, and on the basis of our results we suggest a mechanism where the first reaction of the nitrene is protonation to give the cation **13**, and the nucleophilic adducts are derived from such a species. Direct reaction at the nitrene stage would explain the products that we obtained. However, this interpretation is inconsistent with the LFP results, which clearly point to a nitrenium intermediate. That the LFP transient in Fig. 1 is not a singlet arylnitrene can be argued on two grounds. First, the transient is too long-lived for such a species,⁸ and secondly, it is not observed in 100% acetonitrile. The singlet nitrene would be found in both water and acetonitrile.



The 300 nm λ_{max} of the 4-alkoxyphenylnitrenium ions are at considerably lower wavelength compared with the λ_{max} of other arylnitrenium ions which lie in the region 400–460 nm.^{4,6,7} However, this is not unreasonable recognizing that the cation is better represented as an *O*-alkylated quinone imine (**15**). A similar situation is seen in the cation **16**, a 4-methoxybenzyl cation where the electron-withdrawing CF_3 groups favour an alkylated quinone methide structure.¹³ In fact further comparison with the *C*-protonated anisole **17** suggests that there is a common chromophore in all three structures, that of a 3-methoxycyclohexa-1,4-dienyl cation.

The present study provides a further example of arylnitrene protonation by water alone, and emphasizes that these nitrenes are remarkably basic, especially when they bear electron-donating substituents. This study also shows that 4-alkoxyphenylnitrenium ions, or, as they are better described, *O*-alkylated benzoquinone imines, have significant lifetimes in aqueous solution, and thus are viable intermediates in mechanistic models that explain biological effects associated with 4-alkoxyanilines and their derivatives.

Acknowledgements

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