

New Nitronate σ Complexes and the Mechanism of Nucleophilic Aromatic Photosubstitution Para to a Nitro Group

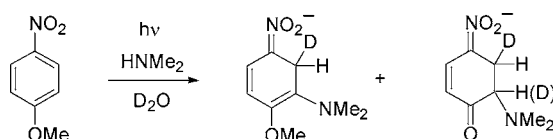
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ABSTRACT



Photolysis of 4-nitroanisole with aliphatic amines gives mainly N-substituted 4-nitroanilines. Reactions of this type have been widely attributed to a geminate radical mechanism. We questioned this interpretation and have searched for and found by NMR spectroscopy a new class of stable nitronate adducts generated under the reaction conditions. The adducts imply that photosubstitution by amines para to the nitro group occurs by meta σ complex formation followed by an unprecedented sigmatropic rearrangement.

Nucleophilic aromatic photosubstitutions of the S_N2 Ar* type commonly show strong regioselectivity for reaction meta to an electron-withdrawing, activating group such as nitro.^{1,2} These fast, efficient reactions are of interest for photoremovable blocking groups^{3–5} and photoaffinity probes.⁶ Improved understanding of their mechanisms might facilitate their application. A rationale stemming from the energy gap law for radiationless transitions has been advanced to explain predominant meta regioselectivity.⁷ (Regiochemistry is referenced to the nitro group.) The mechanism for these cases involves direct formation of a meta σ complex by addition of a nucleophile to the excited-state aromatic molecule. The cause of the less common cases of photosubstitution para to

an electron-withdrawing group remained puzzling. After the energy gap model,⁷ para photosubstitution was attributed⁸ to a different mechanism named $S_N(ET)Ar^*$.² This involves electron transfer from nucleophile to excited aromatic to give a triplet exciplex followed by geminate radical coupling to make the para σ complex. While strong evidence supports its application to some cases,^{9,10} its use to interpret reactions of aliphatic amines with nitroaryl ethers^{11–14} seemed to us weakly supported and problematic.

Some of the problems stem from chemistry reported for other systems. Photolysis of aromatic carbonyl compounds with amines has been thoroughly studied.¹⁵ These reactions involve electron transfer or exciplex formation analogous to

(1) Karapire, C.; Icli, S. In *Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 37, pp 37-1–37-14.

(2) Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*; VCH Publishers: New York, 1991; Chapter 6.

(3) Specht, A.; Goeldner, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2008.

(4) Corrie, J. E. T.; Barth, A.; Munasinghe, V. R. N.; Trentham, D. R.; Hutter, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 8546.

(5) Banerjee, A.; Grewer, C.; Ramakrishnan, L.; Jaeger, J.; Gameiro, A.; Breitingner, H.-G. A.; Gee, K. R.; Carpenter, B. K.; Hess, G. P. *J. Org. Chem.* **2003**, *68*, 8361.

(6) Fang, K.; Hashimoto, M.; Jockusch, S.; Turro, N. J.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 8543.

(7) van Riel, H. C. H. A.; Lodder, G.; Havinga, E. *J. Am. Chem. Soc.* **1981**, *103*, 7257.

(8) Mutai, K.; Nakagaki, R.; Tukada, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2066.

(9) Yokoyama, K.; Nakagaki, R.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2472.

(10) Wubbels, G. G.; Snyder, E. J.; Coughlin, E. B. *J. Am. Chem. Soc.* **1988**, *110*, 2543.

(11) van Eijk, A. M. J.; Huizer, A. H.; Varma, C. A. G. O.; Marquet, J. *J. Am. Chem. Soc.* **1989**, *111*, 88.

(12) Cantos, A.; Marquet, J.; Moreno-Manas, M.; Gonzalez-Lafont, A.; Lluch, J. M.; Bertran J. *J. Org. Chem.* **1990**, *55*, 3303.

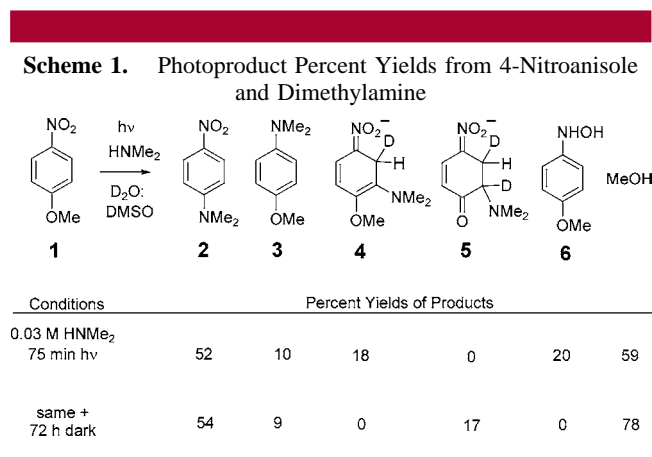
(13) Manickam, M. C. D.; Pitchmani, K.; Srinivasan, C. *Proc. Indian Acad. Sci. Sect. A (Chem. Sci.)* **2003**, *115*, 273.

(14) Bunce, N. J.; Cater, S. R.; Scaiano, J. C.; Johnston, L. J. *J. Org. Chem.* **1987**, *52*, 4214.

that postulated above, but the chemistry results in photoreduction. No case of displacement of a nucleofuge on the aromatic ring from such an exciplex has been reported. The triplet exciplexes dissociate rapidly and nongeminate radical chemistry results. Moreover, aminium radical intermediates undergo fast proton or hydrogen atom transfers that move the electron hole from nitrogen to the α carbon.¹⁶ This would prevent bonding at the amine nitrogen that occurs in the photosubstitutions.

Our studies of base catalysis in meta Smiles photorearrangements¹⁷ showed that meta σ complexes live for tens to hundreds of nanoseconds. This suggested that if meta σ complexes occurred in the para photosubstitutions by amines, they could be trapped by rapid proton-transfer reactions. Proton removal from the nitrogen of intramolecular photoadducts that do not have a nucleofuge at the attack site results in stable dihydrobenzene products.¹⁸ It seemed plausible, moreover, that if meta σ complexes were intermediates in the intermolecular photosubstitutions, they could convert rapidly to para σ complexes by an unprecedented but simple sigmatropic rearrangement. In this case, we predicted for the reaction of 4-nitroanisole with amines that base-dependent photoformation of stable dihydrobenzene adducts would compete with formation of the para photosubstitution products.

Irradiation of 4-nitroanisole (**1**, 0.0060 M) in oxygen-free 40% DMSO-*d*₆/D₂O (v/v) containing 0.030 M dimethylamine for 75 min at 0 °C in a borosilicate NMR tube with 300 nm broadband light filtered through K₂CrO₄ solution caused 29% of the starting material to disappear. The products and percent yields are as shown in Scheme 1. Products **2**, **3**, **6**, and



methanol were confirmed by enhancement of their NMR signals with authentic samples. Product **4** was identified by its NMR spectrum and by COSY, which showed the required couplings: (shifts relative to terephthalate anion, δ 7.86) δ 6.57, 1H, d (J = 10.3 cps); δ 5.72, 1H, d (J = 10.3 cps); δ

3.55, 3H, s; δ 2.65, 6H, s; methylene H not found. Product **5** was also identified by its NMR spectrum and by COSY, which showed the required couplings: δ 7.07, 1H, d (J = 10.1 cps); δ 6.14, 1H, d (J = 10.1 cps); δ 2.70, 6H, s; methylene H not found. The structure of **5** was confirmed by the coincidence of its spectrum with that of an analogous adduct¹⁸ having an ethanolamino group in place of the dimethylamino group of **5**. Additional evidence for the structures of **4** and **5** was obtained by extraction experiments. When the photolyzed reaction solution was extracted with CDCl₃, all nonionic products except methanol were removed to the CDCl₃ phase, but the extraction did not change the amounts of **4** and **5** in the aqueous phase. This confirmed that **4** and **5** are ions.

The data in Scheme 1 show that **4** converts thermally to **5** plus the required 1 equiv of methanol. That the four NMR signals assigned to **4** disappear together and the signals assigned to **5** and methanol arise concurrently is strong evidence for the assignments. The conversion of **4** to **5** plus methanol was faster at pH 10.7 than at pH 11.6; at pH 10.7, only **5** and not **4** could be detected after the photolysis, meaning that the thermal hydrolysis was complete in the photolysis time at that pH. At pH 12, the conversion was not complete in 72 h, and at pH 12.5, **4** was stable.

The percent yield of photosubstitution product **2** (ca. 53%) by direct NMR detection in the reaction of **1** in DMSO-D₂O containing 0.030 M dimethylamine (ca. 0.004 M [OH⁻]) agrees roughly with the yields of photosubstitution products isolated from preparative reactions of **1** and aliphatic amines in water.¹⁹ We found, however, that the ratio of **2** to **4** varied with the hydroxide ion concentration in the photolysis mixture as shown in Table 1. The data show that the yield of **4** increases with increasing hydroxide ion at the expense of **2**.

Table 1. Dependence on Hydroxide Ion Concentration of Relative Yields of Photosubstitution Product vs Photoadduct

conditions		
dimethylamine 0.03 M hydroxide ion 0.004 M	3	1
dimethylamine 0.03 M hydroxide ion 0.01 M	1.5	1
dimethylamine 0.03 M hydroxide ion 0.03 M	1	1

The nitronate ions detected stem from meta attack by the amine. If the S_N(ET)Ar* mechanism operated as suggested for dimethylamine,¹² geminate radical recombination would be expected at both the ortho and para positions. Ortho

(19) Kronenberg, M. E.; van der Heyden, A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 56.

(15) (a) Cohen, S. G.; Parola, A.; Parsons, G. H., Jr. *Chem. Rev.* **1973**, *73*, 141. (b) Inbar, S.; Linschitz, H.; Cohen, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 1048.

(16) Chow, Y. L. *React. Intermed. (Plenum)* **1980**, *1*, 151.

(17) Wubbels, G. G.; Cotter, W. D.; Sanders, H.; Pope, C. J. *Org. Chem.* **1995**, *60*, 2960.

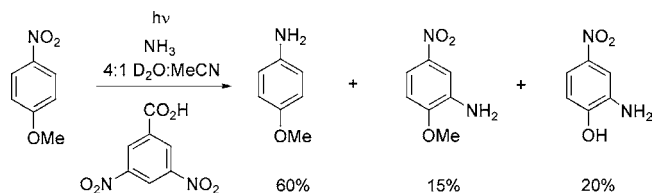
(18) Wubbels, G. G.; Winitz, S.; Whitaker, C. J. *Org. Chem.* **1990**, *55*, 631.

adducts, if formed, would be expected to deprotonate and form stable nitronate ions, as has been observed for an intramolecular case.¹⁸ We found no evidence by NMR for such adducts, even when **1** was irradiated with dimethylamine in the presence of 0.05 M NaOD.

Results similar to those with dimethylamine were obtained with ammonia, methylamine, ethanolamine, and glycine. In particular, NMR spectra of nitronate ions analogous to **4** and **5** in percent yields similar to those above were obtained in every case. Since these amines differ greatly in ionization potential, but not in nucleophilicity, the findings suggest that the chemistry has nothing to do with ionization potential.

We also obtained strong evidence for meta adducts by using an oxidizer of dihydrobenzenes in the photolysis mixture. We had earlier shown for an analogous intramolecular photoreaction of 4-O₂N-C₆H₄-OCH₂CH₂NH₂, that photolysis in the presence of 3,5-dinitrobenzoic acid gave a total 75% yield of isolated aromatized meta hydride displacement products.²⁰ When we irradiated **1** in the presence of ammonia and 3,5-dinitrobenzoic acid, as shown in Scheme 2, we learned (by NMR peak enhancements with authentic

Scheme 2. Photoproducts from **1** with Ammonia in the Presence of 3,5-Dinitrobenzoic Acid



samples) that 95% of the products were attributable to three products, of which 60% was the nitro substitution product, and a total of 35% stemmed from oxidized, meta adducts. This extent of adduct formation is similar to that in Scheme 1 and is strong additional evidence that meta adducts occur in these reactions.

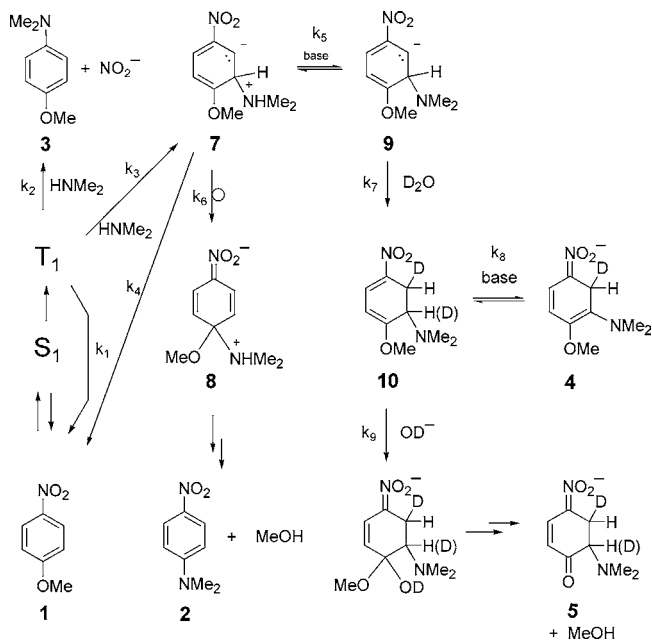
We offer Scheme 3 to interpret our results. The evidence that the photochemistry occurs from the triplet excited state of **1** is that we can sensitize it with the triplet sensitizer, 3-methoxyacetophenone. The triplet can react directly with the amine to displace the nitro group (k_2). This reaction has precedent²¹ and may be rationalized by the energy gap law since the σ complex for nitro displacement is an unstabilized, high energy anion just as are the meta σ complexes. With an easily oxidizable amine such as dimethylamine, the triplet can be photoreduced to the hydroxylamine **6** (Scheme 1), as occurs in the case of isopropyl alcohol as the reductant.²² The photoreduction process (not shown) is probably the outcome of electron transfer and nongeminate radical processes, as it is in carbonyl-amine photochemistry.¹⁵ The

(20) Wubbels, G. G.; Halverson, A. M.; Oxman, J. D.; De Bruyn, V. H. *J. Org. Chem.* **1985**, *50*, 4499.

(21) Letsinger, R. L.; Ramsay, O. B.; McCain, J. H. *J. Am. Chem. Soc.* **1965**, *87*, 2945.

(22) Hashimoto, S.; Kano, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 549.

Scheme 3. Mechanism of the Photoreaction of 4-Nitroanisole with Dimethylamine



first-formed meta adduct **7** is a zwitterion that should be deprotonated (k_5) to give **9** by bases of $pK_a > 10$ at rates near the diffusion limit. The C–N bond of **9** is expected to be stable, enabling **9** to undergo the relatively slow protonation on carbon (k_7) that makes **10**. Structure **10**, as a vinylogous alkyl nitro compound, should have a pK_a of about 9, enabling it to form **4** via k_8 at high pH's. We suggest that a fast sigmatropic shift (k_6) of **7** to give **8** can compete with deprotonation. This leads to the substitution product **2**.

All of our results can be interpreted by the scheme. The rationale it provides for the striking finding that the yield of **4** increases with the hydroxide ion concentration at the expense of the photosubstitution product **2** is unique and powerful support of its validity.

At the level of details, the chemistry proposed for hydrolysis of **4** to **5** plus methanol has precedent in our previous study.¹⁸ That **4** is stable at high pH, and requires a moderately lower pH to hydrolyze is attributable to the prototropic equilibrium of **4** and **10**.

The sigmatropic rearrangement of **7** has no precedent. It would have to be fast enough to compete with deprotonation that limits the lifetime of **7** to tens to hundreds of nanoseconds. Semiempirical AM1 calculations of the relative energies of meta vs para σ complexes in the singlet manifold show, as have previous reports,⁷ that the rearrangement is exothermic by 17 kcal/mol. This is compatible with a very fast reaction.

Our findings provide a mechanistic rationale for two quantitative photosubstitution studies by others that have hitherto lacked explanation. The regioselectivity of photosubstitution by *n*-butylamine on 4-nitroveratrol has been shown to be pH dependent.²³ Displacement of the methoxy groups meta vs para by the amine was 12:1 at pH 12.2 and

3:1 at pH 10.5. If both photosubstitutions proceed from an intermediate analogous to **7** (H at the addition site replaced by methoxy), at high pH the intermediate is substantially deprotonated, leading mainly to the meta photoproduct. At lower pH, it is deprotonated less and rearranges more, giving an increased proportion of the para substitution product, as observed.

The new mechanism can also explain the puzzling observation²⁴ of temperature-dependent regioselectivity in the photolyses of **1** with hydroxide ion. For photolyses with hydroxide ion in alcohol solvents, the ratio of nitrite displacement to methoxide displacement changed from 99:1 at $-20\text{ }^{\circ}\text{C}$ to 1:1 at ca. $100\text{ }^{\circ}\text{C}$, the change being caused by growth in the yield of methoxide displacement. The authors concluded that methoxide displacement must be thermally

(23) Kuzmic, P.; Pavlickova, L.; Velek, J.; Soucek, M. *Collect. Czech. Chem. Commun.* **1986**, *51*, 1665.

(24) Klan, P.; Ruzicka, R.; Heger, D.; Literak, J.; Kulhanek, P.; Loupy, A. *Photochem. Photobiol. Sci.* **2002**, *1*, 1012.

activated whereas nitrite displacement is not, but the reason was not clear. If nitrite displacement stems from direct nucleophilic attack by hydroxide ion on the triplet while methoxide displacement involves meta attack on the triplet by hydroxide ion and thermally activated sigmatropic rearrangement to the para σ complex competitive with decay, the findings are as expected.

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Supporting Information Available: NMR spectra for the data in Scheme 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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