## COMMUNICATION

## Effects of superoxide anion generated from aromatic radical anions produced in nucleophilic aromatic photosubstitution reactions

Maria Cervera and Jordi Marquet

**Abstract**: Superoxide anion is generated from aromatic radical anions produced in nucleophilic aromatic photosubstitutions when the reactions are carried out in non-deoxygenated solutions of polar aprotic solvents. Superoxide anion thus generated displaces cyanide anion from acetonitrile and benzyl cyanide, ethoxide anion from ethyl acetate, and methanesulfenate anion from dimethyl sulfoxide. Hence, non-deoxygenated polar aprotic solvents should be avoided in nucleophilic aromatic photosubstitution reactions.

Key words: superoxide, fluoride, nucleophilic aromatic photosubstitution.

**Résumé**: Lorsqu'on effectue des photosubstitutions aromatiques nucléophiliques dans des solutions non désoxygénées de solvants aromatiques polaires, on génère l'anion superoxyde à partir des anions radicaux aromatiques alors produits. L'anion superoxyde ainsi produit déplace l'anion cyanure de l'acétonitrile et du cyanure de benzyle, l'anion éthylate de l'acétate d'éthyle et l'anion méthanesulfonate du diméthylsulfoxyde. Lorsqu'on effectue des réactions de photosubstitution aromatiques nucléophiles, on doit donc éviter les solvants aprotiques polaires non désoxygénés.

Mots clés : superoxyde, fluorure, photosubstitution aromatique nucléophilique.

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Nucleophilic aromatic photosubstitutions have been the object of intense research since their discovery in 1956 (1). A mechanistic borderline between polar  $S_N 2Ar^*$  (2) and  $S_N 2Ar^*$ -SET (reactions that take place through single electron transfer from the nucleophile to the excited nitroaromatic substrate) has been well established (3, 4). These photoreactions are normally carried out in protic solvents (water is the more common) and without any precautions with regard to the presence of oxygen since its effect on the photoreaction is generally negligible. This has been attributed to the very short lifetime of the nitroaromatic excited states (5) and to the fact that the  $S_N 2Ar^*$ -SET reactions involve a collapse of radicals in the solvent cage (6).

Fluorinated aromatics nowadays constitute an important

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This paper is dedicated to Professor Erwin Buncel in recognition of his contributions to Canadian chemistry.

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<sup>1</sup> Author to whom correspondence may be addressed. Telephone: (3) 581-1029 / (3) 581-1265. Fax:(3) 581-1265 / (3) 581-2477. e-mail: iqor3@cc.uab.es class of compounds because of their wide applications, especially in medicinal chemistry (7). The most common way of introducing a fluorine atom into an aromatic nucleus is based on the use of nucleophilic fluoride anion through nucleophilic aromatic substitution reactions (known as the "Halex method") (8). The efficiency of this method has been much improved by the use of tetralkylammonium fluorides (9). Fluoride anion is strongly solvated in protic solvents, its reactivity being very reduced in these media. Therefore, reactions with fluoride anion are normally carried out in anhydrous polar aprotic solvents where fluoride behaves as a very strong base and nucleophile (10).

Nucleophilic aromatic photosubstitutions show in many cases a different regioselectivity when compared with the corresponding ground state reaction. Moreover, inefficient leaving groups in thermal reactions, such as alkoxy groups, are operative in the photochemical version. Therefore, we decided to explore the nucleophilic aromatic photosubstitution of 4-nitroveratrole (NVT), a typical nitrophenyl ether for which the regioselectivity of the photoreaction can be established, with fluoride anion in non-deoxygenated polar aprotic solvents such as acetonitrile (ACN). However, no fluorinated products were obtained. In Scheme 1 the results of the photoreactions carried out in acetonitrile are described. There is no precedent in the literature for the reaction reported in the Scheme 1. Scheme 1.



<sup>*a*</sup> Medium-pressure Hg lamp (Pyrex filter,  $\lambda > 290$  nm). Room temperature. The products were characterized by comparison with authentic samples. Absolute preparative yields based on nonrecovered starting material. Blank irradiations in the absence of fluoride led in all cases to recovery of the starting material.

Scheme 2.





For the sake of comparison, we carried out the photoreaction of NVT with sodium cyanide in ACN-H<sub>2</sub>O (1 h), obtaining the same photosubstitution product, 2-cyano-4-nitroanisole (46% yield), as the only cyanide substitution product, indicating complete meta regioselectivity. Therefore, it seems that the photoreaction described in Scheme 1 involves the fragmentation of the solvent. However, the only related cases described in the literature refer to reductive cleavage of tertiary or secondary alkylnitriles (11) promoted either electrochemically or by solvated electrons, and to photoinduced reductive cleavage of benzylnitriles (12). In these cases the resulting free radical would be stabilized by conjugative or hyperconjugative effects. No such effects are present in the methyl radical and, in addition, our photoreactions proved to be very sensitive to the presence of oxygen. Thus, the photoreaction in non-deoxygenated ACN led to 17% yield of photosubstitution product, but this yield was increased to 67% by bubbling air into the solution. The photoreaction in the absence of oxygen led to

Scheme 4.



complete recovery of the starting material. These results rule out the hypothesis of a reductive cleavage in the mechanism for the photoreactions described in Scheme 1.

To investigate the evolution of the alkyl fragment, the photoreaction was carried out in benzyl cyanide (instead of ACN) and with air bubbling. The reaction crude was directly analyzed by GC–MS and the products detected are described in the Scheme 2.

From the results reported in Scheme 2 it was clear that the photofragmentation of alkylnitriles is a general process under our conditions, and that the agent responsible for it is an oxidizing species with nucleophilic properties. All products derived from the benzyl moiety are easily justified by considering the radical PhCH<sub>2</sub>OO<sup>•</sup> as a key intermediate (13). These results led us to the hypothesis that the "oxidizing species with nucleophilic properties" was the superoxide anion (O2<sup>-•</sup>) (14). The excellent nucleophilic properties of superoxide anion in polar aprotic solvents are well documented (it reacts with alkyl halides (15) or carbonylic compounds (16)); however, as far as we know no displacement of cyanide from nitriles has been reported (Sawyer and co-workers (18) describe the action of superoxide as a base with acetonitrile, obtaining condensation products). On the contrary, acetonitrile has been used as a solvent in fundamental studies on the reactivity of superoxide anion and its derivatives (18); however, it has been noted that the reactivity of O2<sup>-•</sup> in acetonitrile is different from that in other solvents (for example, ref. 19), the lifetime of O2<sup>-•</sup> being typically 10 times shorter in the nitrile.

Sawaki and Ogaka (20) reported the reaction between superoxide and acetonitrile in the presence of an easily oxidizable species such as dimethyl sulfoxide as leading to acetamide and dimethylsulfone through the attack of superoxide on the nitrile. However, when the reaction was carried out Scheme 5.



in the absence of the oxidizable species, these authors described the disappearance of the superoxide anion. No explanation was advanced for this behavior.

We have confirmed the role played by the superoxide anion in our reactions by carrying out the photoreaction of NVT with potassium superoxide in acetonitrile and in inert atmosphere, in the presence of the 18-crown-6 (Scheme 3). Direct analysis of the reaction crude by GC showed only the presence of starting NVT and 2-cyano-4-nitroanisole. The displacement of cyanide from acetonitrile in the presence of superoxide anion seems to be a ground state reaction, and this was shown by the detection of cyanide anion (Prussian blue test) in a solution of potassium superoxide and 18-crown-6 in acetonitrile.

After the identification of the agent responsible for our photoreactions an immediate question arises: how is the superoxide anion produced? A still unsolved paradox in ground state aromatic chemistry is the fact that when an electronically poor aromatic (e.g., polynitrobenzenes) substrate is placed in the presence of not easily oxidizable anions such as alkoxy or cyanide, not only the Meisenheimer complexes, but also the corresponding radical anions, can be detected (21). It is known that the concentration of radical anions depends on the concentration and nature of the nucleophile, and on the concentration of Meisenheimer complexes present in the solution (normally very low in ground state chemistry) (22). Therefore, the simplest hypothesis is that production of significant amounts of superoxide anion in our photochemical reactions originates by interaction of dioxygen with the radical anion of the aromatic substrate (NVT), and that this radical anion is present in a significant concentration under our photochemical conditions due to the enhanced reactivity of the nucleophile (fluoride) versus the excited state of the aromatic substrate (NVT is not a very electronically poor substrate), affording a sufficiently large concentration of Meisenheimer complexes. The dependence of the photoreaction upon the nature of the nucleophile and on the concentration of Meisenheimer complexes is demonstrated by the fact that the reactions of Scheme 1 fail when attempted with bromide (a weaker nucleophile

Scheme 6.



in anhydrous acetonitrile) instead of fluoride. In addition, the radical anion of NVT (23) was detected by UV–vis spectroscopy when NVT was irradiated in the presence of TBAF in acetonitrile, under inert atmosphere, but this radical anion could not be detected when bromide was used. These results strongly support our hypothesis. In Scheme 4 a simplified mechanistic proposal is described.

As expected, this behavior was not restricted to nitriles. The photoreaction of NVT in the presence of TBAF·3H<sub>2</sub>O in ethyl acetate gave rise to 2-ethoxy-4-nitroanisole (Scheme 5A), whereas in dimethyl sulfoxide (DMSO), 1,2-dimethoxy-3methyl-4-nitrobenzene, 1,2-dimethoxy-4-methyl-5-nitroben-2-methoxy-5-nitrophenol were obtained zene, and (Scheme 5B). These results support our previous conclusions and can also be justified by considering the superoxide anion as responsible. Thus, and for the case of ethyl acetate, it is well known that superoxide anion reacts with esters producing alkoxy anions (17). Here, the ethoxy anion would act as a nucleophile towards NVT in a nucleophilic aromatic photosubstitution reaction (last step of Scheme 4, RO<sup>-</sup> instead of CN<sup>-</sup>). In the case of the photoreaction carried out in DMSO, the main photoreaction corresponds to the methylation of the aromatic ring. This result suggests the operation of methyl radicals as reaction intermediates. It is known (24) that hydroxyl radicals ('OH) add to DMSO producing methyl radicals through decomposition of intermediate species such as  $Me_2S(O^{\bullet})OH$ . The presence of hydroxyl radicals can be justified by assuming that superoxide anion behaves towards DMSO in a similar way as towards ACN (Scheme 6), through nucleophilic displacement of, in this case, methanesulfenate anion. The methanesulfenate anion thus produced would be responsible for the observed 2-methoxy-5-nitrophenol through a nucleophilic attack upon the excited state of NVT and subsequent hydrolysis, probably at work-up, since no phenol was observed in the photoreactions carried out in ACN, either in ethyl acetate or in a blank irradiation in the absence of fluoride anion.

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