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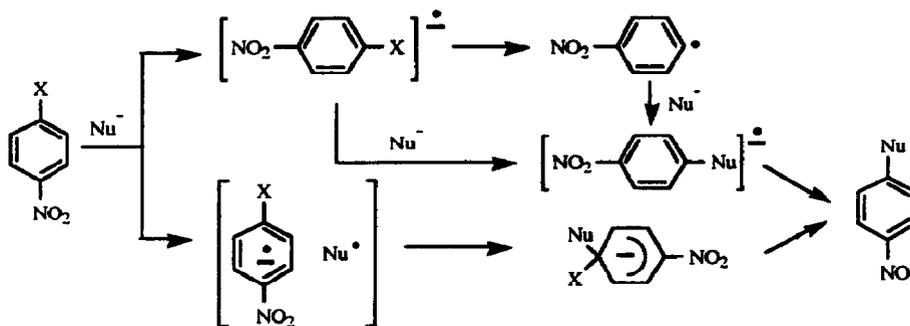
Reductively Activated "Polar" Nucleophilic Aromatic Substitution. II.¹ The Reaction of *p*-Dinitrobenzene and *p*-Nitrobenzotrile with Charged and Neutral Nucleophiles.

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Abstract: Electrochemical studies indicate that although the reactions of *p*-dinitrobenzene and *p*-nitrobenzotrile with phenolate or phenol in DMF show radical features, they can not be attributed to the direct reaction of the nucleophile on the substrate radical anion. Reductive activation is feasible in certain cases (reaction of *p*-dinitrobenzene with phenol). However, substrate radical anion formation is not responsible for it.

In recent years an interesting controversy has appeared in the chemical literature concerning (in part) the mechanism of nucleophilic aromatic substitution reactions on aromatic compounds, as dinitrobenzenes, nitrobenzophenones, nitrobenzotriles, polyfluoronitrobenzenes, etc., able to stabilize radical anions. Except for the very particular case of *o*-iodonitrobenzene² no example of the S_{RN}1 chain mechanism³ for nitroaryl derivatives has so far been demonstrated. However, many of those reactions show radical features. One interpretation suggests the intermediacy of radical anions, formed through electron transfer from the nucleophile to the substrate, prior to the σ-complex (which we can call S_NAr-SET mechanism)⁴. Another proposal involve direct reaction of the nucleophile on the substrate radical anion^{5,1} (S_{RN}2 mechanism⁶). It has been this last proposal (extended^{5a} to many well demonstrated S_{RN}1 cases) that has found strong resistance in the chemical community⁷ (all three mechanistic possibilities are shown in scheme 1).



Scheme 1

Abe and Ikegami⁸ observed the presence of the radical anions in the reactions of dinitrobenzenes with OH⁻ in aqueous DMSO and they postulated that the radical anions were intermediates in these reactions. Sammes et al.⁹ have studied the displacement of nitro groups from *p*-dinitrobenzene and other nitrocompounds by various phenoxide ions in DMSO. These reactions yielded substituted diphenyl ethers. They showed that the reactions were inhibited by radical scavengers and they concluded that those reactions

were radical in nature. Shein et al.¹⁰ demonstrated the formation of *p*-dinitrobenzene radical anion when this substrate was reacted with a series of anion nucleophiles, among them phenoxide ion. On the other hand, it has been shown in the literature^{5b} that the reactions of *p*-nitrobenzotrile with sodium phenoxide, although not stimulated by light could be inhibited by radical scavengers. Those results (and others) prompted Denney and Denney⁵ to postulate the general operativity of a mechanism that included as a key step the reaction of a nucleophile with the radical anion derived from the aromatic substrate (S_{RN}2 mechanism).

However, thermodynamic and kinetic considerations indicate that outer sphere electron transfer will be very slow in strongly endergonic processes as the ones here considered, and that in those endergonic processes a very fast follow up step is compulsory for the reaction to be feasible¹¹. This fast follow up step can be present in the S_NAr-SET scheme, but this is not the case in the S_{RN}2 one, where a presumably high barrier radical anion - nucleophile reaction follows the first electron transfer step. It is worth remembering that an inner sphere electron transfer step had to be proposed¹² to solve a similar question concerning aliphatic S_{RN}1 processes initiated by nitronates. Therefore, we thought that the S_{RN}2 hypothesis deserved a closer examination. Definitive answers should come from electrochemical experiments, and in this context we present here the preliminary results of a study on the possible influence of cathodic stimulation on the reactions of *p*-dinitrobenzene (*p*-DNB) and *p*-nitrobenzotrile (*p*-NBN) with charged and uncharged nucleophiles (phenolate and phenol as examples respectively), in DMF as a solvent.

Table 1. First and Second Reduction Potentials of *p*-Dinitrobenzene and *p*-Nitrobenzotrile, Measured by Cyclic Voltametry in Glassy Carbon (13°C)

Substrate ^a	Solvent	E ^o /V ^b	E ₂ ^o /V ^b
<i>p</i> -Dinitrobenzene	DMF	-0.56	-0.79
<i>p</i> -Nitrobenzotrile	DMF	-0.73	-1.30

a) Substrate 2.0 mM solutions containing 0.1M Tetrabutylammonium tetrafluorate. b) Standard potential vs. SCE.

In table 1, the first and second reduction potentials of *p*-DNB and *p*-NBN, measured in our reaction conditions are given. Cyclic voltametry experiments in dry DMF show two reversible peaks corresponding to the first and the second reduction of the substrate in both cases. The reaction of *p*-DNB with excess phenoxide ion in DMF was almost instantaneous, yielding 4-nitrophenyl phenyl ether, and no radical anion could be detected by UV/Vis spectroscopy. The reaction was slower when using [PhO⁻]/[substrate] < 1. Experiments carried out in these conditions, keeping a constant potential (-0.7V) and analyzing the mixture by cyclic voltametry gave the same voltogram as blank experiments, indicating that no reductive activation of the reaction was present at least at the level of the first reduction wave. Next, the *p*-DNB radical anion was electrochemically generated in DMF, and its possible reaction with phenoxide ion monitored by UV/Vis spectroscopy. *p*-DNB radical anion has a very characteristic absorption spectra¹³ (λ_{max} = 400 nm, λ_{max} = 920 nm, this last band appears as a very useful terminal absorption in the UV/Vis spectrum, 800 nm, since our systems show no other absorptions in this part of the spectrum), and resulted to be stable in inert atmosphere. Addition of sodium phenoxide to the radical anion solution produced no reduction of the intensity in the absorption spectra of the radical anion, thus demonstrating that direct reaction of the *p*-DNB radical anion and the phenolate nucleophile does not take place in DMF.

The reaction of *p*-nitrobenzotrile (*p*-NBN) with sodium phenoxide yielded 4-phenoxybenzotrile and it showed the same electrochemical features that the *p*-DNB reaction. However, the reaction resulted to be slower, and therefore some additional tests could be performed. In table 2 the yields of the reaction carried out in different conditions are compared. Thus, a certain yield reduction is observed when the reaction is carried out in the presence of sulfur (exp. 2). Also, the reaction with air bubbling (exp. 6) gives a much lower yield than the reaction in inert atmosphere (exp. 5). Those experiments confirm earlier reports^{5b} on the influence of radical scavengers on the reaction. However, electrolysis at -0.9V (first reduction wave, exp. 8) also resulted in an important yield reduction indicating that external radical anion generation was deleterious for the

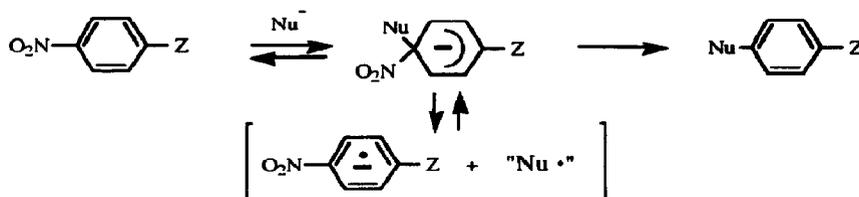
substitution reaction. Entry 9 corresponds to a reaction carried out under constant potential, but using a potential value that is placed before the first reduction wave. In this case the yield is lower than the blank reaction (exp. 7 in this case) but higher than the reaction at -0.9V . The obvious interpretation is that at -0.6V the electrode acts as an oxidant with respect to the radical species present in the reaction (the same effect as oxygen or other radical scavengers used in the literature). Those results completely eliminate the attack of the nucleophile on the substrate radical anion ($\text{SR}_{\text{N}2}$) as an operative step in the substitution mechanism of our reactions, but they support the radical nature of it.

Table 2. Reactions of *p*-Nitrobenzonitrile with Sodium Phenolate.^a

Exp.	Conditions ^b	Additives ^c	Yield(%) ^d
1	DMF, r.t., 3 h.	---	74
2	DMF, r.t., 3h.	Sulfur (1 eq.)	60
3	DMF, 15°C, 1h.	---	12
4	DMF, 15°C, 1h.	hν	19
5	DMF, r.t., N ₂ atm., 1 h	---	43
6	DMF, r.t., air bubling, 1h.	(O ₂)	10
7	DMF, r.t., N ₂ atm., 1 h	e	52
8	DMF, r.t., N ₂ atm., 1h	cathodic reduction, (-0.9V) ^e	25
9	DMF, r.t., N ₂ atm., 1h	cathodic reduction, (-0.6V) ^e	44

a) A 10/1 molar ratio of sodium phenolate to *p*-nitrobenzonitrile was used in all the experiments. b) No precautions were taken to avoid the presence of oxygen unless otherwise stated. c) The photostimulation was attempted with a 1000W tungsten lamp. The cathodic reduction was carried out using a glassy carbon electrode. Numbers between parenthesis correspond to the used molar ratio (referred to *p*-nitrobenzonitrile) in the case of sulfur, or, to the used voltage (vs. SCE) in the electrochemical reactions. d) 4-Phenoxybenzonitrile preparative yield. e) Solutions containing 0.1 M Tetrabutylammonium tetrafluorate.

A first explanation for the so far reported facts would be to consider the $\text{S}_{\text{N}}\text{Ar}$ -SET mechanism. Against it goes the previously commented endergonicity of the electron transfer step and the absence of stimulation by light. However such a mechanism has been proposed in the literature for even less favorable cases that use hydroxide ion as a reductant^{4b,c}. A variation to this mechanism, that would circumvent those objections, would be to consider an inner sphere electron transfer process ($\text{S}_{\text{N}}\text{Ar}/\text{Inner-SET}$, scheme 2). In this mechanism, the radical anion could be produced by homolytic fragmentation of the intermediate σ -complex, following the scheme proposed by Wasgestian^{12b} to justify the appearance of the radical anion when *p*-dinitrobenzene is placed in the presence of cyanide. In this scheme, the radical anion would be in equilibrium with the σ -complex, justifying the observed radical features of all these processes, but not participating in the direct pathway from reagents to products.



Next we decided to test the possibility that the reaction between a radical anion and a nucleophile were feasible with neutral nucleophiles. Thus, we compared the results of cyclic voltametry experiments of *p*-DNB and *p*-NBN in DMF and in the presence and in the absence of phenol. The first reduction wave does not

show any variation, confirming that radical anions do not react with nucleophiles. However, some variations were observed at the second reduction wave level. Electrolysis of the reaction mixture at $-0.9V$ (vs. SCE, glassy carbon electrode) in the case of *p*-DNB led to the monosubstitution product in 28% yield in 10 min. (4.6 faradays). A blank experiment gave no reaction. However, reactions carried out with *p*-NBN using different potentials ($-1.3V$, and $-1.55V$, vs. SCE) were unsuccessful, being nitro group reduction products the only observed reaction. We can therefore conclude that reductive stimulation of nucleophilic aromatic substitution is feasible (see also the following article) in some particular cases, but that the radical anion formation is not responsible for it.

A first interpretation for this reductive activation would be to consider that the substrate dianion formed after the second reduction is basic enough to catalyze the substitution process (a related explanation was given by Chambers and Adams¹⁴ to justify the appearance of nitrophenols in the electrochemical reduction of dinitrobenzenes in not completely dried DMF). However, this scheme would lead to the appearance of relatively large amounts of starting material reduction products (the natural evolution of the protonated dianion), and in our stimulated reaction only very minor amounts of them can be detected. An alternative explanation would include the reduction of the zwitterionic σ -complex¹⁵ that would immediately cleave (the reduction potentials of the zwitterionic σ -complexes should be similar to the ones of the radical anions, thus making their detection difficult by cyclic voltametry). The activation in this last hypothesis would be due to the increase of the σ -complex fragmentation rate (this step is probably the rate determining step in our reactions with neutral nucleophiles)¹⁶. We are currently testing those mechanistic hypothesis and a complete account will be published in the near future.

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