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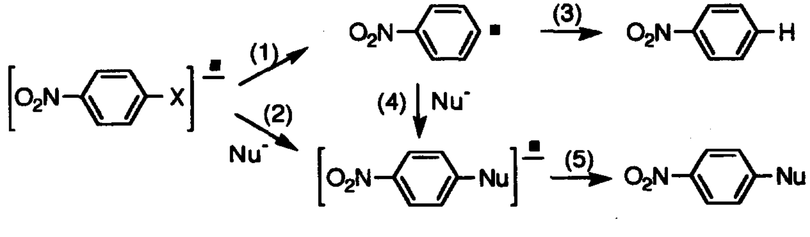
Reductively Activated "Polar" Nucleophilic Aromatic Substitution of Pentafluoronitrobenzene. The S$_{RN}$2 Hypothesis Revisited

Jorge Marquet,* Ziqi Jiang, Iluminada Gallardo, Anna Batlle and Eduard Cayón

Department of Chemistry, Universitat Autònoma de Barcelona. 08193 Bellaterra, Barcelona. Spain.

Abstract : The reactions between pentafluoronitrobenzene and several nucleophiles, in aqueous media, can be photo- and electro-stimulated (reductively). Our results indicate we are in the presence of a chain reaction type that includes direct attack of the nucleophile on the radical anion of the substrate.

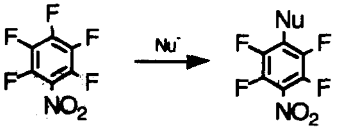
Even though anion radicals have been proposed[1], in some cases, as intermediates (prior to the σ-complex) in the addition-elimination mechanism of nitroaryl derivatives nucleophilic aromatic substitution (S$_N$Ar), except for the very particular case of o-iodonitrobenzene[2] no example of the S$_{RN}$1 chain mechanism[3] (pathway through steps (1), (4) and (5) in Scheme 1) for nitroaryl halides is known (this fact has been attributed[4] to the stability[5] of the π* radical anion when a nitro group is present, which precludes its necessary fragmentation to the aryl radical and halide). Curiously enough, not much attention has been given to an alternative mechanistic hypothesis that could help to explain some still puzzling features in "polar" S$_N$Ar reactions[6]. That is the direct reaction of the nucleophile on the substrate radical anion (pathway through steps (2) and (5) in Scheme 1). This mechanism (S$_{RN}$2) was considered[7] as an hypothesis in the early literature but rejected on experimental grounds. There are also several disperse evidences in the literature[8] for reactions of nucleophiles with aromatic radical anions that do not dissociated. A recent article[9] has reinvigorated the discussion about the occurrence of such a mechanism in some of the processes previously assigned to the S$_{RN}$1 mechanism.



Scheme 1

In order to confirm the existence, and the possibilities of such a mechanism, pentafluoronitrobenzene (PFNB) was considered as a substrate and aqueous solution as reaction media. The addition of the well known stability of the nitroaromatic radical anions[5] (increased in basic water solution) to the strength of the C-F bond should help to the aim of cancelling the step (1) in Scheme 1 that leads to the S$_{RN}$1 mechanism and the dehalogenation reaction[10] (step 3 in Scheme 1). The reactions of PFNB with some nucleophiles[11] (methoxide, amines, etc.) are known, and even some kinetic studies[12] (for the methoxydefluorination) have been reported, being the S$_N$Ar mechanism the postulate mechanism for those reactions, but they have been always carried out in the absence of water.[13]

Table 1. Reactions of PFNB with Nucleophiles. Preparative and Mechanistic Studies.



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Exp	NuH	Conditions[a]	Additives[b]	Preparative Yield(%) of product 1[c]	(k_{add}/k_0)[d]
1	MeOH	MeOH/H_2O (2:1) K_2CO_3, r. t. 10 min	---	86	---
2	MeOH	MeOH/H_2O (9:1) K_2CO_3, r. t. 10 min	Galvinoxyl (5)	--	$<10^{-2}$
			Galvinoxyl (1)	--	0.47
			Galvinoxyl (0.25)		0.80
		MeOH/H_2O (2:1) K_2CO_3, r. t. 10 min	1,3-DNB (1)	--	0.39
			1,3-DNB (0.5)	--	0.43
			1,3-DNB (0.25)	--	0.76
3	MeOH	MeOH/H_2O (2:1), r. t. $NaHCO_3$, 20 min	hv	--	$>10^2$
4	MeOH	MeOH/H_2O (2:1), r. t. $NaHCO_3$, 20 min	Cathodic reduction (-1V)	--	$>10^2$
5	C_6H_5OH[e]	CH_3CN/H_2O (5:1) K_2CO_3, r. t. 10 min	---	72	---
6	C_6H_5OH[f]	CH_3CN/H_2O (5:1) K_2CO_3, r. t. 5 min	Galvinoxyl (1)	--	0.44
			Galvinoxyl (0.5)	--	0.55
			1,3-DNB (0.5)	--	0.90
7	C_6H_5OH[c]	CH_3CN/H_2O (5:1) NaOAc, r. t. 30 min	hv	--	1.90
8	C_6H_5OH[c]	CH_3CN/H_2O (5:1) NaOAc, r. t. 10 min	Cathodic reduction (-1V)	--	$>10^2$
9	C_6H_5SH[c]	CH_3CN/H_2O (5:1) K_2CO_3, r. t. 4 min	---	86	---
10	C_6H_5SH[c]	CH_3CN/H_2O (5:1) NaOAc, r. t. 4 min	Galvinoxyl (0.5)	--	0.85
11	C_6H_5SH[f]	CH3CN/H_2O (9:1) r.t. 2 min	1,3-DNB (1.0)	--	0.65
			1,3-DNB (0.5)	--	0.86
12	C_6H_5SH[c]	CH_3CN, r.t. 15 min	Cathodic reduction (-1.15V)	--	>15

a) The bases were used in excess. b) The photostimulation was carried out with a medium pressure Hg lamp with pyrex filter. The electrostimulation was carried out using a glassy carbon electrode. Numbers between parenthesis correspond to the used molar ratio (referred to PFNB) in the case of Galvinoxyl, and 1,3-DNB (1,3-dinitrobenzene), or, to the used voltage in the electrostimulated reactions. c) The new products gave correct elemental analyses. Their full characterization will be reported elsewhere. Small amounts of the corresponding ortho-substituted products were also obtained. d) Ratio between the rate of production of 1 in the presence of the additive and the same for a blank reaction, carried out in exactly the same conditions, but in the absence of the additive. e) Stoichiometric amount of NuH. f) Excess of NuH.

In Table 1 the preparative results of the reactions of PFNB with a series of nucleophiles in aqueous solutions are shown. Mechanistic tests[14] have been performed, and the results are also indicated. Adjusting the strength of the used base (which suggests that the anions are the real nucleophiles), monosubstitutions (4-substituted-2,3,5,6-tetrafluoro-nitrobenzenes, **1**), and reactions slow enough to perform mechanistic studies were achieved. It is remarkable that in exp. 1-4 no phenol (**1**, Nu = OH) could be detected, indicating that the reaction has a high selectivity for the methoxide ion over OH^-. The reactions were relatively insensitive to the presence of oxygen but they were quenched by variable amounts of stronger radical scavengers and electron transfer quenchers such as galvinoxyl and 1,3-dinitrobenzene (exp. 2, 6, 10, 11). Moreover, they could be photostimulated (exp. 3, and 7), and electrostimulated[15] (exp. 4, 8, and 12). With thiophenol as a nucleophile in aqueous solution, the reaction was too fast to attempt any photostimulation or electrostimulation. Using acetonitrile (not dried) as a solvent, electrostimulation was achieved (exp. 11). Those data would normally lead to the proposal of an $S_{RN}1$ mechanism[14] but in this case there are several important facts that do not fit with its overall scheme:

a) PFNB radical anion is stable in front of fragmentation. We have measured the lifetime of PFNB radical anion in DMF (t = 0.02 s), and methanol/water, pH 8 (t = 0.2 s) from cyclic voltametry experiments. The relatively large values obtained suggest, that for this substrate, the rate determining step in an hypothetical $S_{RN}1$ cycle should be the C-halogen bond fragmentation (step (1) in the Scheme 1). In this situation, the very different reaction rates ($OH^- << RO^- < RS^-$) exhibited for the used nucleophiles in the experiments of Table 1 can not be justified.

b) Product analyses indicate that methoxide ion and phenoxide ion act as oxygen nucleophiles (exp. 1 and 5, Table 1). However, it is well known that, in front of aryl radicals, methoxyde ion gives rise to hydrogen transfer,[16] while phenoxyde ion behaves as a carbon nucleophile.[17]

c) The relative insensitiveness of our reactions to the presence of oxygen discards the intermediacy of an aryl radical in our reactions. However, it is known that radical anions are much less reactive than aryl radicals, and we have observed in some other cases the very small effect that the presence of oxygen produces in the reactions of nitrophenyl radical anions[18] in aqueous solutions. Stronger radical scavengers interact[18] with nitrophenyl radical anions and this is just what we observe.

Table 2. First and Second Reduction Potentials of Nitro- and Polyfluoronitroaromatics in Different Solvents, Measured by Cyclic Voltametry in Glassy Carbon (13°C).

Substrate[a]	Solvent	E^o/V^b	E_{p2}/V^c
NB	DMF[d]	-1.05	-2.15
NB	$MeOH/H_2O$ (5:1), pH 8[e]	-0.83	-1,14
TTFNB	DMF[d]	-0.77	-1.48
TTFNB	$MeOH/H_2O$ (5:1), pH 8[e]	-0.76	-1.10
PFNB	DMF[d]	-0.79	-1.54
PFNB	$MeOH/H_2O$ (5:1), pH 8[e]	-0.66	-1.10

a) NB = nitrobenzene, TTFNB = 2,3,4,5-tetrafluoronitrobenzene, PFNB = pentafluoronitrobenzene (2mM). b) Standard potential vs. SCE c) Peak potential vs. SCE. d) 0.1M Tetrabutylamonium tetrafluoroborate. e) 0.1 M NaCl

In Table 2, the reduction potentials (first, E^o, and second, E_{p2}) for nitrobenzene and some polyfluorosubstituted nitrobenzenes are shown. On introducing the fluorine substituents, and on changing the solvent from DMF to methanol/water, the absolute values are strongly reduced. The E_{p2} values correspond to the reduction potentials of the radical anions. Those reduction potentials can be correlated with the electrophilic ability of the corresponding radical anion if we consider the nucleophile attack within the Prost-Shaik single electron transfer framework[19]. Therefore, the electronic affinity, and possibly their ability as electrophiles (at least against easily polarizable nucleophiles) for the more substituted polyfluoronitrobenzenes radical anions in aqueous solvents such as methanol/water are similar to that of the unsubstituted or less substituted neutral molecules in DMF.

Our results indicate we are in the presence of radical chain reactions that can be photo- and electrostimulated (reductively), and that aryl radicals are no real intermediates in them. On the other hand the electrochemical measurements indicate PFNB radical anion in water still has good electrophilic properties. All this suggest that nucleophile attack takes place directly on the radical anion (step 2 in Scheme 1), being the reactions reported in Table 1 clear cut examples of $S_{RN}2$ nucleophilic aromatic substitutions. In principle, this mechanism could be elicited, electrochemically or photochemically, in less favourable cases. We are currently studying this possibility and a complete account will be published in the near future.

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