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Reductively Activated "Polar" Nucleophilic Aromatic Substitution. III.[1]
The Reactions of Polyfluoronitrobenzenes with Methanol.

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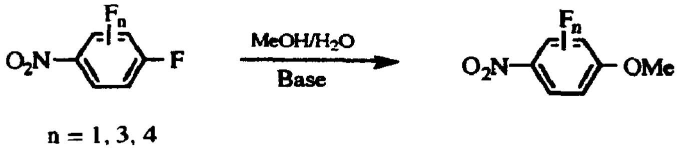
Abstract : The nucleophilic aromatic substitution reactions of pentafluoronitrobenzene (PFNB) and 2,3,4,5-tetrafluoronitrobenzene with methanol are both reductively activated. However, the first one is sensitive to the presence of radical scavengers but the second is not. In addition, the kinetic behavior of both reactions in the absence of stimulation is very similar suggesting they are examples of second stage rate determining S_NAr mechanism. Kinetic studies also show that no real photochemical stimulation exist in those reactions. The reported facts are not compatible with the previously proposed (for the reaction of PFNB with methanol) $S_{RN}2$ mechanism. A new mechanistic rationale is discused.

The preceeding paper in this Journal[1] was devoted to test the possible operation of the $S_{RN}2$ mechanism[2] in the reactions of *p*-dinitrobenzene and *p*-nitrobenzonitrile with nucleophiles in DMF. The final conclusion was that no reaction between the radical anions and the nucleophiles could be observed in any case. However, that paper describes that activation by cathodic reduction could be achieved in the reaction of *p*-dinitrobenzene with phenol but not in the corresponding reaction of p-nitrobenzonitrile. Evidently this activation was not attributed to the eliciting of a $S_{RN}2$ process, and other possibilities were considered. In the first paper of this series[3], we studied the nucleophilic aromatic substitution reactions of pentafluoronitrobenzene (PFNB) with several nucleophiles in aqueous solutions. Those reactions showed sensitivity to the presence of radical scavengers, and they were photostimulated and electrostimulated. However, the operation of an $S_{RN}1$ mechanism was discarded since the PFNB is very stable with respect to fragmentation (it even dimerizes before undergoing any cleavage)[4], methanol and phenol acted as nucleophiles through the oxygen atom, and the reactions were relatively insensitive to the presence of oxygen. In that paper[3] we attributed those contradictory facts to the operation of an $S_{RN}2$ mechanism. However, the results and conclusions reported in the preceeding paper[1] have prompted us to give a closer look at the reactions of pentafluoronitrobenzene comparing them with the ones of some others polyfluoronitrobenzenes. Here we report the preliminary results of a mechanistic study on the thermal reactions of 3,4-difluoronitrobenzene (DFNB), 2,3,4,5-tetrafluoronitrobenzene (TFNB), and pentafluoronitrobenzene (PFNB) with methanol, and on the corresponding photochemical and electrochemical stimulated reactions. Those new results have forced us to abandon the $S_{RN}2$ hypothesis for the reactions of polyfluoronitrobenzenes with nucleophiles.



Scheme 1

The reactions of DFNB and TFNB, with methanol in aqueous solution and in the presence of carbonate as a base (scheme 1) produced 3-fluoro-4-methoxynitrobenzene[5] (62% yield, room temp., 90 min.) and 4-methoxy-2,3,5-trifluoronitrobenzene[5] (81% yield, room temp., 20 min.) respectively and they were studied in the absence and in the presence of radical scavengers (variable concentrations of *m*-dinitrobenzene and of galvinoxyl). No effect was observed in any case. Comparison of those results with the reported ones for the corresponding reaction of PFNB (that leads to 4-methoxy-2,3,5,6-tetrafluoronitrobenzene[6] and where significant effects were present)[3] gave surprising results, specially in the case of TFNB (considering the original $S_{RN}2$ proposal) since its first and second reduction potentials in $MeOH/H_2O$ ($E^o/V = -0.76$, and $E_{p2}/V = -1.10$) were very similar to the ones reported for PFNB ($E^o/V = -0.66$, and $E_{p2}/V = -1.10$)[3].

Kinetic studies were carried out on the reaction of TFNB (as an example of areaction insensitive to the presence of radical scavengers) and on the reaction of PFNB (as the best candidate to react following an $S_{RN}2$ pathway). Good pseudo first order kinetics were obtained in all the cases (indicating that probably those are not chain reactions) and the results are summarized in Table 1.

Table 1.- Kinetics of the Reaction of TFNB and PFNB with Methanol in Water.

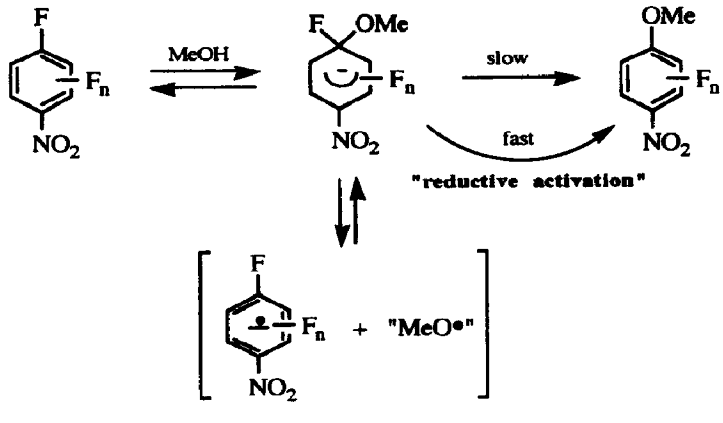
Exp.	Subst.	Conditions[a]	Temp.[b] °C	$10^5 k_{obs}$[c] s^{-1}	$\Delta H^{\ddagger}$[d] kJ mol^{-1}	$-\Delta S^{\ddagger}$[d] J mol^{-1} K^{-1}
1	TFNB	No base added	35	e		
2		Phosphate buffer[f]	35	4.2±0.1		
3		$NaHCO_3$ [0.059M]	30	3.21±0.11	77.9	98.9[g]
4			40	7.98±0.38		
5			45	15.96±0.57		
6			50	23.94±1.1		
7			55	34.4±1.9		
8	PFNB	No base added	35	e		
9		Phosphate buffer[f]	35	10.5±0.6		
10		$NaHCO_3$ [0.059M]	30	9.59±0.13	80.6	79.6[g]
11			35	21.3±5.7		
12			40	28.3±1.5		
13			45	50.73±2.8		
14			55	127.8±3.0		

a) Reactions were carried out under pseudofirst order conditions using a mixture of MeOH/Water (3:1 v/v, [MeOH] = 18.95 M) as solvent. [TFNB] = [PFNB] = 0.01M. b) Indicated temperatures ± 0.02°C. c) Disappearance of starting material was monitorized in the UV spectrum (λ_{max} (PFNB) = 246 nm; λ_{max} (TFNB) = 254 nm). Standard errors indicated. cc > 0.999 in all the cases. d) Calculated from the Eyring equation. e) No measurable rate. f) The pH 7 buffer solution was prepared by adding 29.1 ml of NaOH 0.1M to 50 ml of a 0.1 molar solution of KH_2PO_4. g) Value calculated taking [MeOH] = 18.95M, and considering that the reactions are first order in methanol.

Exp. 1 and 2, in the case of TFNB and 8 and 9 in the case of PFNB show that those reactions are typical examples of base catalyzed nucleophilic aromatic substitutions. Thus, no reaction is observed in the absence of base (exp. 1 and 8), but using a phosphate buffer (pH 7 in both cases), the reactions go to products with measurable rates (exp. 2 and 9). This result (that could correspond to a true general base catalysis or to a specific base catalysis followed by general catalysis by the conjugated acid), suggests[7] a nucleophilic aromatic substitution mechanistic scheme with a limiting second stage. This is a typical scheme when activated fluoroaromatics react with neutral nucleophiles[8], and in our case this situation seems to be even more evident since the σ-complex is expected to be rather stable. The activation parameters (Table 1) have the expected values[9] for second stage rate determining S_NAr reactions carried out in aqueous solutions.

The high similarity between the kinetic behavior of the PFNB and TFNB reactions with methanol summarized in table 1 forces us to postulate a common mechanism for both reactions. However, the reaction of PFNB shows[3] a significant sensitivity to the presence of radical scavengers while the corresponding reaction with TFNB does not. The obvious interpretation is that radicals are present in the reaction of PFNB but they are not in the direct pathway between reagents and products. This leads us to a Wasgestian[10] type mechanistic scheme (scheme 2) where the substrate radical anion is produced by an inner sphere electron transfer process, through σ-complex homolitic cleavage (perhaps with the help of a second nucleophile molecule). Since the second step seems to be rate determining in our nucleophilic aromatic substitution reactions, the σ-complex will be in equilibrium with the starting materials and also with the radical anion. Depending on this second equilibrium position, the presence of the corresponding radical anion will be apparent[11], and the reaction will show sensitivity to the radical scavengers (case of PFNB[3], and others reported in the literature[1, 2b, 12]), or not (case of TFNB).

Another interesting difference between the reactivity of PFNB and TFNB is their response to photochemical activation. We had previously published[3] that the reactions of PFNB with methanol in aqueous solution, and in the presence of sodium bicarbonate as a base, could be stimulated by UV light. A similar result was impossible to achieve with TFNB or DFNB. Now we have stablished the nature of the UV light activation in the PFNB case as pseudostimulation. Good pseudozero order kinetics were obtained at several temperatures (no change of the rate constant with the temperature) in the reactions of PFNB with methanol in the presence of $NaHCO_3$ and under UV irradiation, indicating that no stimulation of a ground state chain reaction was happening. On the contrary, under UV light the reaction becomes a typical photochemical reaction, its rate only depending on the number of absorbed photons. This result indirectly supports the mechanism hypothesis postulated in scheme 2 for the ground state reaction.



Scheme 2

In spite of the fact those reactions (PFNB and TFNB) show all the features of second stage rate determining "polar" S_NAr reactions, and that radicals do not seem to be involved in the direct pathway from reagents to products, they can be reductively activated. In a previous work[3], this activation had been studied for the reaction of PFNB with methanol and phenol in the presence of sodium bicarbonate. Here we have studied the reactions of PFNB anbd TFNB with methanol in the absence of any added base. In these conditions the unstimulated reactions have a negligible rate (see exp. 1 and 8, table 1). However, under cathodic stimulation (glassy carbon electrode), a 25% yield of 4-methoxy-2,3,5,6-tetrafluoronitrobenzene[6] and 40% yield of 2,4-dimethoxy-3,5,6-trifluoronitrobenzene[6] were obtained in the PFNB case (-0.75V, 65% total substitution yield, 10 min., 1.22 faradays, room temperature), and a 26% of 4-methoxy-2,3,5-trifluoronitrobenzene[5] in the TFNB case (-0.8V, 10 min., 1.18 faradays, room temperature). In this last case, only traces of the disubstitution product were present in the reaction crude. The corresponding reaction of DFNB was unsuccessful, nitro group reduction being the only detected process.

The reported facts indicate that a modest sensitivity of a reaction to the presence of radical scavengers or to light irradiation not necessarily means the operation of a chain radical process. On the other hand, a S_NAr mechanism with the second step as a rate determining step seems to be a necessary condition for the reductive activation to be feasible. The $S_{RN}2$ mechanistic scheme is not at all appropriate to justify those facts, probably being the reductively stimulated reactions described here new examples of the process introduced in the preceeding article (*p*-dinitrobenzene reductively activated reaction). A scheme that would agree with the reported facts is shown in scheme 2. We are currently trying to establish the exact nature of the observed activation and a complete account will be published in the near future.

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