Does the Nucleophilic Substitution of Halogen in *o*- and *p*-Halonitrobenzenes with Cyanoacetate Carbanions Proceed via Single Electron Transfer and a Nonchain Radical Process?

Mieczysław Mąkosza,* Renata Podraza, and Andrzej Kwast

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warsaw, Poland

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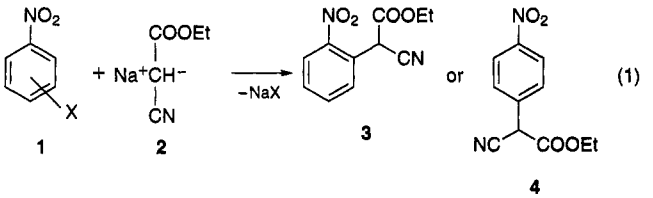
The mechanistic pathway proposed by Zhang et al. (Zhang, X.-M.; Yang, D.-L.; Liu, Y.-C. *J. Org. Chem.* **1993**, *58*, 224) for nucleophilic substitution of halogen in *o*- and *p*-halonitrobenzenes, SET and nonchain radical process, was shown to be based on erronous experimental results. There is no inhibition of this reaction by dinitrobenzenes, and order of reactivity of *p*-halonitrobenzenes is in full accord with the addition–elimination mechanism. On this basis and subsequent discussion the proposed mechanism (Zhang, X.-M.; Yang, D.-L.; Liu, Y.-C. *J. Org. Chem.* **1993**, *58*, 224) cannot be accepted.

Nucleophilic aromatic substitution is a rich field of organic chemistry of particular interest because of its great practical importance and the many mechanistic pathways by which it can proceed.[1] Although the stoichiometry of these reactions implies more or less complicated ionic processes,[2] for some of them, multistep pathways involving single electron transfer (SET) and chain or nonchain free radical reactions were postulated and convincingly evidenced.[3] The great intellectual attractivness of SET as the crucial step in nucleophilic reactions resulted in attempts to apply this concept to some other processes with reasonable justification. Unfortunately, this elegant and fruitful concept is sometimes expanded over justified limits. An example of such overextension has been recently published in this journal by Zhang et al.[4]

The authors of the cited paper promote an idea that nucleophilic substitution of the halogen in *o*- and *p*-halonitrobenzenes **1** with ethyl cyanoacetate carbanion **2** (eq 1) proceeds not as a reasonably well-documented,



1 2 3 4 (1)

X = F, Cl, Br, I

typical addition–elimination process via formation of the short-lived anionic σ-adduct intermediates (often referred to as Meisenheimer complexes[2]) but via a single electron transfer from the carbanion to the halonitrobenzene, dissociation of the resulting radical anion to the nitroarene radical, and finally radical–radical coupling (eq 2). The discussion and experimental results supporting

$$\mathrm{ArX} + \mathrm{N\bar{u}} \xrightarrow{\mathrm{SET}} \overline{\mathrm{Ar\dot{X}\ \dot{N}u}} \rightarrow \overline{\mathrm{Ar\dot{X}\ \dot{N}u}} \rightarrow \mathrm{ArNu} + \bar{\mathrm{X}} \quad (2)$$

this hypothesis seem to us to be questionable, inconsistent, and partially erroneous.

The mechanistic supposition presented in the cited paper was based on the earlier ESR study of the same authors,[5] in which they reported that the corresponding radical anions were detected and the kinetics of their formation and decay was found to be in agreement with a nonchain radical process. In the paper under consideration the authors attempted to provide evidence for the postulated mechanism via examination of the effects of strong electron acceptors such as *o*-, *m*-, and *p*-dinitrobenzenes, and also some radical scavengers on the reaction of **1** with **2**, carried out in DMSO at 90 °C. According to the data reported in that paper, small amounts of dinitrobenzenes added (20–30% based on **1** and 2.5-3% based on the carbanion taken in a 7-fold excess) dramatically decreased the yields of the substitution products, whereas effects of radical scavengers, such as galvinoxyl or phenyl *tert*-butyl nitrone, were very small or none. In the authors' opinion the results fully support the proposed reaction scheme (eq 2) in that radical anions are involved in the process as intermediates (destroyed by the strong electron acceptors which therefore can inhibit the reaction), and the process is nonchain. The radicals are formed and react within the solvent cage so they are not capable of being captured by radical scavengers.

Apart from the question of why dinitrobenzenes can intervene in the process occurring within the solvent cage whereas radical scavengers cannot, such an effective inhibition of the reaction by a relatively small amount of the added electron acceptor could be expected only when a chain process takes place and electron transfer

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Table 1

entry	X in 1	additives[a]	time (h)	product	yield[b] (%) this work	yield[b] (%) lit.[c]
1	4-F		0.5	3	97–100	98.7
2	4-F	*p*-DNB (0.26)	0.5	3	110–112	0
3	4-F	*m*-DNB (0.29)	0.5	3	89–99	10.9
4	4-F	*o*-DNB (0.28)	0.5	3	91–93	7.5
				4	95–98[d]	
5	4-Cl		4	3	82–87	76.4
6	4-Cl	*p*-DNB (0.36)	4	3	115–120	3.7
7	2-F		0.5	4	98–100	
8	2-Cl		4	4	97–98	90.9
9	2-Cl	*o*-DNB (0.31)	4	4	111–117	14.1
10	2-NO_2		0.5	4	96–99	
11	4-NO_2		0.5	3	87–93	

[a] Molar ratio in relation to on **1** in parentheses. DNB = dinitrobenzene. [b] From HPLC calculated on **1**. [c] From Zhang et al.[4] [d] Calculated on *o*-DNB added.

(ET) from the intermediate radical anion to the halonitroarene is a propagation step. Otherwise, the addition of the "inhibitor" may result only in a partial consumption of the carbanion (rather negligible because of its large excess) as a consequence of the ET from it to the dinitrobenzene, being a stronger electron acceptor than **1**, and should not affect the substitution. Following the authors' reasoning one should expect that the electron transfer from **2**, used in a great excess relative to dinitrobenzenes which are stronger electron acceptors than halonitrobenzenes, should be a fast reaction. Thus, dinitrobenzenes should react primarily with **2** but not with the halonitrobenzene anion radicals.

Moreover, two of the dinitrobenzenes chosen as strong electron acceptors are well known as efficient nitroarylating agents in S_NAr-type reactions.[2] In fact, the mobility of the nitro group in such reactions is comparable to that of fluorine, so the mostly expected effect of *o*- and *p*-dinitrobenzenes added to the reaction system containing an excess of the carbanion should be substitution of the nitro group in the dinitrobenzenes with a rate equal to or higher than that of the halogen in the substrate **1**.

The above considerations suggested that the previous work contains errors and prompted us to reexamine some experiments described in the cited paper. Our results along with those taken from the paper[4] are given in Table 1. The reactions were carried out and the resulting mixtures were analyzed following exactly the procedures published therein.

As we had expected, no inhibition was observed in the reaction of *p*-fluoronitrobenzene with cyanoacetate carbanion in the presence of *p*-dinitrobenzene. On the contrary, the latter entered the substitution reaction with the nucleophile so that the total yield based on the fluoroarene amounted 110–112% which is striking when compared to 0% reported in the cited paper. This experiment was repeated several times, giving invariably the same result. The fast and efficient substitution of the nitro group rather than inhibition of the process was also observed in the cases of the other tested reactions. Entries 10 and 11 in Table 1 definitely prove the reactivity of the *o*- and *p*-dinitrobenzenes and, hence, their uselessness as inhibitors in the aromatic nucleophilic substitution reactions.[6] On the other hand, *m*-dinitrobenzene exerted no effect on the reaction of **2** with *p*-fluoronitrobenzene (entry 3).

Valuable information about the mechanism of the substitution reactions can be drawn from the order of the relative rates of substitution of different halogens. Rough

Table 2

X in 4-$XC_6H_4NO_2$	I	Br	Cl	F	F[a]	F[b]
rel rate referred to 2-$ClC_6H_4NO_2$	0.43	0.88	0.56	14.2	13.8	12.6
rel rate referred to 4-$IC_6H_4NO_2$	1.0	2.0	1.3	33.0	32.1	29.3

[a] Na^+ complexed with Kryptofix [221]. [b] Ph_4P^+ salt of ethyl cyanoacetate was used.

examination of the yields of the reaction of **2** with 4-fluoro-, -chloro-, -bromo-, and -iodonitrobenzenes led the authors of the cited paper to formulate the following order of the rate of substitution: F ≫ I > Br > Cl, which—with the exception for fluorine—was "in sharp contrast" to that typical for the S_NAr mechanism. On the other hand, for the reactions involving dissociation of the radical anions of the haloarenes to form the aryl radicals (e.g., $S_{RN}1$ scheme), the place of fluorine in the reactivity order is just opposite to that observed in the reaction examined.[3a] In attempts to hold up the proposed mechanism the authors explained this discrepancy by proposing that the interaction of the hard cation (Na^+) with the hard fluoride anion in the transition state of the dissociation step is the phenomenon which would accelerate dramatically the substitution of fluorine compared to that of the other halogens.

In our opinion this explanation is defective for at least two reasons: (i) such an effect should also operate in S_{RN} 1-type substitution of fluorine in non-electron-deficient aryl fluorides which, according to our knowledge, is not observed, and (ii) in DMSO solution Na^+ cations are strongly solvated so their interaction with the anions formed are rather low. Nevertheless, we have tried to obtain a somewhat more accurate picture of the relative reactivities of halonitrobenzenes and of the influence of the counterion, especially on the rate of the substitution of fluorine. In order to minimize the interaction between the counterion and the leaving halide, two modifications were done: (i) the sodium cations were complexed with an appropriate cryptand and (ii) the sodium cation of **2** was replaced with much softer tetraphenylphosphonium cation. The relative rates of the halogen substitution in 4-halonitrobenzenes with **2** were derived from a series of competitive reactions in which 2-chloronitrobenzne was used as the reference reagent. The experiments were repeated a few times with different molar ratios of 4-halo- and 2-chloronitrobenzene, and the reaction mixtures were analyzed (GLC) when the conversion of the reagents was ca. 5–10%.

The data collected in Table 2 show unambiguously that (i) the relative rates of substitution of different halogens are in an order which is in full accord with that expected for the ionic S_NAr mechanism (F ≫ Br ≥ Cl ≥ I) and (ii) the minimization of the counterion interaction does not affect the rate of the substitution of fluorine, which is certainly much faster than that of the other halogens. The earlier mentioned ESR and other spectral studies which did not indicate any radical anions derived from 4-fluoronitrobenzene (known to be the most stable anion radical in the 4-halonitrobenzene family) in its reaction with **2**, therefore cannot be explained by the unusual instability of the radical anion, caused by such interactions—as it was suggested in the cited paper. One

(6) Fragmentation of the dinitrobenzene anion radicals into nitrobenzene radicals is to our knowledge not known, so the formation of the substitution products in this reaction is unlikely to follow the radical mechanism according to eq 2.

can simply presume that the fast nucleophilic substitution reaction of fluorine prevents the ET process from producing sufficient, detectable concentrations of anion radicals.

Another area of doubt is connected with the cage character of the key steps of the postulated mechanism. The process has been shown to be completely insensitive to both radical and anion radical scavengers so it is clear that if any paramagnetic intermediates are involved, they cannot be of "free" character. On the other hand, a cage pair of reactive species, formed close to each other and surrounded by solvent molecules, exists only until a diffusion process separates them to the distance where they behave as kinetically free intermediates.[7,8] In the opinion widely represented in the literature the cage process can be expected only in cases of very fast reactions.[8,9] For instance, even the relatively fast coupling of alkyl radicals and ketyls ($k \simeq 10^8$ M^{-1} s^{-1})[9a] or some molecular radical rearrangements (5-hexenyl radical derivatives cyclization, $k \simeq 10^5-10^6$ s^{-1})[9b,c] are believed to be too slow to compete with the escape of the radicals from the cage. The rate of the fast anion radical fragmentation is also an important factor determining the possibility of the subsequent radical geminate coupling.[9d] The slowest reaction known to us, considered as a cage process, is substitution of iodine in 2-iodonitrobenzene with enolate which proceeded partially via a nonchain electron transfer process, as postulated by Gali.[10] The intermediate 4-iodonitrobenzene anion radical is known[11] to decompose at a rate of 8×10^4 s^{-1}, a value which seems to be too small to make this mechanistic supposition fully convincing. In fact, the possibility of the involvement of relatively stable anion radicals in nonchain (in cage) reactions has not been fully clarified yet. Nevertheless, the anion radicals of halonitrobenzenes investigated by Zhang et al. are much more stable since their fragmentation rates are lower by 5–6 orders of magnitude.[11] This implies that the solvent cage containing a quite stable anion radical/Na^+ pair and stabilized radical should exist for many seconds and even in minutes in DMF at 90 °C, which is extremely difficult to accept.

It is surprising that the authors have disregarded the well-documented addition–elimination mechanism for nucleophilic substitution of halogen in *o*- and *p*-halonitrobenzenes and formation of the anionic σ-adducts (the Meisenheimer-type complexes) as the intermediates in these reactions.[2] It should be also mentioned that the formation of the anionic σ-adducts of carbanions and *p*-halonitrobenzenes is well known to proceed faster in the *ortho* position as the first step of the vicarious or oxidative nucleophilic substitution of hydrogen.[13] Perhaps reversible formation of the σ^H adducts of the cyanoacetate carbanions to *p*-halonitrobenzenes preceeds the halogen substitution.[14] Both types of σ-adducts can be formed also *via* SET and subsequent radical-anion radical coupling. Therefore, the authors' observations of ESR spectra can be rationalized.[2b,12]

Our reasoning and experimental results presented here are inconsistent with the mechanistic hypothesis of a nonchain radical nucleophilic substitution for the reaction of cyanoacetate carbanion with halonitrobenzenes formulated by Zhang et al.[4] Most of the crucial experimental results reported in that paper are in disagreement with our findings. The same authors have recently published results of kinetic studies of the reaction between **2** and 4-chloronitrobenzene.[15] Since the calculations of the rate constants and activation parameters of the particular reaction steps were based on the assumed mechanism (eq 2) the results do not provide additional support for this scheme and therefore may be suspect. Thus, although we cannot exclude participation of some single electron transfer processes in the first step of the reaction (σ-adducts formation) or in reversible side reactions, the picture proposed by Zhang et al. cannot be accepted.

Experimental Section

HPLC analysis were made using a Shimadzu C-R4A apparatus with a UV–vis SPD-6A detector on a reversed-phase RP-18 column and a water–methanol (v:v, 40:60) mixture as the eluent. GLC analysis were performed using 3% SE-30 on Chromosorb W column.

Materials. Ethyl cyanoacetate and dimethyl sulfoxide (DMSO) were purified as described by Zhang et al.[4]

A solution of the sodium salt of ethyl cyanoacetate was prepared from ethyl cyanoacetate and sodium hydride (ca. 50% suspension in oil, washed with hexane) in DMSO in concentration of 0.35 M as described in Zhang et al.[4]

The complexed sodium salt of **2** was prepared by stirring the sodium salt of ethyl cyanoacetate solution with 1.1 equiv of Kryptofix 221 for 30 min.

A solution of the tetraphenylphosphonium salt of ethyl cyanoacetate was prepared as follows: Sodium hydride (1.3 mmol) (washed with hexane to remove oil) was suspended in dry benzene (5 mL), and ethyl cyanoacetate (1.5 mmol, 169 mg) was added. The mixture was stirred for 30 min, and the solvent was evaporated. The residue was then stirred with a solution of tetraphenylphosphonium bromide (1.3 mmol, 568 mg) in chloroform (5 mL) for 5 h. The mixture was filtered, the solution was evaporated thoroughly under reduced pressure, and the residue was dissolved in DMSO (3.7 mL).

Ethyl Cyano(2-nitrophenyl)acetate (4) and Ethyl Cyano(4-nitrophenyl)acetate (3). To a suspension of oil-free sodium hydride (4.1 mmol) in DMSO (2 mL) was added a solution of ethyl cyanoacetate (4.2 mmol, 475 mg) in DMSO and the resulting mixture stirred for 10 min. 2-Chloronitrobenzene or 4-fluoronitrobenzene (2.0 mmol) in DMSO (2 mL) was added, and the mixture was stirred at 90 °C for 2 h and then cooled to room temperature, poured into acidified (HCl_{aq}) water, and extracted with hexane/ethyl acetate 1:1. The combined extracts were washed with water and dried over

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$MgSO_4$, and the solvent was evaporated. The crude products were purified by column chromatography (SiO_2, hexane/AcOEt 1:1) and used as standards for further quantitative experiments.[16]

All other reagents were commercial.

Reactions of 2 with Halonitrobenzenes and Additives. A solution of halonitrobenzene (0.05 mmol) and dinitrobenzene (amount specified in Table 1) in DMSO (9 mL) was thermostated at 90 ± 1 °C under nitrogen. A solution of the sodium salt of ethyl cyanoacetate (1.0 mL) was added. The reaction mixture was stirred for a definite time and quickly cooled to room temperature. A sample of the mixture was then taken, quenched with nitric acid, diluted to exact volume, and analyzed by HPLC.

Competitive Reactions of 2-Chloro- and 4-Halonitrobenzenes. 2-Chloronitrobenzene and 4-halonitrobenzene (combined amount 1.0 mmol) in a molar ratio varying from 3:1 to 1:9, respectively, were dissolved in DMSO (9 mL) and thermostated at 90 ± 1 °C under nitrogen. A 0.35 M solution of the appropriate salt of ethyl cyanoacetate (0.5 mL) was added. After ca. 2, 4, and 6 min samples (2 mL) of the reaction mixture were poured into acidified water (in order to estimate the reaction conversion an internal standard was added) and extracted with hexane/AcOEt 1:1. The extracts were washed with water, dried over $MgSO_4$, concentrated, and analyzed by GLC.

(16) ^{1}H-NMR and MS spectra in full accord with the structures of the products were obtained.