Nucleophilic Aromatic Substitution for Heteroatoms: An Oxidative Electrochemical Approach

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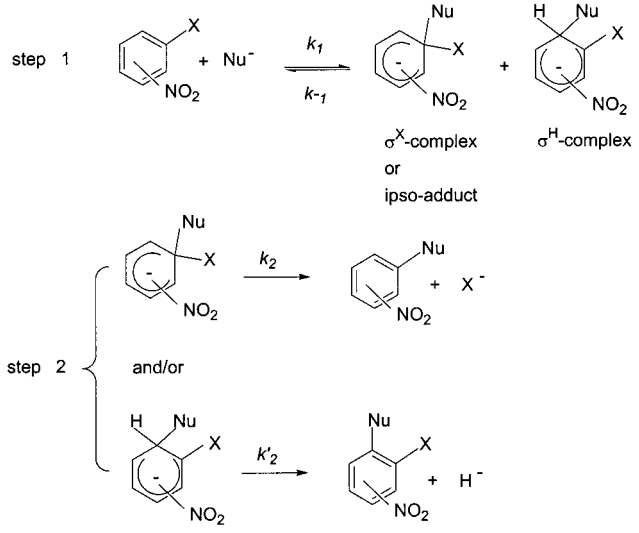
The nucleophilic aromatic substitution for heteroatom through electrochemical oxidation of the intermediate *σ*-complexes (Meisenheimer complexes) in simple nitroaromatic compounds is reported for the first time (NASX process). The studies have been carried out with hydride, cyanide, fluoride, methoxy, and ethanethiolate anions and *n*-butylamine as a nucleophile, at the cyclic voltammetry (CV) and preparative electrolysis level. The cyclic voltammetry experiments allow for detection and characterization of the *σ*-complexes and they have led us to a proposal for the mechanism of the oxidation step. Furthermore, the power of the CV technique in the analysis of the reaction mixture throughout the whole chemical and electrochemical process is described.

Introduction

There are several mechanisms for aromatic nucleophilic substitution.[1] When activating groups are present on the ring, the S_NAr mechanism is generally found. The S_NAr mechanism consists of two steps. In the first step, the intermediates, also known as *σ*-complexes, are formed. These *σ*-complexes may be σ^H-complexes and σ^X-complexes or ipso adducts. The Ar−X bond (in the *σ*-complexes) is broken in the second step. Thus, either the formation or the decomposition of the anionic intermediates, *σ*-complexes, may be rate limiting (Scheme 1).

These σ^H-complexes may be converted into products of hydrogen-atom replacement in three ways, vicarious nucleophilic substitution,[2−7] chemical oxidation,[8−10] and electrochemical oxidation.[11,12] Recent papers[11] have established the mechanism of electrochemical oxidation of σ^H-complexes. The oxidation occurs in a three-step mechanism: a initial electron transfer on the electrode, one chemical reaction, and a second electron transfer probably in solution (Scheme 2).

Scheme 1



Furthermore, the electrochemical oxidation[11] of σ^H-complexes formed by addition by CN^- to nitroarenes occurs, with good yield, giving rise to a rearomatized compound in which a loss of H^- is formally constituted. It is particularly interesting to note that in the cases where a low yield of NASH product (nucleophilic aromatic substitution for hydrogen) is observed, the product NASX (nucleophilic aromatic substitution for heteroatom) is obtained.

The conversion of σ^X-complexes into products by a X-atom replacement[1] is strongly dependent on the nature of the leaving group, the nature of the nucleophilic reagent, and the medium effects. The solvent is an important parameter determining the energetics of S_NAr substitutions. Changes in reactivity due to the transfer from protic to dipolar aprotic solvents have specially been

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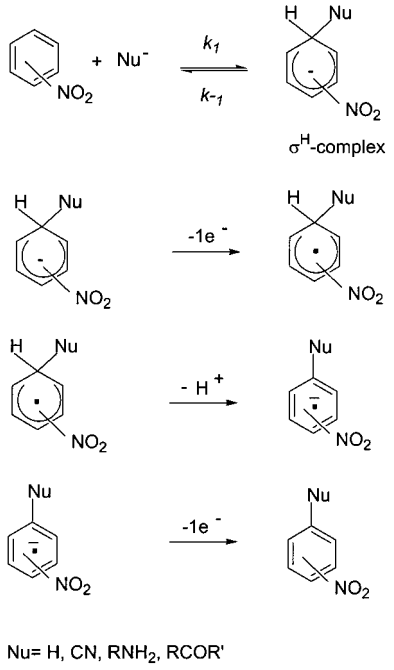
Scheme 2



studied.[1b] S_NAr reactions occurs most readily in HMPA,[13] less rapidly in Me_2SO,[14] and still less rapidly in DMF.[1b]

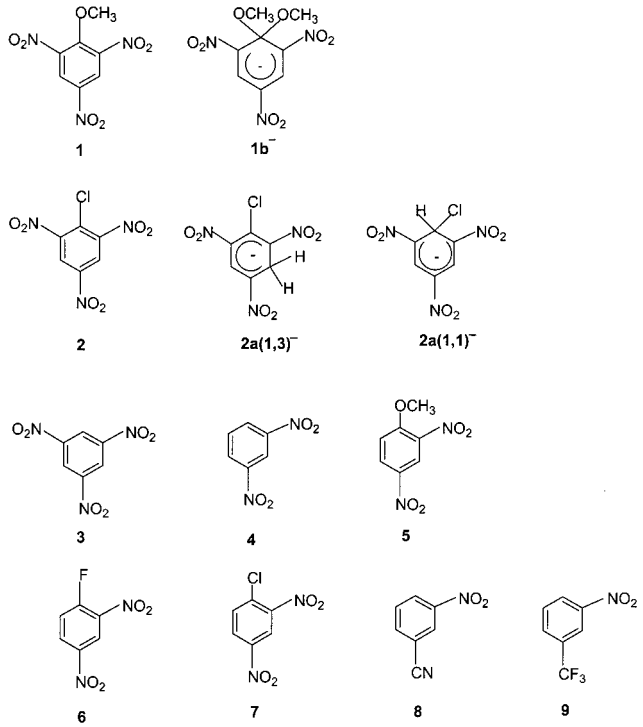
The electrochemical methods[11] are a powerful tool to study the σ^H-complexes formed "in situ" and to force the substitution reaction to occur. Here, our work will show that a similar approach can be used to study the σ^X-complexes so as to generalize the possibilities of electrochemistry in S_NAr reactions. We focus our attention on the following points: (a) determination of the efficiency of the nucleophilic aromatic substitution (determining the type of σ-complexes present in the solution—σ^H- or σ^X-*complexes*-— and their relative proportions); (b) establishment of the mechanism of the electrochemical oxidation of the σ^X-*complexes*; and (c) preparation of rearomatized (substitution) products in preparative useful yields by electrochemical oxidation of the σ^X-*complexes* in DMF at 10 °C. (d) The electrochemical methods turn out to be very general and open new possibilities for the preparation of compounds not easy to obtain by traditional chemical methods.

To establish the mechanistic details and the synthetic scope of the electrochemical method, this study has been carried out for a wide series of nitroderivatives **1**−**9** (Chart 1): 2,4,6-trinitroanisole **1**, 1-chloro-2,4,6-trinitrobenzene **2**, 1,3,5-trinitrobenzene **3**, 1,3-dinitrobenzene **4**, 2,4-dinitroanisole **5**, 1-fluoro-2,4-dinitrobenzene **6**, 1-chloro-2,4dinitrobenzene **7**, 3-nitrobenzonitrile **8**, and α,α,α-trifluoro-3-nitrotoluene **9** with five anionic nucleophiles, H^-, CN^-, F^-, CH_3O^-, and $C_2H_5S^-$, and one neutral nucleophile, *n*-$BuNH_2$, in DMF as a solvent.

Results and Discussion

Mechanism of the Electrochemical Oxidation of σ^X-Complexes or Ipso Adducts. In this section, the σ-complexes **1b**$^-$, **2a(1,1)**$^-$, and **2a(1,3)**$^-$ (Chart 1) are studied. Their synthesis, purification, characterization, and kinetics have been previously described.[15,16]

Chart 1



Electrochemical Behavior of 1b$^-$**.**[17] A typical voltammogram in DMF, at low scan rates, is shown in Figure 1 a. No reduction waves are observed in the first cathodic scan, whereas an irreversible one-electron oxidation wave appears in the oxidation scan (ca. 1.12 V). On the second cathodic scan, a reversible one-electron reduction wave (ca. −0.73V) is observed.[18] This reduction wave corresponds to the product formed in the first anodic process.

The peak intensity for the oxidation wave (analyzed by comparison with the oxidation of tris(4-bromophenyl)-amine) corresponds to a one-electron process. The shape of the voltammograms (peak width) indicates that the electron transfer is fast with kinetic control by chemical reaction.[19] The peak potential is not concentration dependent (in the range 2−20 mM), and the peak potential variation with the scan rate is 35 mV by unit log v (scan rate) at low scan rates. The voltammogram of **1b**$^-$ presents a single reversible oxidation one-electron wave, with $E° = 1.20$ V, at $v \geq 16.125$ V s^{-1} (Figure 1d). Thus, we should conclude that the initially produced radical reacts by a first-order reaction pathway in a stepwise EC mechanism.

After exhaustive (1 F) controlled-potential electrolysis (1.3 V) of a solution of **1b**$^-$, cyclic voltammetric analysis

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(17) Compound **1b**$^-$ can be isolated as a pure crystalline potassium salt[15] (see the Experimental Section).

(18) (a) $E° = -0.73$ V vs SCE. This potential is identical to the one found for the reduction of **1**.[18b] (b) Guirado, G. Unpublished results.

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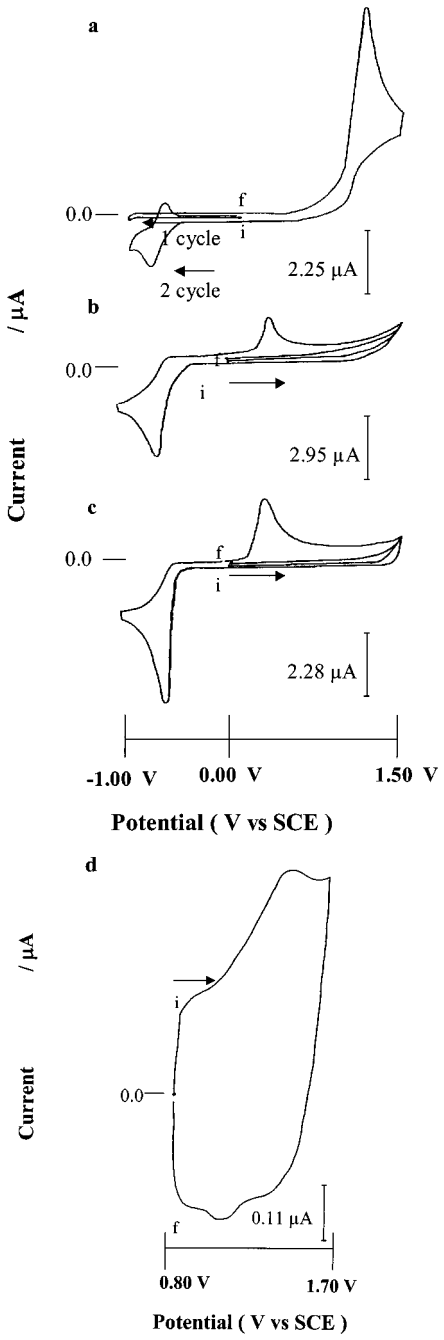

Figure 1. (a) Cyclic voltammetry of $\mathbf{1b}^-$ (10.0 mM) in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range 0.00/-1.00/1.50/0.00 V (two cycles). (b) Cyclic voltammetry, after exhaustive electrolysis (1 F) of a 6 mM solution of $\mathbf{1b}^-$ at 1.30 V in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range 0.00/1.50/−1.00/0.00 V (two cycles). (c) Cyclic voltammetry of **1** (6.0 mM) in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range 0.00/1.50/−1.00/0.00 V (two cycles). (d) Cyclic voltammetry of $\mathbf{1b}^-$ (6.0 mM) in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 16.125 V/s, platinum disk ultramicroelectrode (9.6 μm diameter). The scan is in the potential range 0.80/1.70/0.80 V.

of the mixture (Figure 1b) indicates that **1** (Figure 1c[20]) is the only final product formed, and it is produced in quantitative yield. On the first anodic scan, the oxidation wave, at 1.12 V, does not exist; only after the reduction

Scheme 3

$$\mathbf{1b}^- - 1e^- \longrightarrow \mathbf{1b}^\bullet \qquad E^\circ = 1.2\ V \qquad \text{eqn 2.1}$$

$$\mathbf{1b}^\bullet \xrightarrow{k} \mathbf{1} + {}^\bullet OCH_3 \qquad k \approx 10^5\ s^{-1} \qquad \text{eqn 2.2}$$

$$\mathbf{1b}^- - 1e^- \longrightarrow \mathbf{1} + {}^\bullet OCH_3 \qquad \text{eqn 2.3}$$

of the product formed in the first cathodic scan does a new oxidation wave appear (ca. 0.2V). The same behavior is shown by an authentic sample of **1** (Figure 1c). Furthermore, the final product **1** was identified by GC−MS, ^{1}H NMR, and ^{13}C NMR analyses (see the Experimental Section).

In summary, our experimental results show that after exhaustive oxidation (1 F) of the σ^X-complex or ipso adduct $\mathbf{1b}^-$, the rearomatized (formally substituted) compound **1** is obtained. The voltammograms show that the oxidation of σ^X-complex or ipso adduct $\mathbf{1b}^-$ occurs through a two-step mechanism (stepwise mechanism EC): a fast electron-transfer on the electrode, and a chemical reaction that is the rate-determining step (Scheme 3)

The first step involves the loss of one electron from the σ^X-complex or ipso adduct $\mathbf{1b}^-$, and then it leads to the formation of the corresponding radical $\mathbf{1b}^\bullet$. This radical undergoes a first-order C−O bond cleavage to give the final rearomatized product **1**. In cases where $CH_3O^\bullet$ must be produced, dismutation to methanol and formaldehyde is postulated.[21] We would like to remark that ***1** is obtained after the loss of just **one electron** by 1 mol of **1b**$^-$*.

Electrochemical Behavior of $\mathbf{2a}^-$ [22] ($\mathbf{2a(1,1)}^-$ and $\mathbf{2a(1,3)}^-$). A fresh sample of $\mathbf{2a}^-$ (see the Experimental Section) was used in the electrochemical studies. The voltammograms show the electrochemical behavior of $\mathbf{2a}^-$; in all cases, starting with a cathodic scan, no reduction waves appear in the first scan, so neither **2** nor **3** is initially present in the mixture of reactants. Figure 2a shows that upon starting with an anodic scan, two waves with $E_p = 0.68$ V and $E_p = 1.24$ V are observed. When this anodic scan is followed by a cathodic scan, two waves with $E_p = -0.53$ V and $E_p = -0.56$ V appear. These reduction waves[18b] correspond, respectively, to 1-chloro-2,4,6-trinitrobenzene **2** and 1,3,5-trinitrobenzene **3** formed in the oxidation scan.

When the anodic scan is reversed after the first oxidation wave ($E_p = 0.68$ V) (Figure 2b) only one reduction wave is obtained ($E_p = -0.53$ V). Thus, the oxidation wave at $E_p = 1.24$ V appears to be connected with the reduction wave at $E_p = -0.56$ V. That is to say, **2** is obtained after oxidation of $\mathbf{2a(1,3)}^-$ (the σ^H-complex) and **3** is obtained after oxidation of $\mathbf{2a(1,1)}^-$ (the σ^X-complex or ipso adduct). Scheme 4 summarizes these results.

(20) The reduction wave of **1** is reversible at high scan rate ($v > 75$ V s^{-1}) and 2−20 mM concentration, moreover at scan rate of 1 V s^{-1} and a low concentration ($c < 1$ mM).[18b] KBF_4 (0.1 M) is needed to observe the reduction wave of **1** reversible if $c < 2$ mM.

(21) (a) Melloni, G. *J. Org. Chem.* **1992**, *57*, 1444. (b) Similar reactions have been proposed in the literature.[21c] (c) Gallardo, I.; Guirado, G.; Marquet, J. *J. Electroanal. Chem.* **2000**, *488*, 64.

(22) Compound $\mathbf{2a}^-$ was obtained in a solid form from crystalline tetramethylammonium salt[16] (see the Experimental Section). The ^{1}HNMR studies indicates that $\mathbf{2a}^-$ is a mixture (70:30) of adducts: **(1,1)** σ^X-complex and **(1,3)** σ^H-complex, respectively.

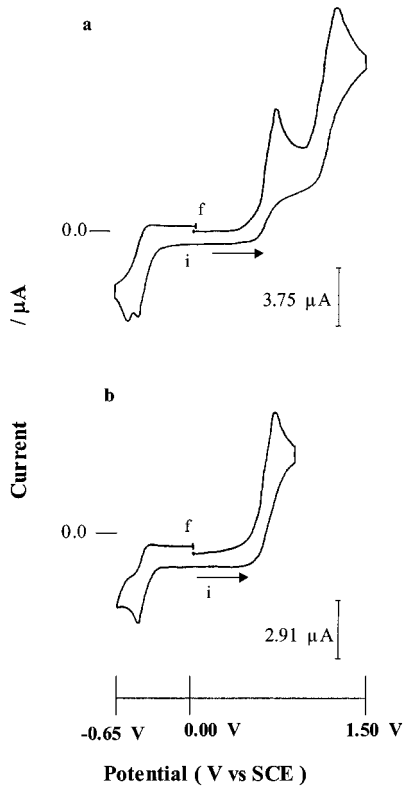

Figure 2. (a) Cyclic voltammetry of **2a**$^-$ (mixture **2a(1,1)**$^-$ and **2a(1,3)**$^-$) (6.0 mM) in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range 0.00/1.50/−1.00/0.00 V. (b) Cyclic voltammetry of **2a**$^-$ (**2a(1,3)**$^-$) (6.0 mM) in DMF + 0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/1.00/−1.00/0.00 V.

Since the electrochemical oxidation mechanism of σ^H-complexes involves two electrons (NASH process)[11] and we have just shown that the corresponding oxidation of σ^X-complex involves one-electron (NASX process), it is possible to determine by direct measure of the relative intensity of the peak potentials, their relative concentrations. From the voltammogram (Figure 2), the ratio of σ^H-complex/σ^X-complex = 30:70 is in good accordance to what is reported in the literature.[16]

In summary, the cyclic voltammmetry allows us to (a) determine the type and number of the evident extension of this work, (b) determine the σ-complexes present in the solution (number of waves, peak potential wave) and their relative amounts (intensity of peak wave), and (c) establish the clean evolution of the σ-complexes to the rearomatized nitroaromatic compounds when oxidized by observing the reduction of the rearomatized products. (d) It should be possible, in principle, to achieve the final substitution products by performing exhaustive electrolysis of solutions of σ -complexes at precise applied potentials. Therefore, the evident extension of this work is to obtain substituted products, by means of electrochemical oxidation methods, in the S_NAr reactions with different nucleophiles.

Synthetic Scope. The σ-complexes were prepared by careful stoichiometric addition of different Nu^- (CN^-, F^-, CH_3O^-, $C_2H_5S^-$, and *n*-$BuNH_2$) to solutions 25 mM of the nitroarenes, **2**−**9**, in dry DMF + 0.1 M *n*-$BuNBF_4$ under inert atmosphere at 10 °C. Their characterization was carried out by means of cyclic voltammetry (oxidation peak potential and intensity of the remaining nitroarene reduction wave) (columns 6, 10, and 4, Tables 1 and 2). In all cases, the yield of formation of σ-complexes is superior to 40% and its formation is fast.

After exhaustive controlled potential electrolysis, at oxidation peak potential (column 8, Tables 1 and 2) plus c.a. 100 mV, the rearomatized substituted compound (NASX product: ArNu, column 9, Tables 1 and 2) is obtained. Electrochemical efficiency goes from 0.50 to 2.00 (column 11, Tables 1 and 2). The values higher than 1.0 can be explained considering that the electrochemical oxidation of σ^X-complexes produces the displacement of the fast equilibrium (Scheme 4) to the right; that is to say, more reactant σ -complexes[23] are produced during the electrochemical reaction. The reaction is clean, recovering only starting material (column 2, Tables 1 and 2) apart from the substitution product. When CN^- (Table 1, entries 3, 4, 7, and 8; Table 2, entries 1, 2, 5, 6, and 7) (Scheme 5)[11a] and *n*-$BuNH_2$ (Table 1, entries 6 and 9; Table 2, entry 3) are used, a NASH product was obtained in a yield lower than 15%.

In the reaction between CH_3O^- and 1,3-dinitrobenzene (1:1) (Table 2, entry 4), 100% σ-complex is produced and only 5% of the substituted product, 3-nitroanisole, is obtained (NASX process). The formation of 1-hydride-1-methoxy-2,4-dinitrocyclohexadienyl anion (95%) leads, after one-electron oxidation, to starting material (95%).

It is important to underline that the oxidation peak potential of σ^X-complexes is very dependent on the nature of leaving group, X^-. For Cl^- or F^-, the potential is ∼1.35−1.40 V, for CH_3O^-, it is ∼ 0.90−1.00 V, and for NO_2^-, it is ∼0.60−0.80 V vs SCE. For the σ^H-complexes the oxidation peak potential is mainly dependent on the number of nitro groups present in the aromatic ring:[11] oxidation peak potential for two nitro groups complexes < oxidation peak potential for three nitro groups complexes.

The results described in Tables 1 and 2 demonstrate that the electrochemical methodology is a powerful tool for the synthesis of fluorine, thiolate, and alkoxy compounds and for the amination and the cyanation of aromatic compounds.

Halogen as Leaving Group. Synthesis of Fluoro Compounds 6 (Table 1, Entry 1). Using, for instance, chloronitro,compounds, we obtain fluoronitro compounds by replacement of a Cl for a F. By mixing 1-chloro-2,4-dinitrobenzene **7** with tetramethylammonium fluoride under nitrogen atmosphere in DMF and followed by electrochemical oxidation at 1.4 V passing 1 F, we obtain Sanger's reactant in good yield (60%). The products can be easily separated by column chromatography. Furthermore, the reactant is fully recovered (40%), and the electrochemical reaction is therefore totally selective. Electrochemical oxidation of intermediate σ-complexes allows the substitution of other halogens (chloride) by fluoride in very mild conditions and it is therefore complementary to the well-known fluorodenitration[24] as an election method to introduce fluorine in aromatic compounds. Our results open a new way for obtaining fluoro compounds, which are especially important due to their chemical and biological applications.

(23) For the NASH, the H^+ loss after the first one-electron oxidation inactivates the nucleophile and the reaction stops.

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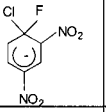
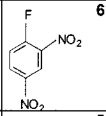
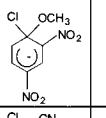
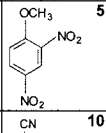
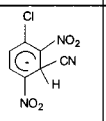
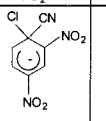
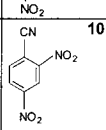
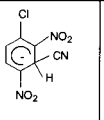
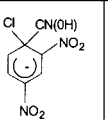
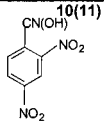
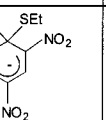
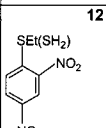
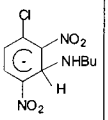
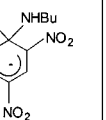
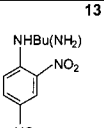
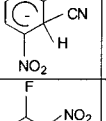
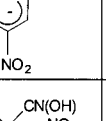
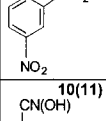
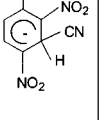
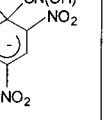
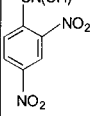
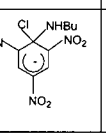
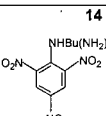
Table 1. Exhaustive Electrolysis of σ^X-Complexes (Column 7) (Halogen as Leaving Group)

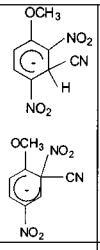
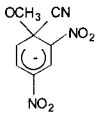
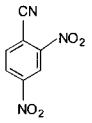
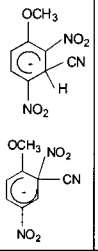
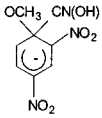
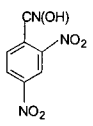
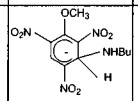
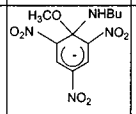
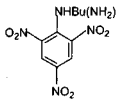
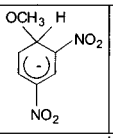
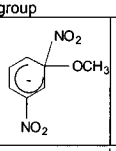
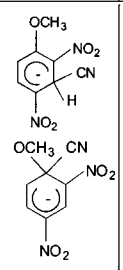
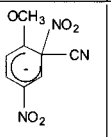
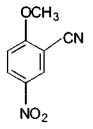
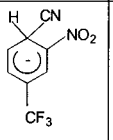
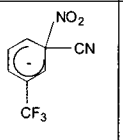
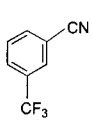
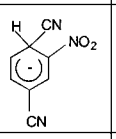
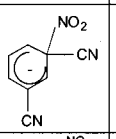
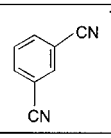
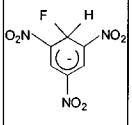
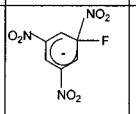
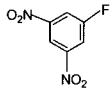
Entries	Ar-X	Nu^- Ar-X:Nu^-	[a]TOTAL σ– Complexes (%)	[b]Others σ^H– Complexes	Epa (V) of Others σ^H– Complexes	σ–^{X} Complex	Epa (V) σ–^{X} Complex	NASX Product (Ar-Nu)	[c]Yield (%) NASX	r (r= |Ar-Nu|/ |TOTAL σ-Complexes|)
X=Halogen										
1[h]	7	F^- 1:1	40	-	-		1.39	**6** 	60[d]	1.50
2	7	$^-OCH_3$ 1:1	40	-	-		1.24	**5** 	80[d]	2.00
3	7	CN^- 1:1	58		0.59[e]		1.38	**10** 	25[f]	0.63
4	7	CN^- + H_2O 1:1:1	58		0.59[e]		1.38(1.24)	**10(11)** 	10(20)[f]	0.25(0.50)
5	7	^-SEt 1:1	58	-	-		1.38	**12** 	73[d](10)	1.26(0.17)
6[h]	7	$BuNH_2$ 1:2	43		1.12[g]		1.35	**13** 	80[d](5)	1.86(0.12)
7	6	CN^- 1:1	47		0.56[e]		1.38	**10** 	34[f]	0.85
8	6	CN^- + H_2O 1:1:1	47		0.56[e]		1.34(1.28)	**10(11)** 	18(16)[f]	0.45(0.40)
9	2	$BuNH_2$ 1:2	70	-	-		1.35	**14** 	95[d](5)	1.36(0.07)

[a] The σ-complexes were carefully prepared by addition of the nucleophile to solutions of nitroarenes 25 mM in DMF/0.1 M n-Bu_4NBF_4 under inert atmosphere at 10 °C. [b] Other Meisenheimer complexes present in the mixture. [c] The oxidation products were analyzed by cyclic voltammetry,[11a,21b] gas chromatography/mass spectroscopy, and ^{1}H NMR. [d] Shift of the equilibrium to the right. [e] The electrochemical oxidation of the σ^H-adduct leads to a NASH product described in ref 11. [f] Excess of cyanide can be eliminate by electrochemical oxidation at 1.33 V. [g] The electrochemical oxidation of the σ^H-adduct leads to a NASH product (15%) that will be described in ref 11b. [h] Blank reactions (without oxidation of the mixture) led to less than 10% yields of substitution products. All the potentials are given vs SCE reference electrode.

Synthesis of Thio Compounds 12 and Alkoxy Compounds 5 (Table 1, Entries 5 and 2, Respectively). Upon oxidation of the intermediate σ-complex, the chlorine atom in chloronitro compounds can be easily replaced by an SH−R group. Thus, by mixing 1-chloro-2,4-dinitrobenzene **7** with sodium ethanethiolate under nitrogen atmosphere in DMF followed by electrochemical oxidation at 1.4 V vs SCE passing 1 F we obtain a mixture of the ethyl 2,4-dinitrophenyl thioether (73% yield) and 2,4-dinitrothiophenol (10% yield) (Table 1, entry 5). The products were easily separated by column chromatography. Furthermore, the unreacted starting material was also recovered. Following the same procedure, good results were also obtained when potassium methoxide was used instead of sodium ethanethiolate (Table 1, entry 2).

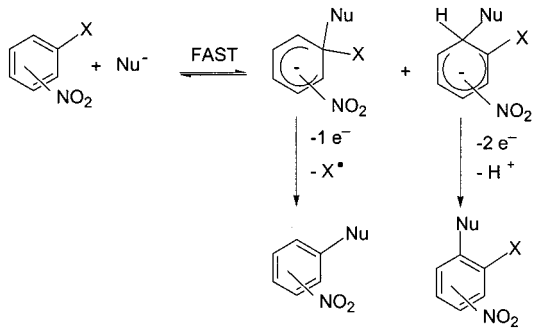
Amination (Compounds 13 and 14) and Cyanation Processes (Compound 10) (Entries 6, 9 and 3, 4, 7, 8, Respectively). Good results were obtained for both processes, especially in the case of amines where substitution percentages are between 80 and 95% (Table 1, entries 6 and 9).

Table 2. Exhaustive Electrolysis of σ^X-Complexes (Column 7) (Leaving Group Other Than Halogen)

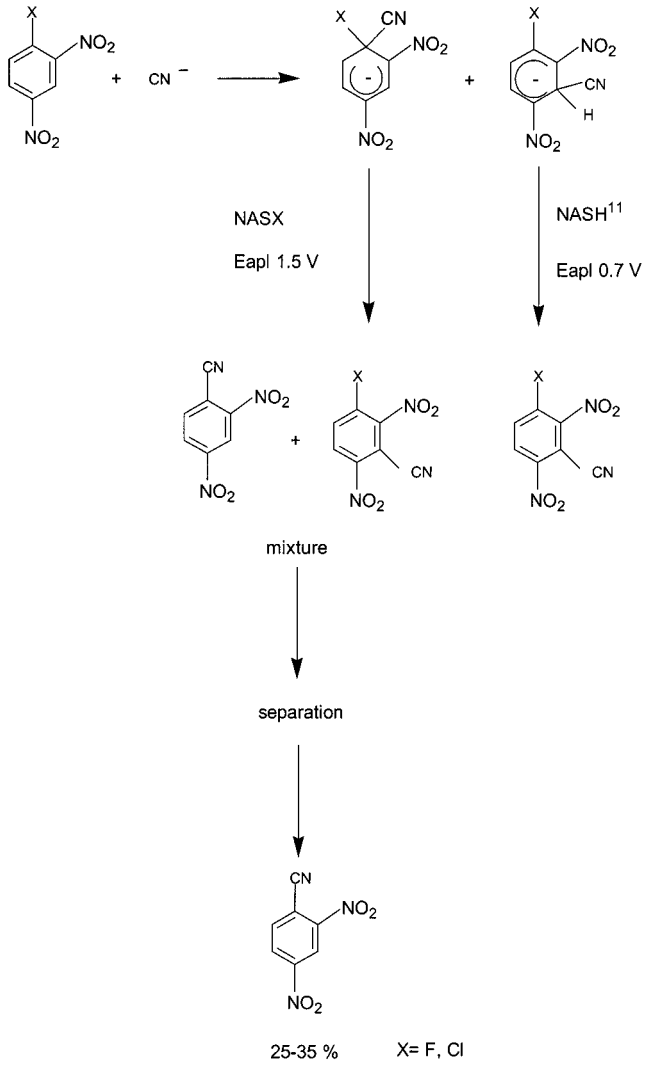
Entries	Ar-X	Nu^- Ar-X:Nu^-	[a]TOTAL σ– Complexes (%)	[b]Others σ– Complexes	Epa (V) of Others σ– Complexes	σ–^{X} Complex	Epa (V) σ–^{X} Complex	NASX Product (Ar-Nu)	[c]Yield (%) NASX	r (r= |Ar-Nu|/ |TOTAL σ-Complexes|)
X=Methoxy group										
1	**5**	CN^- 1:1	40		0.61[e](0.60)		0.83	**10** 	26[d]	0.65
2	**5**	CN^- + H_2O 1:1:1	40		0.61[e](0.60)		1.18(0.83)	**10** (**11**) 	13[d](11)	0.33(0.28)
3	**1**	$BuNH_2$ 1:4	80		1.03		1.03	**14** 	60(10)	0.75 (0.12)
X=Nitro group										
4	**4**	$^-OCH_3$ 1:1	100		0.72[f]		0.77	**15** 	5	0.05
5	**5**	CN^- 1:1	40		0.61[e,g](0.83)		0.60	**16** 	26[d]	0.52
6	**9**	CN^- 1:2	50		0.58[e]		0.86	**17** 	27	0.54
7	**8**	CN^- 1:2	70		0.65[e]		0.94	**18** 	50	0.50
8	**3**	F^- 1:2	100		1.09[f]		0.78	**19** 	10	0.10

[a] The σ-complexes were carefully prepared by addition of the nucleophile to solutions of nitroarenes 25 mM in DMF/0.1 M *n*-Bu_4NBF_4 under inert atmosphere at 10 °C. [b] Other Meisenheimer complexes present in the mixture. [c] The oxidation products were analyzed by cyclic voltammetry,[11a,21b] gas chromatography/mass spectroscopy, and ^1H NMR. [d] Shift of the equilibrium to the right. [e] The electrochemical oxidation of the σ^H-adduct leads to a NASH product described in ref 11. [f] The electrochemical oxidation of this σ-adduct leads to the reactant. [g] The same experiment was described in entry 1. All the potentials are given vs SCE reference electrode.

Scheme 4



Scheme 5



The case of cyanation, even though the yields are not very high, demonstrates the possibilities of the electrochemical technique, since it is well-known that no heteroatom substitution is produced in standard S_NAr conditions when cyanide is used as a nucleophile.[2] The results reported in Table 1 (entries 3, 4, 7, and 8) indicate that upon oxidation of the σ^X-complex, moderate yields of cyanide displacement of halogen are obtained (as far as we know this constitutes the first report of such a substitution). Notice that cyanide has a strong tendency to attack nonsubstituted positions in the aromatic rings, and we have recently reported that by applying a lower potential (corresponding to the oxidation of the σ^H-complexes) to related reaction mixtures, selective oxidative hydrogen substitution is produced.[11]

Leaving Groups Other Than Halogens (Table 2). In Table 2, the oxidative substitution of leaving groups other than halogens is described. Thus, a very poor leaving group such as methoxide can be replaced by very inactive nucleophiles (from the point of view of the S_NAr of heteroatom, as commented in a previous paragraph) such as cyanide, in moderate yields (Table 2, entries 1 and 2) and *n*-$BuNH_2$ in good yield (Table 2, entry 3). Therefore, it is not possible to substitute the CH_3O^- group for the ^-SEt group. Compounds **1** and **5** with ^-SEt as nucleophile have produced 60% formation of σ-complexes, but after total oxidation **1** and **5** have been recovered. The synthetic utility of nucleophilic displacement of a nitro group activated by ortho or para functions other than nitro are demonstrated very early in the chemical literature. [13] Few synthetically useful S_NAr reactions involving displacement of NO_2 group in *m*-dinitrobenzene have been reported.[13b] In Table 2 (entries 4−7), different examples of oxidative nitro group substitution in *m*-dinitrobenzene by different nucleophiles (CH_3O^-, CN^-) are described with preparative yields that go from modest to good. Again, cyanide proves to be a fair nucleophile in our conditions, as it even able to displace a nonactivated nitro group.

Finally, in entry 8, fluoride displacement of a nitro group in 1,3,5-trinitrobenzene is described.

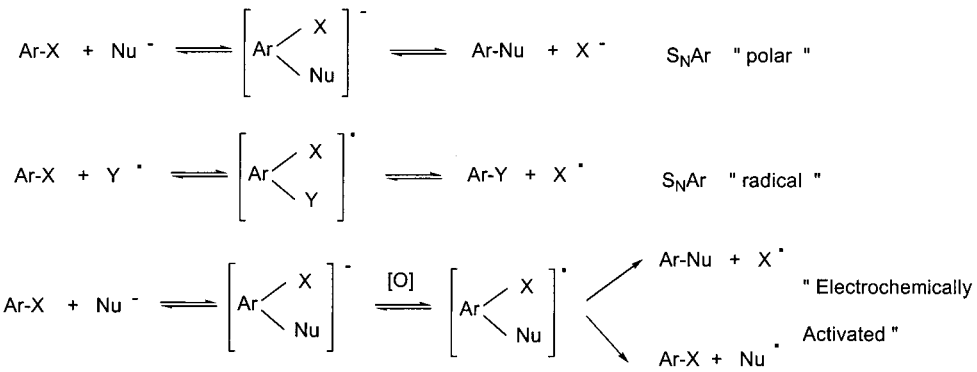
Summary

The electrochemical oxidation of ipso Meisenheimer complexes has been studied by means of cyclic voltammetry and a mechanism linking intermediates and products has been proposed (Scheme 3). Interestingly enough, electrochemical oxidation of these σ^X-complexes allow to "jump" from the "polar"[2] S_NAr mechanism (first reaction) to the "radical"[25] ipso substitution in aromatic compounds (second reaction), taking the best part of each: easy manipulation of reagents ("polar"), and activation of the intermediate towards decomposition into products ("radical"). In Scheme 6 is depicted a comparison of the three mechanisms.

The use of cyclic voltammetry as a tool in this field opens multiple applications. For example, the kind and the number of Meisenheimer complexes present in a mixture can be characterized and quantified. It is also possible to know whether the final product obtained as a result of the Meisenheimer complex oxidation will be the substitution product or the initial compound, considering that in most cases the classical nucleophilic aromatic substitution is not synthetically useful due to poor yields and slowness. Our electrochemical approach opens a new route in the field of the synthesis of aromatic derivates, since electrochemical activation makes it possible to overcome the chemical drawbacks broadening the synthetic applications of S_NAr reactions.

As we have described here, it is possible to know the electrochemical features of the Meisenheimer complexes, and their oxidation mechanisms. By applying the oxidation potential of the Meisenheimer adduct, precursor of the substituted product in a controlled potential electrolysis, the substitution product is obtained in most cases in a selective way.

Scheme 6



Experimental Section

General Considerations. DMF ("SDS pour syntheses peptidiques") and NBu_4BF_4 (Fluka puriss.) were used without further purification.

1,3,5-Trinitrobenzene (**3**) was from Supelco. 1,3-Dinitrobenzene (**4**), 1-fluoro-2,4-dinitrobenzene (**6**), 1-chloro-2,4-dinitrobenzene (**7**), 3-nitrobenzonitrile (**8**), α,α,α-trifluoro-3-nitrotoluene (**9**) were from Aldrich. 1-Methoxy-2,4-dinitrobenzene (**5**) was from Acros.

All the reactants available commercially were of the highest purity available and were used without further purification.

Synthesis of Starting Materials. 1-Methoxy-2,4,6-trinitrobenzene **1** was synthesized in our laboratory. Following the method described in the literature,[26] 20 mL of concentrated H_2SO_4 was added slowly to a mixture of 40 mL of fuming HNO_3. The mixture was cooled in an ice bath, followed immediately by addition of 20 mL of H_2SO_4. Next, 4-methoxybenzoic acid (33 mmol) was added carefully to the acidic mixture. The ice bath was removed, and the mixture was heated at 70−75 °C for 3 h. After cooling, the mixture was poured into ice−water. The solid was collected and dried. The product obtained was identified as 1-methoxy-2,4,6-trinitrobenzene **1** (6,8 g, 85%).

1,1-Dimethoxy-2,4,6-trinitrocyclohexadienyl Anion 1b⁻ Potassium Salt. The compound was synthesized following a method described in the literature:[15] A solution of CH_3OK/CH_3OH was prepared adding metallic potassium to anhydrous methanol. 1-Methoxy-2,4,6-trinitrobenzene (0.4 mmol) was dissolved in 5 mL of anhydrous dioxane, under nitrogen atmosphere. The CH_3OK/CH_3OH solution was added to the 1-methoxy-2,4,6-trinitrobenzene **1** solution under nitrogen atmosphere. The solution became red and a solid began to precipitate. The solid was collected and dried. It was identified as **1b⁻**.

1-Chloro-2,4,6-trinitobenzene **2** was synthesized in our laboratory. Following the method described in the literature,[27] 15 mL of $POCl_3$ was added to 22 mmol of picric acid. Next, 2.5 mL of pyridine was added carefully. The mixture was heated to 120−125 °C for 1 h. After the mixture was cooled to room temperature, it was poured into ice−water. The solid was collected and dried. It was identified as 1-chloro-2,4,6-trinitrobenzene **2** (3.9 g, 72%).

Synthesis of a 2a⁻ in a Solid Form. Following the method described in the literature,[16] A solution of dry powdered tetramethylamonium borohydride (2.0 mmol in 5 mL of tetrahydrofuran) was added to a solution of 1-chloro-2,4,6-trinitrobenzene **2** (2.0 mmol in 5 mL of tetrahydrofuran). The suspension was stirred and kept under nitrogen atmosphere for 2 h. The product formed was precipitated by addition of 50 mL of dry ether, collected by suction under nitrogen atmosphere, washed with dry ether, and dried by passing dry nitrogen through it. Yield: 70%. Compound **2a⁻** is a 30:70 mixture of 1,1-dihydride-3-chloro-2,4,6-trinitrocyclohexadienyl anion **2a(1,3)⁻** tetramethylamonium salt and 1-chloro-1-hydride-2,4,6-trinitrocyclohexadienyl anion **2a(1,1)⁻** tetramethylamonium salt.

All products were identified by comparison of their spectroscopic behavior with that reported in the literature for each case.

General Procedure for NASX in Nitroarenes. A solution of nitroarene (2−9) 25 mM in 5 mL of DMF, which contains 0.1646 g of NBu_4BF_4 (0.1 M) as supporting electrolyte, was prepared under nitrogen atmosphere. The corresponding σ^X-complex was prepared by careful addition of the nucleophile (tetraethylammonium cyanide, tetramethylammonium fluoride, sodium ethanethiolate, *N*-butylamines, or potassium methoxide) to a solution of the nitroarene under nitrogen atmosphere.

The oxidation peaks of σ-complexes were measured by cyclic voltammetry. An electrolysis was carried out at values of potential ca. 100 mV more positive than the value measured for each σ^X-complex. A carbon graphite electrode was used as a working electrode.

After an exhaustive controlled potential electrolysis, the electrolysis was stopped. The mixture was extracted between toluene/water. The organic layer was dried with Na_2SO_4 and evaporated affording a residue that was analyzed by gas chromatography. The final products were analyzed by gas chromatography/mass spectroscopy, ^1H NMR, and cyclic voltammetry. The analysis showed the presence of nitoaromatic compounds.

Compounds **3**−**11** and **15**−**19** were identified by comparison of their spectroscopic behavior with commercial samples. Compounds **12**−**14** were identified by comparison of their spectroscopic behavior with the reported in the literature in each case.[28−30]

Instrumentation and Procedures. All the potentials are referred vs SCE. The instrumentation and procedures were the same as previously described.[11,21b,31]

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