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Electrochemical C–H Functionalization of Arenes and Heteroarenes

Iluminada Gallardo and Gonzalo Guirado

Abstract Electrochemical methodology has been exploited to develop new synthetic routes and to rationalize the mechanism for the C–H functionalization of arenes and heteroarenes. The advantages of the electrochemical approach to perform nucleophilic aromatic substitution reactions, such as a low cost and availability of reagents, atom economy and high yields, provide an environmentally friendly way to functionalize arenes and heteroarenes.

Keywords Arenes · Cyclic voltammetry · Electrochemistry · Electrolysis · Heteroarenes · $S_N{}^H$ and $S_N{}^X$ reactions

Contents

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Abbreviations

Ac	Acetyl
Ar	Aryl
BDE	Bond dissociation energy
BMIM	1-butyl-2-methylimidazolium
Bu	Butyl
DDQ	2,3-dichloro-5,6-dicyano- 1,4-benzoquinone
DISP	Disproportionation mechanism. Homogeneous electron transfer
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
E	Electric potential
E^0	Standard potential
E_p	Peak potential
E_{pa}	Anodic peak potential
E_{pc}	Cathodic peak potential
ECE	Electrochemical–Chemical–Electrochemical mechanism. Heterogeneous electron transfer
ET	Electron transfer
Et	Ethyl
GC	Gas chromatography
Hex	Hexyl
I	Current
i-Pr	*iso*-propyl
L	Liter(s)
MS	Mass spectrometry
Me	Methyl
mol	Mole(s)
$S_N{}^H$	Nucleophilic aromatic substitution of hydrogen
$S_N{}^X$	Nucleophilic aromatic substitution of halogen X or other good leaving groups
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ph	Phenyl
R	Alkyl
rt	Room temperature
RTILs	Room temperature ionic liquids
s	Second(s)
SCE	Saturated calomel electrode
S_NAr	Aromatic nucleophilic substitution

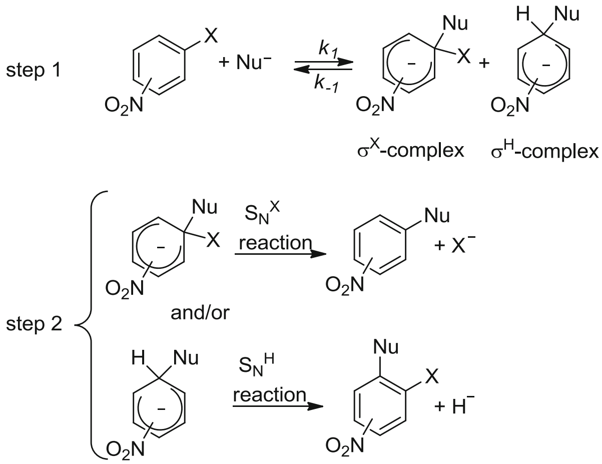
t-Bu	*tert*-butyl
$TBABF_4$	Tetrabutylammonium tetrafluoroborate
THF	Tetrahydrofuran
v	Scan rate
V	Volt

1 Introduction

There are several mechanisms for aromatic nucleophilic substitution [1–5]. It has been well established that the S_NAr mechanism is generally operating in the series of those aromatic and heteroaromatic compounds where activating groups are present in an aromatic ring. The S_NAr mechanism consists of two steps. As a result of the first step, the key intermediates, also known as σ-complexes, are formed. These σ-complexes may be of different nature, namely σ^H-complexes and σ^X-complexes. The cleavage of either C–H (in case of σ^H-complexes) or C–X bond (where X is a heteroatom in σ^X-complexes) is observed at the second step, thus giving rise to the $S_N{}^H$ or $S_N{}^X$ products, respectively. It is worth noting that either formation or decomposition of the anionic intermediates, σ-complexes, may be the rate limiting step of the reactions (Scheme 1).

Conversion of σ^X-complexes into $S_N{}^X$ products through X^- elimination is strongly dependent on the nature of the leaving group, the used nucleophilic reagent, and the effect of media, but, in general, it used to be the fast step of the reactions. The departure of the hydride anion from σ^H-complexes is a more complicated process, since it is a very poor leaving group. However, the $S_N{}^H$ reactions in which an aromatic hydrogen atom is replaced by a nucleophilic reagent are well known. Until 2001, the conversion of aromatic compounds into the $S_N{}^H$ products proved to occur by two ways: (1) through vicarious nucleophilic substitution of hydrogen, which has been extensively studied, especially in case of carbanionic nucleophiles [4–15]; (2) by means of chemical oxidation of intermediate σ^H-complexes [16–20]. Indeed, rearomatization of σ^H-complexes through formal displacement of H^- is a process which requires an appropriate chemical oxidant.

One of the relatively new approaches is electrochemical oxidation. Terrier and co-workers [21], using electrochemical methods, have established the reaction mechanism leading to the rearomatized products for 2-nitropropenide adducts of nitrobenzofuroxans and nitrobenzofurazans. In 2001, in the molecular electrochemistry laboratory of the University Autonomous of Barcelona (UAB), it was demonstrated that electrochemical methods proved to be a powerful tool to study the following aspects of the S_NAr reactions: (a) to establish the mechanism of electrochemical oxidation of σ^H- and σ^X-complexes [22, 23]; (b) to determinate the efficiency of nucleophilic aromatic substitution reactions (determining the type of adducts which were present in solutions, σ^H- and σ^X-complexes, and their relative proportions) [22, 23]; (c) to obtain S_NAr products in good preparative yields [22–28], (d) to force nucleophilic substitution of hydrogen to occur [29], and



Scheme 1 Plausible mechanisms for S_NAr reactions

(e) to perform a thermodynamic elucidation of σ^H-complexes, as intermediates of the $S_N{}^H$ reactions [30].

2 Mechanisms for Electrochemical Oxidation of σ-Complexes

The σ^H-adduct (with H^- as nucleophile, $\mathbf{1H^-}$) and the σ^X-complex (with CH_3O^- as nucleophile, $\mathbf{2CH_3O^-}$) of 2,4-dinitroaniline and 2,4,6-trinitroanisole, respectively, were chosen as model compounds to establish the mechanism of electrochemical oxidation (Scheme 2). These compounds, $\mathbf{1H^-}$ and $\mathbf{2CH_3O^-}$, can be isolated as pure crystalline compounds in the form of tetramethylammonium [14, 15] and potassium [31] salts, respectively.

The combined use of cyclic voltammetric analysis (**1**, $\mathbf{1H^-}$, **2**, and $\mathbf{2CH_3O^-}$solutions) and controlled-potential electrolysis ($\mathbf{1H^-}$, and $\mathbf{2CH_3O^-}$solutions), as electrochemical methods [32, 33], allows the mechanism for electrochemical oxidation of these σ-complexes in DMF + 0.1 M $TBABF_4$ to be established.

2.1 Electrochemical Oxidation of σ^X-Complexes

Cyclic voltammograms[1] for the compound $\mathbf{2CH_3O^-}$ at low and fast scan rates are shown in Fig. 1a, b. At low-scan rates (Fig. 1a), no reduction waves have been

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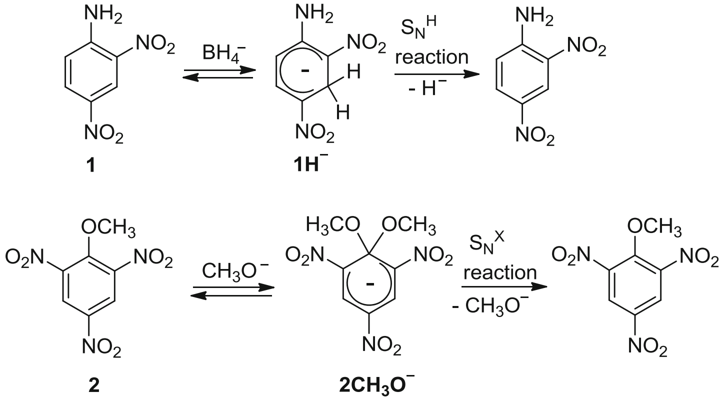
[1] The experimental cyclic voltammograms of Fig. 1 were also simulated (Digisim Software) [23].



Scheme 2 Model compounds used to elucidate S_N^H and S_N^X mechanisms

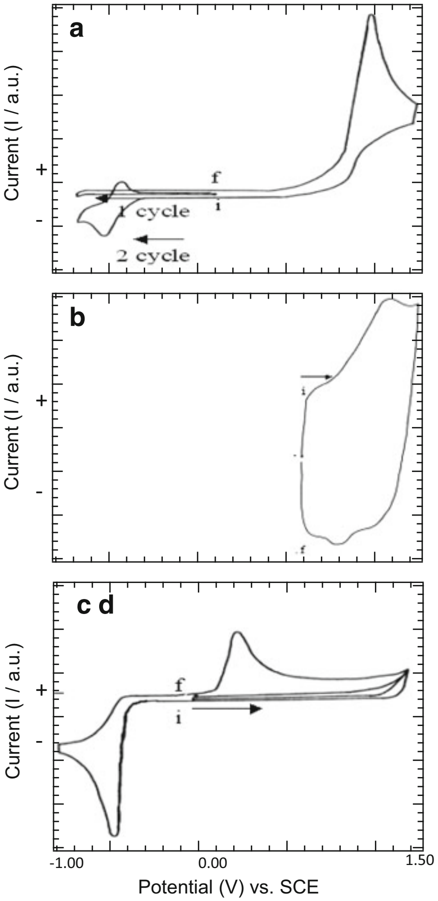


Fig. 1 Cyclic voltammetry (arbitrary I units). Two cycles. Scan potential range: 0.00 to −0.50 to 1.50–0.00 V. (**a**) $2CH_3O^-$, 1.0 V s^{-1}; (**b**) $2CH_3O^-$, 16 000 V s^{-1}; (**c**) $2CH_3O^-$, 1.0 V s^{-1}, after electrolysis (1.3 V, 1 F); (**d**) 2,4,6-trinitroanisole, 1.0 V s^{-1}

observed for the first cathodic scan, whereas an irreversible one-electron oxidation wave appears in the oxidation scan (ca. 1.12 V). In the second cathodic scan, a reduction wave (ca. −0.73 V) is observed. This reduction wave corresponds to the product formed in the first anodic process.

The peak current value 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 voltammogram (peak width) indicates that the step of electron transfer is fast and does occur under kinetically controlled chemical reaction [32]. The peak potential is not dependent on the concentration in the range 2–20 mM, and the peak potential variation with scan rates is 35 mV by unit log *v* (scan rate).

At $v \geq 16{,}000\ \mathrm{V\ s^{-1}}$ (Fig. 1b), the voltammogram of $\mathbf{2CH_3O^-}$ presents a single reversible oxidation one-electron wave ($E^0 = 1.20$ V). Thus, it could be concluded that the initially produced radical reacts according to the first order chemical reaction through a stepwise EC mechanism.

The first step involves the departure of one electron from the σ^X-complex, $\mathbf{2CH_3O^-}$, and it leads to the formation of the corresponding radical species, $\mathbf{2CH_3O^\cdot}$. This radicals undergo the first order C–O bond cleavage to give the final rearomatized product, 2,4,6-trinitroanisole. In all cases where $\mathbf{CH_3O^\cdot}$ must be produced, dismutation to methanol and formaldehide is postulated [34, 35].

After controlled-potential electrolysis (at 1.3 V and 1 F) of $\mathbf{2CH_3O^-}$ solution, cyclic voltammetric analysis of the reaction mixture (Fig. 1c) indicated that 2,4,6-trinitroanisole was the only final product formed, and it was produced in quantitative yield. In the first anodic scan, the oxidation wave, at 1.12 V, does not exist; only after cathodic reduction, the product formed has a new oxidation wave (ca. 0.2 V). The same behavior is shown by an authentic sample of 2,4,6-trinitroanisole (Fig. 1d). Furthermore, the final 2,4,6-trinitroanisole was identified by GC-MS, ^{1}H NMR, and ^{13}C NMR analyses.

In summary, these experimental results show that, after exhaustive oxidation of $\mathbf{2CH_3O^-}$, the re-aromatized 2,4,6-trinitroanisole is obtained. The voltammograms show that oxidation of σ^X-complexes $\mathbf{2CH_3O^-}$occurs through a two-step mechanism (stepwise EC mechanism): a fast electron transfer on the electrode, and a chemical reaction that is the rate determining step (Scheme 3).

It is worth to note that 2,4,6-trinitroanisole is obtained after the loss of just one electron by one mol of $\mathbf{2CH_3O^-}$ (S_NAr reaction).

2.2 *Electrochemical Oxidation of σ^H-Complexes*

Cyclic voltammograms[2] for compound $\mathbf{1H^-}$ at low and fast scan rates are shown in Fig. 2a, b. At low-scan rates (Fig. 2a) no reduction waves have been observed in the first cathodic scan, whereas an irreversible two-electron oxidation wave appears in

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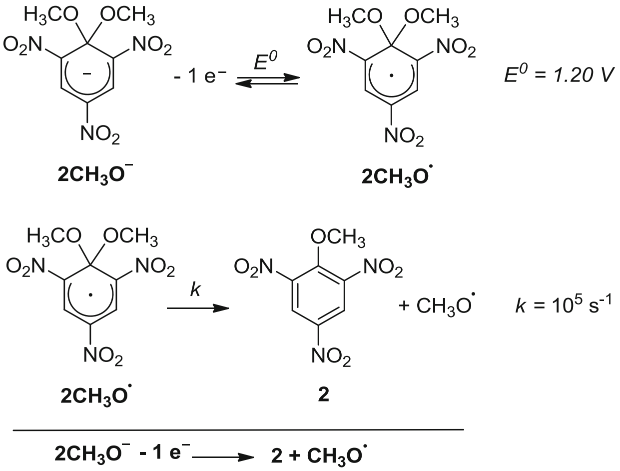
[2] The experimental cyclic voltammograms of Fig. 2 were also simulated (Digisim Software) [22].



Scheme 3 The EC mechanism for electro-oxidation of the σ^X-complex $\mathbf{2CH_3O^-}$

the oxidation scan (ca. 0.30 V). On the second cathodic scan, a reduction wave (ca. -1.03 V) is observed. This reduction wave, at -1.03 V, corresponds to the product formed in the first anodic process.

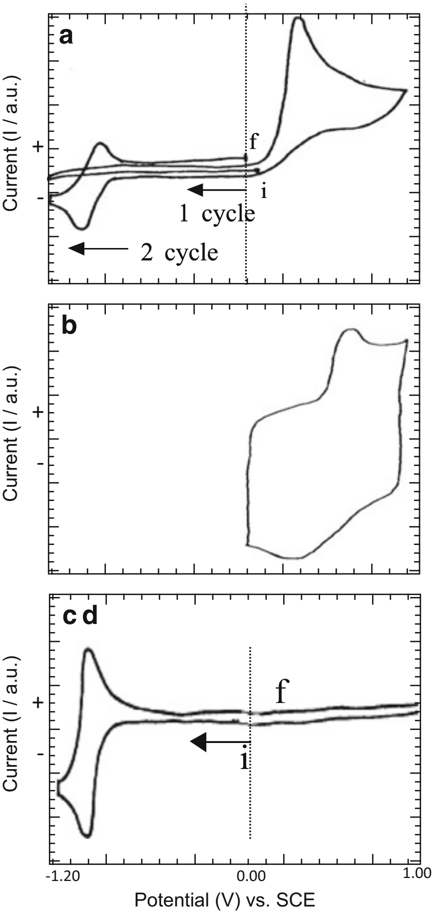
The current peak value for the oxidation wave [analyzed by comparison with the oxidation of *tris*(4-bromophenyl)amine] corresponds to a two-electron process. The shape of the voltammogram (peak width) indicates that the electron transfer is fast and takes place under kinetically controlled chemical reaction [32]. The peak potential is not concentration dependent (in the range 2–20 mM), and the peak potential variation with scan rates is 35 mV by unit log v (scan rate).

At $v \geq 380\ \mathrm{V\ s^{-1}}$ (Fig. 2b), the voltammogram of $\mathbf{1H^-}$ presents a single reversible oxidation one-electron wave ($E^0 = 0.325$ V). It is (if there are no chemical reactions) linked with electron transfer, and a one-electron wave is observed.

After controlled-potential electrolysis (at 0.50 V and 2 F) of $\mathbf{1H^-}$ solution, cyclic voltammetric analysis of the reaction mixture (Fig. 2c) indicates that 2,4-dinitroaniline is the only final product formed, and it is produced in the quantitative yield. The same behavior has been shown by an authentic sample of 2,4-dinitroaniline (Fig. 2d). Furthermore, the final 2,4-dinitroaniline was identified by GC-MS, ^{1}H NMR, and ^{13}C NMR analyses.

In summary, the experimental results show that after exhaustive oxidation of the adduct $\mathbf{1H^-}$, 2,4-dinitroaniline is obtained as a result of the formal loss of two electrons and a proton [Eq. (4) of Scheme 4]. The voltammograms show that oxidation of σ^X-complex $\mathbf{1H^-}$ takes place through a three-step mechanism: a fast electron transfer on the electrode, a chemical reaction, and the second electron transfer in solution (DISP mechanism), or on the electrode (the ECE mechanism) [32].

Fig. 2 Cyclic voltammetry (arbitrary I units). Two cycles. Scan potential range: 0.00 to −1.00 to 0.75–0.00 V. (**a**) $1H^-$, 1.0 V s^{-1} (two cycles); (**b**) $1H^-$, 380 V s^{-1}; (**c**) $1H^-$, 1.0 V s^{-1}, after electrolysis (0.5 V, 2 F); (**d**) 2,4-dinitroaniline, 1.0 V s^{-1}



Three mechanistic, kinetically equivalent, hypotheses have been formulated: Eqs. (1)/(2a)/(3a), (1)/(2b)/(3b), and (1)/(2b)/(3c). In all cases the first step [Eq. (1)] involves the loss of one electron by the σ^H-complex $\mathbf{1H}^-$, with the formation of the corresponding radical $\mathbf{1H}^\cdot$. This radical undergoes the fist-order C–H bond cleavage to give 2,4-dinitroaniline and a hydrogen atom [Eq. (2a)], as proposed by Terrier for the related systems [21], or the radical-anion of 2,4-dinitroaniline and a proton [Eq. (2b)], as earlier proposed by Sosonkin et al. [36]. The final oxidation of hydrogen [Eq. (3a)] can be performed by the radical $\mathbf{1H}^\cdot$, while oxidation of the radical-anion of 2,4-dinitroaniline [Eq. (3b, 3c)] can be performed by the $\mathbf{1H}^\cdot$ or by electrode, respectively. However, it is accepted[3] [22, 37] that compound $\mathbf{1H}^-$ is transformed according to the mechanism described

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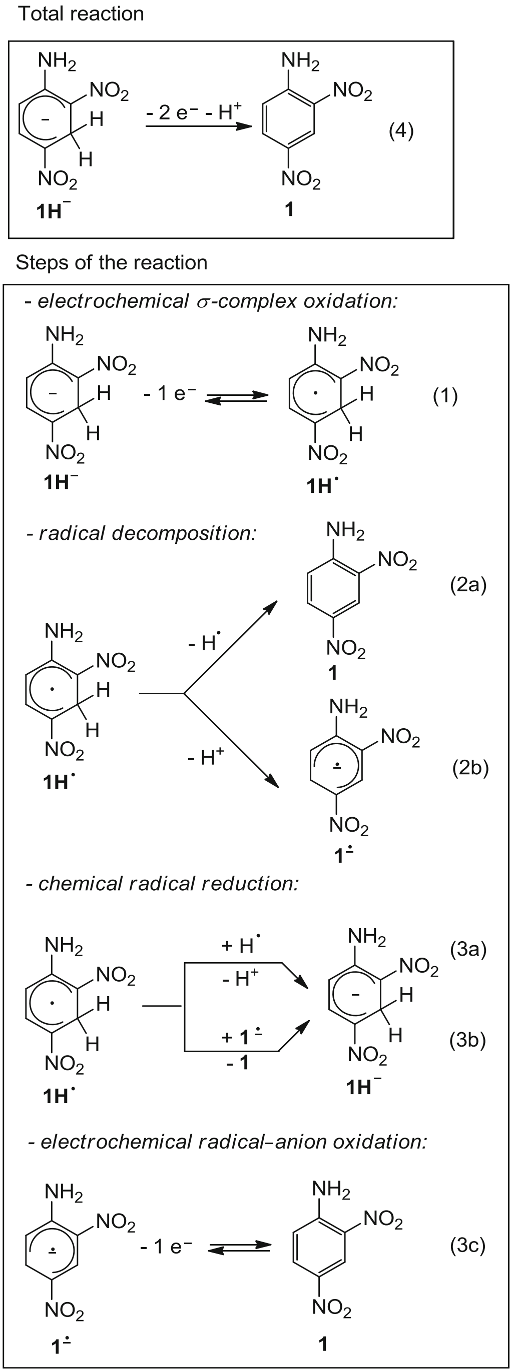
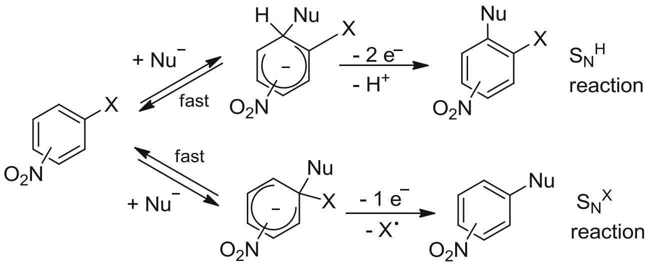
[3] The C–H acidity of cyclohexadienyl radicals of $1H^\cdot$ type, where the corresponding aromatic radical-anion is stabilized by electron attracting groups, is very significant [36].

Scheme 4 The ECE/DISP mechanism for oxidation of the σ^{H}-complex $\mathbf{1H^{-}}$





Scheme 5 Electrochemically promoted $S_N{}^H$ and $S_N{}^X$ reactions

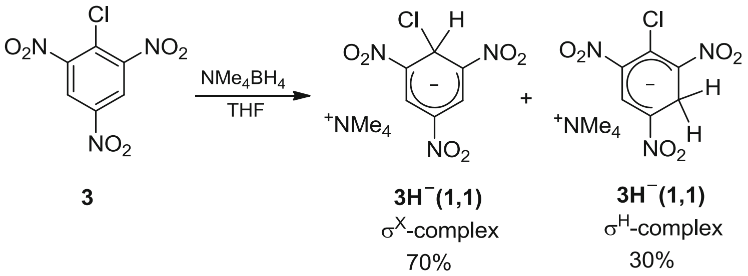
by Eqs. (1)/(2b)/(3b), or (1)/(2b)/(3c). In spite of the relatively fast cleavage of $\mathbf{1H}^{\cdot}$ (k ~ 10^3 s^{-1}), there are no experimental data providing unequivocal evidence for disproportionation mechanism (DISP)/Electrochemical-Chemical-Electrochemical mechanim (ECE) (Eqs. (1)/(2b)/(3b)/Eqs. (1)/(2b)/(3c)) for the last step of the reaction [38]. It should be noted that 2,4-dinitroaniline is formed by the loss of two electrons from the compound $\mathbf{1H}^-$ (the $S_N{}^H$ reaction).

2.3 Electrochemical Oxidation of Mixtures of σ^H- and σ^X-Complexes

Since the mechanism for electrochemical oxidation of σ^H- and σ^X-complexes involves either two electrons ($S_N{}^H$ reaction) or one electron ($S_N{}^X$ reaction), respectively (Scheme 5), it is possible to determine their relative concentrations in a mixture of σ-complexes by direct measuring the peak current values on voltammograms.

This situation is exemplified by the reaction of 1-chloro-2,4,6-trinitrobenzene with the hydride anion (Scheme 6). The compound $\mathbf{3H}^-$ [39] is formed as a 30:70 mixture of 1,1-dihydro-3-chloro-2,4,6-trinitrocyclohexadienyl $\mathbf{3H}^-$(**1**,**3**) and 1-chloro-1-hydro-2,4,6-trinitrocyclohexadienyl $\mathbf{3H}^-$(**1**,**1**) tetramethylammonium salts. A freshly prepared sample of the compound $\mathbf{3H}^-$ was used in the electrochemical studies [23].

Figure 3 shows a cyclic voltammogram for compound $\mathbf{3H}^-$ at a low-scan rate (see footnote 1). In all cases, starting with a cathodic scan, no reduction waves appear in the first scan, so neither 1-chloro-2,4,6-trinitrobenzene (the $S_N{}^H$ product), nor 1,3,5-trinitrobenzene (the $S_N{}^X$ product), are initially present in the reaction mixtures. Figure 3a shows that, upon starting with an anodic scan, two well-defined waves at 0.68 V and 1.24 V are observed. When the anodic scan is followed by a cathodic scan, two waves, at −0.53 V and −0.56 V, are observed. These reduction waves correspond to 1-chloro-2,4,6-trinitrobenzene (the $S_N{}^H$ product) and 1,3,5-trinitrobenzene (the $S_N{}^X$ product), respectively [23, 40].



Scheme 6 The formation of σ-complexes of 1-chloro-2,4,6-trinitrobenzene with the hydride anion H^{-}as nucleophile

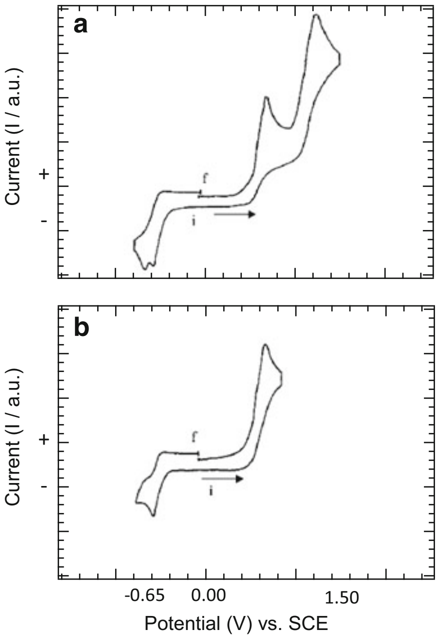
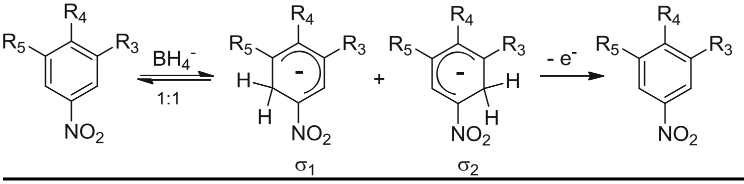


Fig. 3 Cyclic voltammetry (arbitrary I units). (**a**) $\mathbf{3H^{-}}$ [mixture $\mathbf{3H^{-}}$(**1**,**3**) and $\mathbf{3H^{-}}$(**1**,**1**)], 1.0 V s^{-1}. The scan is performed in the potential range from 0.0–1.5 to −1.0 to 0.0 V; (**b**) $\mathbf{3H^{-}}$ [mixture $\mathbf{3H^{-}}$(**1**,**3**) and $\mathbf{3H^{-}}$(**1**,**1**)], 1.0 V s^{-1}. The potential scan range is from 0.0–1.0 to −1.0 to 0.0 V

When the anodic scan is reversed after the first oxidation wave (0.68 V) (Fig. 3b) only one reduction wave is obtained (−0.53 V). Thus, the oxidation wave at 1.24 V appears to be connected with the reduction wave at −0.56 V. That, is to say, 1-chloro-2,4,6-trinitrobenzene is obtained due to the oxidation of $\mathbf{3H^{-}}$(**1**,**3**) (σ^{H}-complex, the S_N^{H} reaction), while 1,3,5-trinitrobenzene is derived from the oxidation of $\mathbf{3H^{-}}$(**1**,**1**) (σ^{X}-complex, the S_N^{X} reaction).

It follows from the voltammogram (Fig. 3a) that the ratio of [σ^{H}-complex]: [σ^{X}-complex] = 30:70, which is in good agreement with that reported in the

Table 1 Electrochemical characteristics for σ^H-complexes and reaction products with the hydride anion H^- as nucleophile



R_3	R_4	R_5	$E_{pa}(\sigma_1)^{a,b}$ (V) (%)^c	$E_{pa}(\sigma_2)^{a,b}$ (V) (%)^c	$E^{0\ a,d\ (\text{oxidation product})e}$ (V)
CN	H	H	0.19 (100%)	–	−0.90
NO_2	H	H	0.39 (100%)	–	−0.82
NO_2	CH_3	H	–	0.25 (100%)	−0.96
NO_2	OCH_3	H	–	0.30 (100%)	−1.00
NO_2	F	H	0.44(20%)	0.33(80%)	−0.79
NO_2	Cl	H	0.44(22%)	0.32(70%)	−0.78
NO_2	Br	H	0.44(30%)	0.32(70%)	−0.78
NO_2	NH_2	H	–	0.30(100%)	−0.95
NO_2	H	CN	0.60(100%)	–	−0.62
NO_2	H	NO_2	0.77(100%)	–	−0.58
NO_2	CH_3	NO_2	0.62(100%)	–	−0.68

[a] All the potentials are given vs. SCE reference electrode

[b] Peak potentials obtained by cyclic voltammetry when two isomeric adducts were formed, E_{pa} were assigned on the basis of analytical and ^1H NMR data [35, 38]

[c] Yields of σ-complexes

[d] Standard potential of oxidation product [35, 40]

[e] The S_N^H products (100% yields) were obtained by exhaustive electrolysis of the σ^H-complexes (E_{pa} +0.1 V, 2 F). The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR

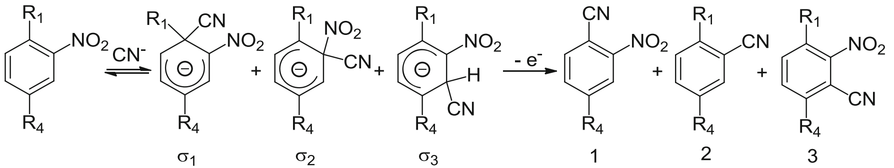
literature [39]. Then, you can determine a number of σ-complexes formed and their concentrations. Using appropriate potentials, the electrolysis of σ-complexes can give rise to either S_N^H products or both S_N^H and S_N^X products.

2.4 *Electrochemical Features of σ^H- and σ^X-Complexes*

Two series of compounds were prepared in order to distinguish the electrochemical behavior of σ^H- and σ^X-complexes. The first one, σ^H-complexes (H^- as nucleophile) of nitroaromatic compounds with a different number of nitro groups in the ring (Table 1) [22]. The second one, σ^H- and σ^X-complexes of nitroaromatic compounds with diverse leaving groups (Table 2) [23].

The σ^H-complexes (H^- as nucleophile) were prepared by stoichiometric addition of tetramethylammonium borohydride to solutions of nitroarenes in DMF + 0.1 M $TBABF_4$ under inert atmosphere. The electrochemical experiments (cyclic voltammetry and electrolysis) are analogous to those which have been described for **1H**$^-$ (Sect. 2.2). The results are summarized in Table 1.

Table 2 Electrochemical characteristics for σ-complexes and reaction products with the cyanide ion as nucleophile



R_1	R_4	Nu/Ar[a]	σ (%)	$E_{pa}(\sigma_1)$[b] (V)	$E_{pa}(\sigma_2)$[b] (V)	$E_{pa}(\sigma_3)$[b] (V)	1[c–e] (%)[f]	2[c–e] (%)[f]	3[c–e] (%)[f]
H	CN	2	70	0.65	0.94	–	45	50	–
H	CF_3	2	50	0.58	0.86	–	35	27	–
OCH_3	NO_2	1	40	0.83	0.60	0.61	26	26	15
Cl	NO_2	1	58	1.38[g]	–	0.59	25	–	7

[a] Molar ratio of nucleophile (Nu) and nitroarene (Ar)
[b] All potentials are given vs. SCE reference electrode
[c] The $S_N{}^H$ and $S_N{}^X$ products were obtained by exhaustive electrolysis at E_{pa} + 0.1 V
[d] The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR
[e] Blank reactions (without oxidation of mixture) led to less than 10% yields of substitution products
[f] This yield is calculated on the σ-complex formed. The remainder relates to recovered reactants
[g] Excess of the cyanide can be eliminated by electrochemical oxidation at 1.33 V

Quantitative (100%) yields for the formation of σ^H-complexes were observed, since no reduction waves for nitroarenes have been observed in the first cathodic scan. When two σ^H-complexes are present in solution, two waves in the first anodic scan have to appear (two-electron-irreversible oxidation wave for each compound). For 1-fluoro-2,4-dinitrobenzene, 1-chloro-2,4-dinitrobenzene, and 1-bromo-2,4-dinitrobenzene, two types of σ^H-complexes have been identified, probably 1,3- and 1,5-adducts. The oxidation peak potential (E_{pa}) is mainly dependent on the number of electron-withdrawing groups: E_{pa} increases with the number of nitro- or cyano groups available in an aromatic ring. Exhaustive electrolysis of σ^H-complexes (by the loss of two electrons and one proton) leads to the corresponding nitroarene in 100% yield.

The σ-complexes of nitroaromatic compounds with the cyanide ion were prepared by stoichiometric addition of CN^- to solutions of nitroarenes in DMF + 0.1 M $TBABF_4$ under inert atmosphere. The electrochemical experiments (cyclic voltammetry and electrolysis) are analogous, as it has been described for **3H**$^-$ (Sect. 2.3). The results are summarized in Table 2.

It is important to underline that the oxidation peak potentials of σ^X-complexes are higher than those of σ^H-complexes, and the oxidation peak potential is dependent on the nature of the leaving group. Indeed, for Cl^- 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. All electrolyses have been carried out at a potential higher than E_{pa} of the corresponding σ^X-complex, and the assembly implying that the $S_N{}^H$ and $S_N{}^X$ products are recovered.

In summary, the use of electrochemistry allows: (a) determining the type of σ-complexes which are present in the solution (number of waves, peak potential wave) and their relative amounts (intensity of peak wave), (b) establishing the oxidative conversion of the σ-complexes into re-aromatized nitroaromatic compounds by observing the reduction in the re-aromatized products, and (c) achieving the final substitution products by performing exhaustive electrolysis of solutions of σ-complexes at a precise value of applied potential.

3 Synthetic Applications of Electrochemical $S_N{}^H$ Reactions

Until now, the electrochemical methodology described has been useful to establish the $S_N{}^H$ and $S_N{}^X$ reaction mechanisms. However, (a) the replacement of a hydrogen atom by another one (the hydride ion H^-as nucleophile), although being very efficient, has no synthetic value [22], and (b) the use of halogenated aromatic compounds as staring materials in the S_NAr reactions realized by electrochemical methods does not provide advantages over the conventional chemistry [23]. Meanwhile, it is possible to obtain a variety of $S_N{}^H$ products by using nucleophiles other than the hydride ion [24–28].

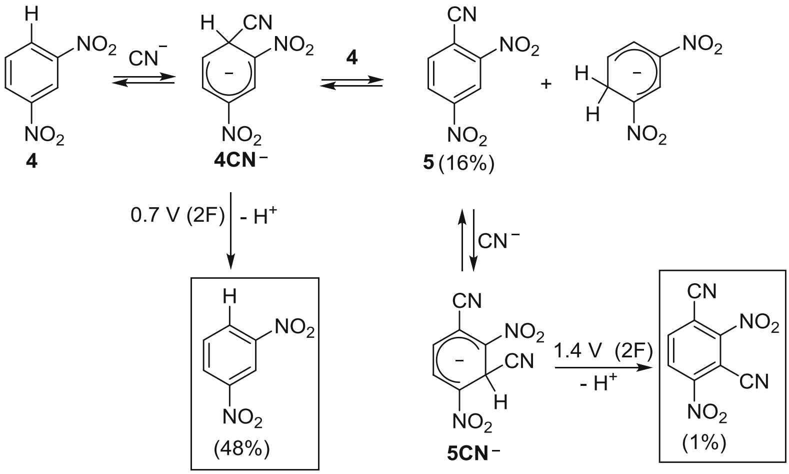
3.1 Cyanation Reactions

The cyanide anion has a strong tendency to attack non-substituted positions in aromatic rings [6, 7]. Therefore, the use of electrochemical methods described in Sect. 2.2 seems to be an appropriate approach for the $S_N{}^H$ cyanation of arenes [22].

The σ^H-complexes formed by the addition of CN^- to nitroarenes (mono-, di-, and tri-nitro derivatives) have been obtained in good yields (38–46%). The electrochemical oxidation of these σ^H-complexes leads to re-aromatized compounds as a result of departure of two electrons and a proton, thus formally corresponding to the formal loss of H^- (Scheme 7, Table 3). The reaction is very clean, recovering only the starting material in addition to the reaction products. Yields are varied from 35 to 86%; where a low yield of the $S_N{}^H$ product is obtained (<15%), the $S_N{}^X$ product is formed in approximately 30% yield.

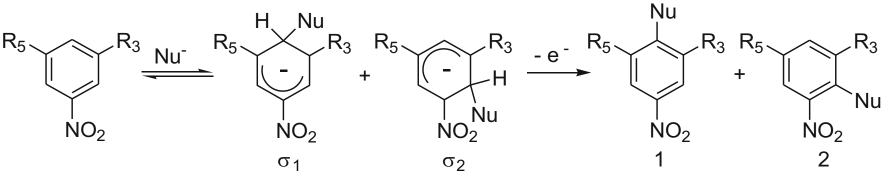
Scheme 7 explains the reactivity of 1,3-dinitrobenzene in the presence of CN^- as nucleophile, and the general character of the process. The first step is a reversible addition of CN^- to 1,3-dinitrobenzene, resulting in the formation of σ^H-complex **4CN**$^-$ (yield 50%). This σ^H-complex, being reacting with 1,3-dinitrobenzene, is converted into re-aromatized 2,4-dinitrobenzonitrile, as a result of the thermal process (yield 16%) [41].

2,4-Dinitrobenzonitrile reacts with an excess of CN^- as nucleophile to give a new σ^H-complex **5CN**$^-$. The σ^H-Complexes **4CN**$^-$and **5CN**$^-$ can be oxidized electrochemically with the formal loss of two electrons and a proton (at +0.70



Scheme 7 Chemical and electrochemical synthesis of 2,4-dinitrobenzonitrile and 2,4-dinitroisophthalonitrile

Table 3 Yields of products obtained by electrochemical oxidation of σ^H-complexes of nitroarenes with various nucleophiles



R_3	R_5	Nu^-	Nu^-/Ar[a]	1[b] (%)[c]	2[b] (%)[c]
NO_2	NO_2	CN^-	1	60	–
		$BuNH_2$	3	30	–
		$CH_3COCH_3/t\text{BuO}^-$	[d]	60	–
		$Bu^-(BBu_4^-)$	1([e])	–(79)	–(14)
NO_2	H	CN^-	1	48	–
		$BuNH_2/t\text{BuO}^-$	[f]	39(49)	–
		$CH_3COCH_3/t\text{BuO}^-$	[d]	80	–
		$Bu^-(BBu_4^-)$	1([e])	43(30)	30(–)
H	H	CN^-	1	–	–
		$BuNH_2/t\text{BuO}^-$	[f]	–	–
		$CH_3COCH_3/t\text{BuO}^-$	[d]	80	–
		BuLi(BuMgCl)	1	41(40)[g]	–(35)[g]

[a] Molar ratio of nucleophile (Nu^-) and nitroarene (Ar)

[b] The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR

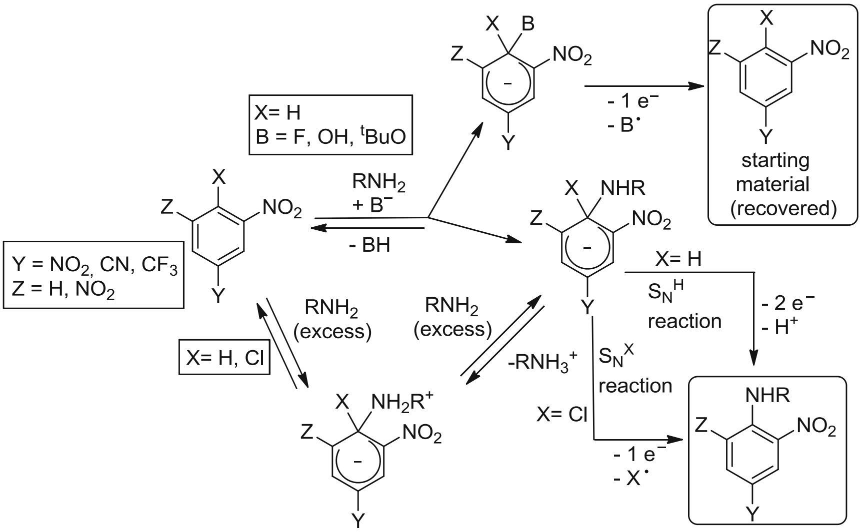
[c] This yield is calculated on the σ-complex formed. The remainder relates to reactants recovered

[d] DMF: acetone = 3:3 mL; Nitroarene: $t\text{-BuO}^-$ = 1:1

[e] $[Me_4NBBu_4]$ = 0.05–0.20 M

[f] Nitroarene: amine: $t\text{-BuO}^-$ = 1:5:2

[g] Also, 2,4-dibutylnitrobenzene is formed in 47% (BuLi) and 10% (BuMgCl) yields



Scheme 8 Electrochemical synthesis of amino substituted nitroarenes

and +1.40 V, respectively), thus affording 2,4-dinitrobenzonitrile (48%) and 2,4-dinitroisophthalonitrile (5%), as the final products. These results, obtained by the joint use of cyclic voltammetry and exhaustive controlled-potential electrolysis, indicate that the oxidation of σ^H-complexes appears to be a new effective approach for cyanation of nitroarenes. Table 3 shows that 2,4,6-trinitrobenzonitrile is derived in 60% yield from a similar S_N^H reaction.

3.2 *Amination Reactions*

A variety of methods for the direct amination of nitrobenzene, that do not require halogenated aromatic compounds, have been reported, including both vicarious (eliminative) [16, 17, 19, 42] and oxidative versions of nucleophilic substitution of hydrogen. Recently, we have described the amination of 1,3-dinitrobenzene promoted by fluoride ions through photochemical activation [43]. Also, the use of $KMnO_4$ as oxidant is of great practical value [3, 44].

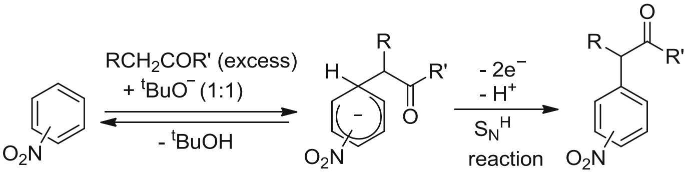
An alternative way to achieve the direct amination of nitroaromatic compounds by using the S_N^H methodology is based on the application of the electrochemical technique (Scheme 8). For this purpose [24], we used two amines (n-$BuNH_2$, and n-$HexNH_2$), and acetamide ($AcNH_2$) in both the presence and without of different bases (t-BuOK, $Bu_4NF.3H_2O$, and Me_4NF). An excess of RNH_2 was varied to optimize the formation of σ^H-complexes of nitroaromatic compounds, and to minimize further amination of the S_N^H products (Table 3). A large excess of amine was used in the reaction with nitrobenzene in order to promote a nucleophilic attack leading to σ^H-complexes. In the presence of base, this percentage increases considerably (60–100%). However, this is not only due to the attack by a deprotonated nucleophile (RNH^-), but also due to the presence of an excess of base. It is remarkable that, both in the presence of external base or without it, the reaction is rather selective. Yields of the $S_N{}^H$ product, derived from the oxidative electrochemical substitution of hydrogen are ranged from fair to good (35–98%), with the exception of N-butyl-3-chloro-2,6-dinitroaniline (15%). In this case, only the starting material (1-chloro-2,4-dinitrobenzene) was recovered as a result of the electrochemical oxidation process.

The reaction of nitroarenes with an excess of nucleophile (RNH_2) (without a base) begins with the formation of a zwitterionic complex at the first step. In the presence of nucleophile (RNH_2) and base the σ-complexes are formed directly. The ratio of σ^H- or σ^X-complexes depends on the nature of substituents. The σ^H-complexes, as the key intermediates, can eliminate two electrons and a proton to give rise to the $S_N{}^H$ products, while the σ^X-complexes, by loss of an electron and $X^\cdot$, can be transformed into the $S_N{}^X$ product. The $S_N{}^H$ products are formed through selective electrochemical oxidation (lower oxidation potential of the intermediates) or from the $S_N{}^X$ compounds. An excess of amine present in the reaction mixture is not oxidized because the oxidation potentials for primary amines are about 1.50 V. The oxidation potential peaks for σ-complexes are lower in all cases. Finally, a comparison of chemical [42, 43] and electrochemical oxidation reactions shows that the electro-oxidation is a more convenient process in those cases when the oxidation peak potentials for σ^H-complexes are more positive than 0.6 V.

3.3 C-Arylation of Ketones

A few examples of the S_NAr reactions on nitroaromatic compounds using anions derived from ketones as nucleophiles can be found in the literature [44]. In particular, the direct coupling of carbon nucleophiles, including ketones, with nitroaromatic compounds in the presence of $KMnO_4$ has recently been described [45]. Also, a photochemical procedure, that despite reasonable yields of nitroaromatic ketones needs special conditions to achieve a good reproducibility, has been reported [18]. Although one of the best alternative to oxidative C-arylation of ketones is vicarious nucleophilic substitution [7], the latter approach fails with nitrobenzene as a substrate, and in all cases an auxiliary leaving group is necessary [46–48]. The formation of O-adduct between acetophenone enolate anion and 1,3,5-trinitrobenzene has been reported [49]. This O-adduct was converted into the corresponding C-adduct, in changing the temperature from −50 to 20ºC.

Synthesis of aromatic ketones, including those derived from mononitrobenzenes, can be achieved in good yields (60–90%) by using controlled-potential electro-oxidation of the corresponding σ^H-complexes [25]. These σ^H-complexes are formed (yields from 50 to 100%) with an excess of ketone and a strong base



Scheme 9 Electrochemical synthesis of nitroaromatic ketones

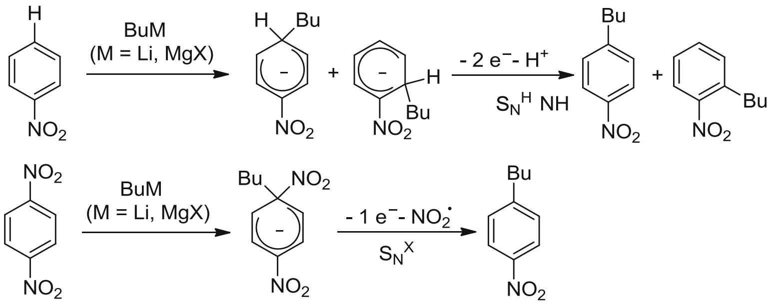
(*t*-BuOK); the latter is necessary to generate a ketone carbanion (Table 3). Good selectivity and high yields of substitution products have been obtained from the reactions of acetone, 2-butanone, and acetophenone with aromatic compounds bearing one, two, and three nitro groups.

Scheme 9 outlines the electrochemical S_N^H reaction. The intermediate σ^H-complex is formed at the first equilibrium step of the reaction between a nitroaromatic compound and ketone (taken in an excess) in the presence of a strong base. Due to the loss of two electrons and one proton (formally the hydride anion) the σ^H-complex is transformed into substitution product. Use of electrochemical methods to oxidize the intermediate σ^H-complexes at the selected potentials allows to obtain not only the desired substitution products, but also to recover the starting materials.

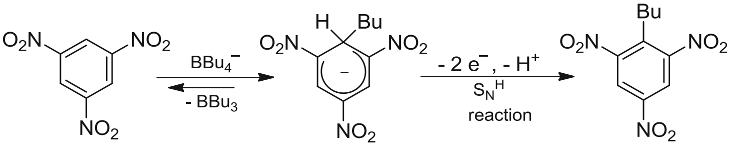
Finally, yields of products obtained electrochemically appear to be better than those from chemical reactions [44].

3.4 Alkylation Reactions with Organometallic Reagents RM and Tetraalkylborates as Nucleophiles

The well-spread industrial process to obtain alkyl substituted nitroaromatic compounds is based on the electrophilic nitration reaction. Since this process is poorly selective, and requires rather drastic conditions [50], a number of alkylation methods have been suggested [2, 3, 51, 52]. Organolithium or organomagnesiun compounds appear to be appropriate reagents to react with nitroaromatics into alkylnitroarenes through the nucleophilic substitution process S_NAr [7, 53–55]. Nevertheless, these reactions are difficult to control [56–58]. Indeed, alkyl lithium or alkyl Grignard reagents (RLi or RMgX, R = Me, Et, Bu) have been found to react with 1,3,5-trinitrobenzene in THF to afford 1,3,5-trialkyl-2,4,6-trinitrobenzene after acidification of the reaction mixture [56–58]. A similar behavior was found for 1,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene. In case of nitrobenzene the reactions lead to the mixtures of alkyl nitrobenzenes and alkyl nitrosobenzenes [59–61]. We used several oxidants, however the reactions with Br_2 and $KMnO_4$ proved to be unselective ones [62], while in the presence of rather expensive DDQ the same reactions gave rather good yields of the substitution products [63]. In the reaction of 1,4-dinitrobenzene with alkylboranes, proceeding in *t*-BuOH in the presence of *t*-BuOK, alkylnitrobenzenes have been obtained in



Scheme 10 Electrochemical synthesis of alkyl substituted nitroaromatic compounds by the reaction of nitrobenzenes with organometallic reagents



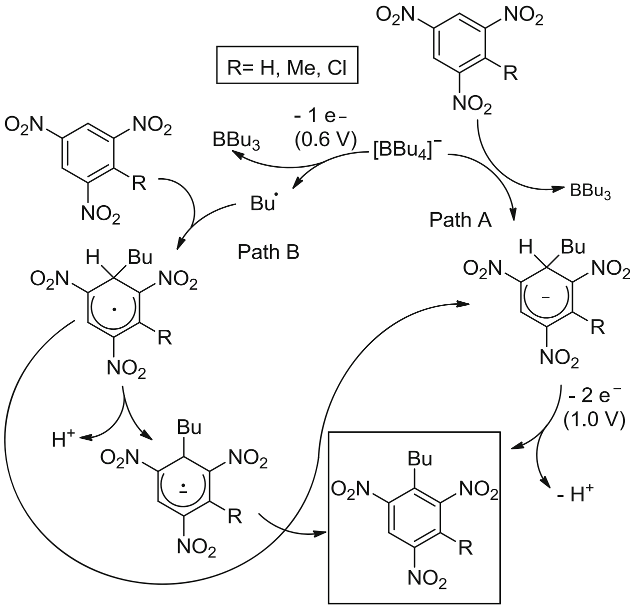
Scheme 11 Electrochemical synthesis of 1-butyl-2,4,6-trinitrobenzene

good yields [64]. Tetralkylborates react with 1,3,5-trinitrobenzene to form the corresponding σ^H-complexes [65].

The electrochemical approach for the alkylation of nitroarenes has also been demonstrated by the transformations of nitroaromatics by action of organometallic compounds RM (M = Li, MgX) (Scheme 10) [26] and tetraalkylborates (Scheme 11) [27].

Several types of σ-complexes are formed. σ^H-Complexes of arenes substituted in various positions of an aromatic ring have been established to react with the loss of two electrons and one proton (the $S_N{}^H$ reaction), while σ^X-complexes ($X = NO_2$, Cl) undergo the departure of one electron and $X^{\cdot}$ (the $S_N{}^X$ reaction). In the reactions of nitrobenzene and 1,3-dinitrobenzene (Table 3), yields of approximately 50% were achieved for monosubstituted arenes, and 10–50% for disubstituted products. Under the same reaction conditions 1,3,5-trinitrobenzene proved to undergo the $S_N{}^X$ process with the loss of $NO_2^{\cdot}$.

Yields of products obtained by electrochemical methods are comparable with those reported in the literature for similar alkylations of aromatic compounds in the presence of chemical oxidants. In spite of experimental difficulties, we have succeeded to alkylate dinitrobenzene. The reaction has to be carried out in THF (highly resistant medium) because DMF undergoes decomposition in the presence of butyl lithium. Use of butyl lithium provides higher yields of the target alkylation products, than butylmagnesium chloride. Also equivalent amounts of reactants, nitroarenes and organometallic reagents, have been found to be essential to provide the best yields of the reaction products.

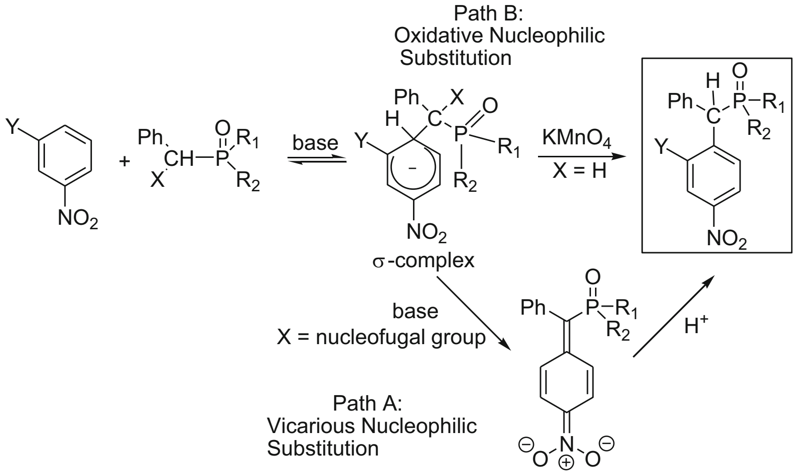


Scheme 12 General electrochemical mechanism for the synthesis of 1-butyl-2,4,6-trinitrobenzene derivatives. BBu_4^- acts as both nucleophile and reducting agent

The tetraalkylborate anion is a good alternative to organolithium or organomagnesium reagents to modify aromatic compounds through the nucleophilic aromatic substitution reactions. Indeed, 1,3,5-trinitrobenzene reacts with tetraalkylborates to form the corresponding σ^H-complexes (Scheme 11), followed by their oxidative transformations according to the S_N^H process (loss of the hydride ion).

1-Butyl-2,4,6-trinitrobenzene was obtained in 79% yield, in addition to dialkyl substituted 1,3,5-trinitrobenzene (14%) and recovered 1,3,5-trinitrobenzene (5%) (Table 3). Importance of the experimental part also has to be emphasized. To obtain the σ^H-complex of nitroarene with tetraalkylborate anion, you have to mix a solution of this anion (taken in an excess) with a solution of nitroarene and to wait for 2 h followed by electrochemical oxidation of the σ^H-complex at 1.06 V.

Tetraalkylborate anion is oxidized into tetraalkylborate radical at 0.60 V (Scheme 12), which is then transformed into Bu˙ that can react with 1,3,5-trinitrobenzene. The resulting radical species eliminate a proton, thus giving the corresponding nitroaromatic radical-anion. The latter is oxidized by the cyclohexadienyl radical (according to the standard potentials of redox pairs) [38, 66]. This reaction is somewhat similar to the termination step in the $S_{RN}1$ aromatic substitution reactions [64, 67, 68]. When the electrolysis is carried out at 1.06 V, the σ^H-complexes are oxidized (path A, Scheme 12), as well as tetraalkylborate anions (path B, Scheme 12). The generation of Bu˙ allows to improve yields of the S_N^H products, but Bu˙ can also attack the S_N^H product to form dialkyl trinitrobenzene. This process appears to be more important at the final stage of the reaction, when



Scheme 13 Vicarious and oxidative nucleophilic substitutions of hydrogen in nitroarenes with phosphorous-containing reagents

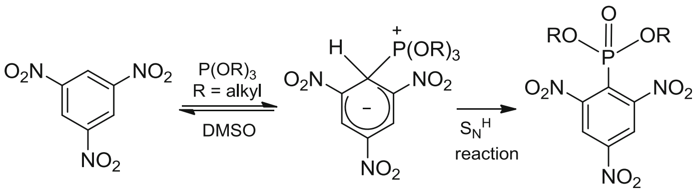
concentration of the monoalkyl arene is much higher than that of the starting nitroaromatic compound.

3.5 Phosphonylation Reactions. Phosphorous-Containing Compounds as Nucleophiles

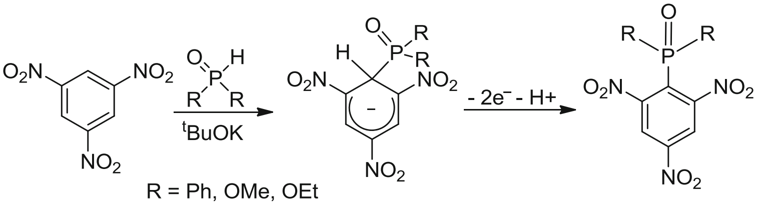
Nucleophilic aromatic substitution of hydrogen ($S_N{}^H$) or good leaving groups ($S_N{}^X$) by action of nucleophiles containing phosphorous is limited to a few examples of synthetic studies aimed at obtaining of aryl substituted phosphonic acids (in particular, for medicinal applications [69]), through either oxidative or vicarious displacement of hydrogen [70, 71]. In these $S_N{}^H$ processes a new C–C bond is formed instead of C–P, when dialkylbenzyl phosphonates are used as nucleophiles in the presence of an external base (Scheme 13). The final $S_N{}^H$ product can be obtained from the intermediate σ^H-complex by the action of the second equivalent of a base, which promotes the β-elimination of HX (vicarious $S_N{}^H$ reaction, path A), or by using chemical oxidants such as potassium permanganate (oxidative $S_N{}^H$ reaction, path B) [72].

The mechanistic study of the reaction of 1,3,5-trinitrobenzene with $P(OAlk)_3$ in DMSO has shown that picryl phosphonate, as the main $S_N{}^H$ product, is formed through the intermediacy of the zwitterionic complex (Scheme 14) [59, 73–75].

The electrochemical method [28] was used to obtain nitroaromatic organophosphorus compounds by reacting 1,3.5-trinitrobenzene with dimethyl or diethyl phosphonates, and oxo(diphenyl) phosphonate as nucleophiles, in the presence of the *t*-BuOK, as shown in Scheme 15.

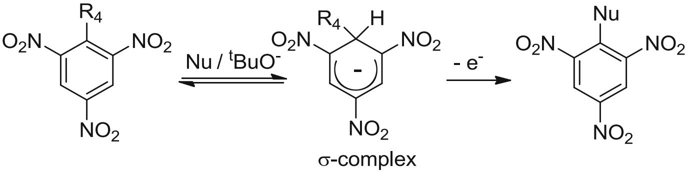


Scheme 14 The S_N^H reaction of trinitrobenzene with trialkylphosphites



Scheme 15 Electrochemical synthesis of dialkyl (2,4,6-trinitrophenyl)-phosphonates

Table 4 Yields of products obtained by electrochemical oxidation of σ-complexes of nitroarenes with phosphorous-containing nucleophiles



R_4	Nu	Molar ratio[a]	σ (%)	$E_{pa}(\sigma)$[b] (V)	Substituion product[c,d] (%)[e]
H	$HPO(OMe_3)_2$	1:2:2	100	0.80	80
		1:1:1	90	0.88	70
	$HPO(OEt_3)_2$	1:1:1	81	0.86	33
	$HPOPh_2$	1:2:2	80	0.83	10
Cl	$P(OMe_3)_3$	1:50:0	100	–[f]	85
		1:5:0	100	1.07	100
	$P(OEt_3)_3$	1:50:0	100	–[f]	85
		1:5:0	100	1.07	93

[a] Molar ratio nitroarene (Ar): nucleophile (Nu): *t*-BuO$^-$

[b] All potentials are given vs. SCE reference electrode

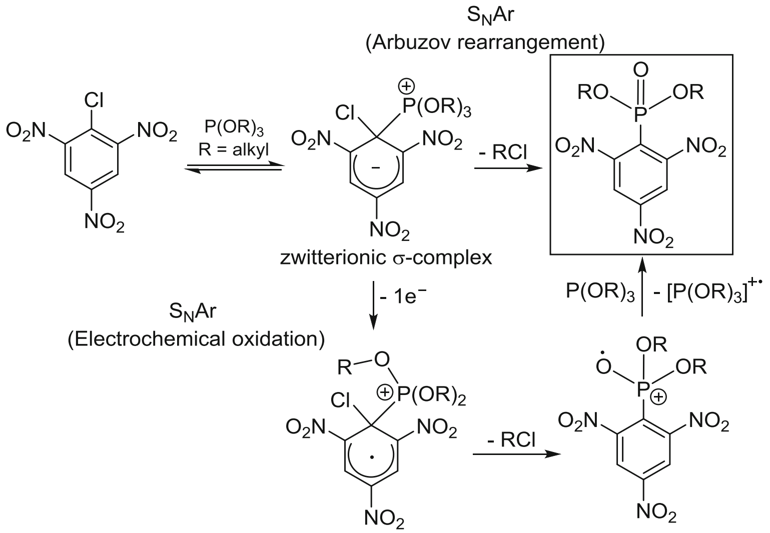
[c] The S_N^H and S_N^X products were obtained by exhaustive electrolysis at E_{pa} + 0.1 V

[d] The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR

[e] This yield has been calculated on the basis of the σ-complex formed. The rest corresponds to recovered reactants

[f] Blank reactions, without oxidation

A typical S_N^H electrochemical process involves the formation of σ^H-complexes (yields 80–100%), and their electrochemical oxidation (the loss of two electrons and a proton) in all cases leads to the S_N^H substitution products, obtained in yields ranging between 10 and 80% (Table 4).



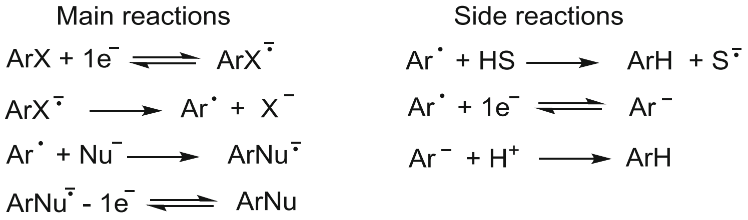
Scheme 16 Electrochemical synthesis of dialkyl(2,4,6-trinitrophenyl) phosphonate with $P(OR)_3$ as nucleophiles without external base

The reaction of 1,3,5-trinitrobenzene with trimethyl or triethyl phosphites as nucleophiles has been shown to give the S_N^H products in moderate yields (60%). On the other hand, good yields of the S_N^X products (85–100%) have been obtained by the reaction of 1-chloro-2,4,6-trinitrobenzene with the same nucleophiles (Table 4). Therefore, the S_N^X products can be obtained by means of either chemical reaction through the Arbuzov rearrangement, or by electrochemical oxidation of the intermediate zwitterionic complex (Scheme 16).

It is worth noting that no substitution products have been obtained in the reaction of 1,3,5-trinitrobenzene with PR_3 nucleophiles without any bases.

4 Electrochemically Induced S_N^X and S_N^H Reactions

Electrochemistry can also be used to induce aromatic nucleophilic substitutions by setting up the electrode potential at the level, which is appropriate to reduce an aromatic substrate. When this electrochemical process is carried out in the presence of a nucleophilic reagent, the S_N^X or S_N^H reactions take place. Indeed, halogenated derivatives of benzophenone, benzonitrile, and naphthalene undergo nucleophilic displacement reactions with thiolates, which are able to occur catalytically [76, 77]. The reaction mechanism involves the formation of the anion radical at the electrode and its further decomposition into a neutral radical, which reacts with a nucleophile, thus yielding the anion-radical of the substitution product. In case of the catalytic reaction, oxidation of the anion-radical species may occur by electron transfer with the substrate and/or the electrode (Scheme 17).



Scheme 17 Electrochemically promoted $S_N{}^X$ reactions

The main competing reactions are the abstraction of H atom from the solvent of neutral radicals, and further reduction in radical species. Liquid ammonia was used as a solvent to avoid the transfer of H atom [78–80].

In both $S_N{}^H$ and $S_N{}^X$ reactions, which have so far been reported [22–28], the electrochemical activation appears to be involved in the reaction mechanism. The σ-complex is formed at the first step, and then it is oxidized electrochemically at the second step of the reaction.

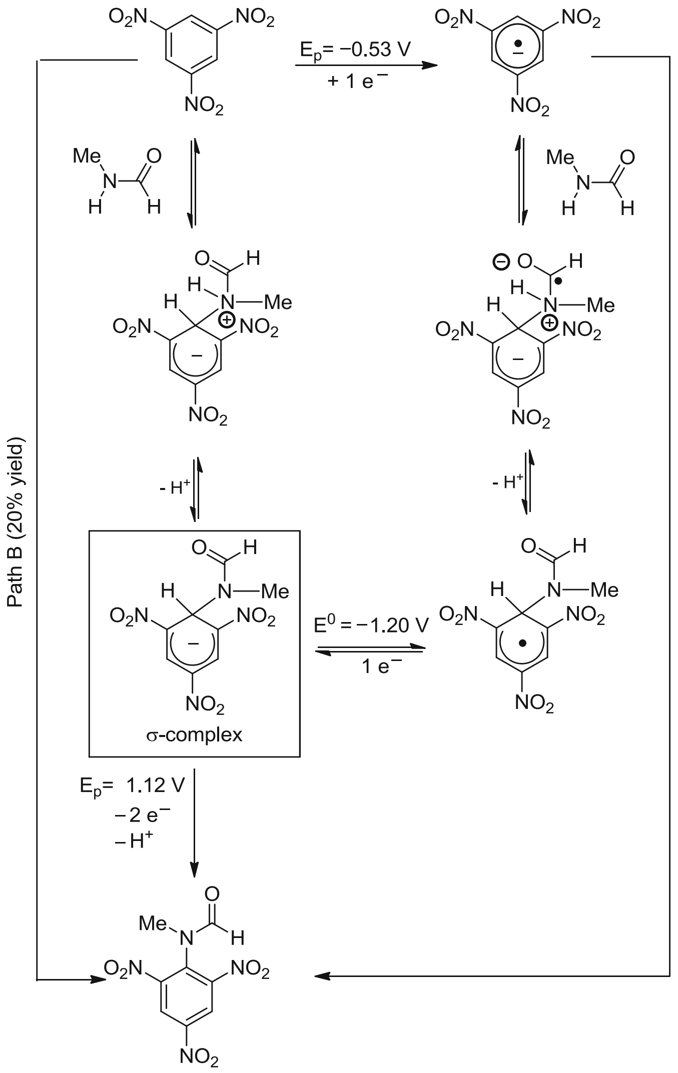
The formation of σ-complex seems to be a crucial step of the reaction between a nucleophile and an electron-deficient nitroarene. At the same time, there might be another strategy. By changing the electron character of substrate through the formation of radical-anions we generate electron rich species, which are able to react with neutral nucleophiles (electron poor). Thus, the choice of appropriate reactants for electrochemical reactions appears to be a crucial point. Indeed, 1,3,5-trinitrobenzene and N-methylformamide (nucleophile/solvent) proved to be suitable reactants [29].

Electrochemical study based on the combination of cyclic voltammetry and electrolysis at controlled-potential enabled the mechanistic aspects and synthetic scopes of the reaction to be established (Scheme 18).

A solution of 1,3,5-trinitrobenzene in N-methylformamide was subjected to electrolysis at −0.70 V (Path A, Scheme 18). The controlled-potential electrolysis was stopped after a passage of one electron per each molecule. The formed anion-radical species of 1,3,5-trinitrobenzene were allowed to react with N-methylformamide. Under the used experimental conditions the σ^H-complexes were the only species present in the reaction mixtures. Exhaustive oxidative controlled-potential electrolysis at 1.30 V gave *N*-methyl-*N*-(2,4,6-trinitrophenyl)formamide ($S_N{}^H$ product) in good yield (80%). Without a preliminary reductive electrolysis (Path B, Scheme 18), the same type of σ^H-complexes proved to be formed, and after exhaustive oxidative controlled-potential electrolysis at 1.30 V, *N*-methyl-*N*-(2,4,6-trinitrophenyl)formamide ($S_N{}^H$ product) was obtained in 20% yield.

Similar results were obtained by using 3,5-dinitrobenzonitrile, 1,3-dinitro-5-trifluoromethylbenzene, and 1,3-dinitronaphthalene as starting materials.

The anodic substitution reaction is another electrochemical approach to induce the $S_N{}^X$ and $S_N{}^H$ reactions. The term "anodic addition reaction" is used in the literature, since an anodic process is exploited for the initial electrochemical generation of radical-cation intermediates [81, 82]. Hence, anodic addition involves

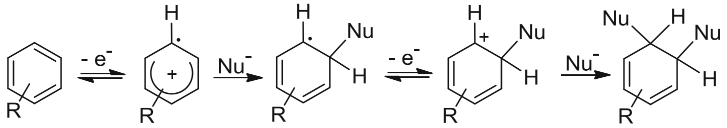


Scheme 18 Electrochemically promoted $S_N{}^H$ process

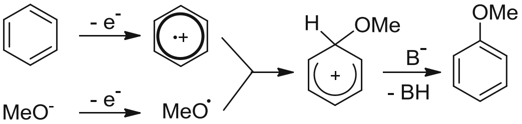
oxidation of an aromatic substrate ArH into the corresponding radical-cation, followed by the nucleophilic addition step (Scheme 19).

If oxidation of nucleophile takes place, the radical formed may react with an aromatic molecule (Scheme 20) [6, 82–84].

Use of the above-described anodic addition reactions enabled to perform hydroxylation of anthracene into 9,10-dihydroxianthracene in a good yield [85, 86], and also acetoxylation of 1,4-dimethoxybenzene into 2,5-dimethoxyphenylacetate in 51% yield [87].



Scheme 19 Anodic Addition. Formation of radical-cations from aromatic substrates



Scheme 20 Anodic Addition. Simultaneous formation of radical-cation from an aromatic substrate and a radical of nucleophile

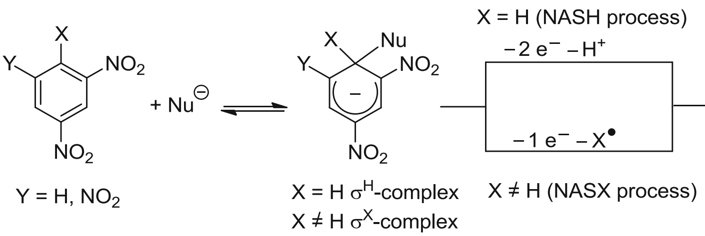
Recent studies demonstrate the achievements reached though anodic oxidation of catechols in the presence of α-oxoketene N,N-acetals [88, 89].

5 Thermodynamic Studies of σ–Complexes

The electrochemical methodology proved to be an excellent approach to obtain substitution products by oxidation of σ-complexes (Scheme 21). Electrochemistry can be exploited to oxidize σ^X-complexes, and this way involves the loss of an electron and a radical $X^\cdot$ ($S_N{}^X$ reaction), or can be used to oxidize σ^H-complexes, and the latter process involves the loss of two electrons and a proton ($S_N{}^H$ reaction). As indicated in the previous sections, the electrochemical method is especially promising in those $S_N{}^H$ reactions which are more difficult to be realized by means of conventional chemical procedures.

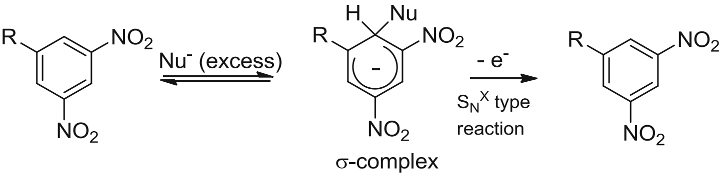
When anionic nucleophiles, such as $BH_4{}^-$, CN^-, CH_2COR^-, R^-, $BBu_4{}^-$, and ^-NHR (R is an alkyl group) are used, the $S_N{}^H$ products can be obtained in good yields through the typical $S_N{}^H$ process (with the loss of two electrons and a proton) [22, 24–27]. In the reactions of 1,3-dinitrobenzene and 1,3,5-trinitrobenzene with other nucleophiles, such as F^-, ^-OH, ^-OR, and ^-SR, the quantitative formation of σ^H-complexes is observed in all cases (Table 5). Following the electrochemical methodology, cyclic voltammetry, and controlled-potential electrolysis, these σ^H-complexes were oxidized at the corresponding potentials, and the starting nitroarenes were recovered in a vast majority of cases. Also, 1-fluoro-3,5-dinitrobenzene (2%), ethyl 3-nitrophenylether (14%), and ethyl 3,5-dinitrophenylether (31%) were obtained. These results indicate that the $S_N{}^H$ process is not realized properly, because yields of the $S_N{}^H$ products in all cases are below 31% (Scheme 22).

The results obtained indicate the complete formation of σ^H-complexes. However, the nature of nucleophiles is important for obtaining either $S_N{}^H$ or $S_N{}^X$ products, including recovery of the starting nitroaromatics. In other words, the



Scheme 21 Electrochemically promoted nucleophilic aromatic substitutions of hydrogen ($S_N{}^H$) or good leaving groups ($S_N{}^X$)

Table 5 Yields of products obtained by electrochemical oxidation of σ-complexes of nitroarenes with ^-OH, ^-OMe, ^-SEt and F^-, as nucleophiles



R	Nu⁻	$E_{pa}(\sigma)$[a] (V)	Final Product[b,c] (%)
H	$^-OCH_3$	0.72	100
	^-OH	0.59	100
	^-SEt	0.47	66[d]
	F^-	0.70	100
NO_2	$^-OCH_3$	1.18	100
	^-SEt	1.06	68[e]
	F^-	1.09	97[f]

[a] All potentials are given vs. SCE reference electrode

[b] Products were obtained after exhaustive electrolysis at E_{pa} + 0.1 V

[c] The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR

[d] Ethyl 3-nitrophenylthioether (14%). The rest corresponds to recovered starting materials

[e] Ethyl 3,5-dinitrophenylthioether (31%)

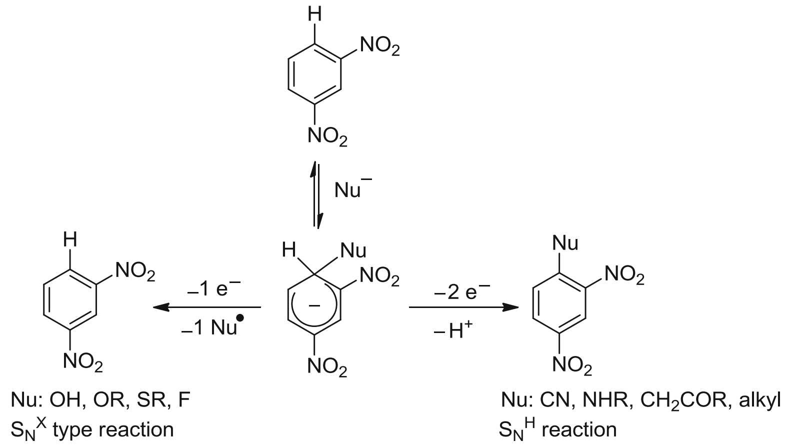
[f] 1-Fluoro-3,5-dinitrobenzene (2%)

difference between C–Nu and C–H bonds in dissociation energies has to be a decisive factor for the transformation of σ^H-complexes [30].

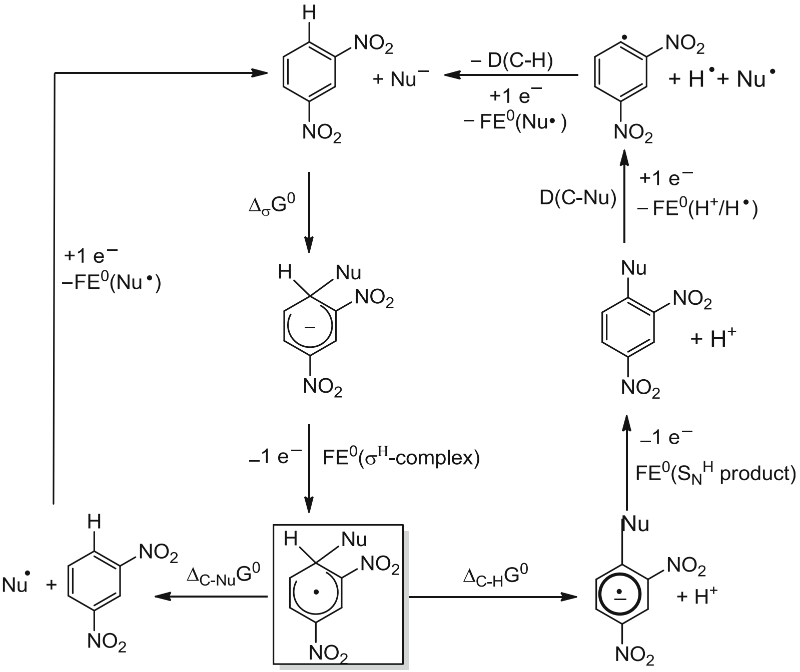
Thermodynamic cycles [90–93] can be used to relate the different energy patterns, such as the Gibbs standard chemical reaction energy ($\Delta_\sigma G^0$), the Gibbs standard electrochemical energy ($-FE^0$) for the transfer of one electron, and bond dissociation energy (Scheme 23).

The thermodynamic cycle begins with the formation of a chemical bond between a nitroarene and a nucleophile ($\Delta_\sigma G^0$) to give the σ^H-complex. The latter is oxidized at the second step with the removal of one electron [$FE^0{}_{(\sigma^H\text{-complex})}$].

The reaction determining step in Scheme 21 is the transformation of the radical derived from the σ^H-complex. It can undergo dissociation of either C–H ($\Delta_{C-H}G^0$) or C–Nu bond ($\Delta_{C-Nu}G^0$) to give radical-anion of the $S_N{}^H$ product or the starting



Scheme 22 A plausible mechanism for the electrochemical oxidation of σ^H-complexes depending on the nature of nucleophiles



Scheme 23 Thermodynamic cycle for the $S_N{}^H$ and $S_N{}^X$ processes

dinitrobenzene, respectively. The radical-anion formed by cleavage of the C–H bond is oxidized into the $S_N{}^H$ product (FE^0). The latter is transformed through homolytic dissociation of the C–Nu bond (D_{C-Nu}) into dinitrophenyl radical that may be homolytically coupled with a hydrogen atom (–$D_{C–H}$). To close the cycle, protons are reduced to hydrogen atoms [–$FE^0_{(H^+/H^\cdot)}$], and nucleophilic radical species $Nu^\cdot$ are transformed into Nu^- [$-FE^0_{(Nu^\cdot/Nu^-)}$]. The formation of dinitrobenzene is observed when the σ^H-complex radicals undergo dissociation of the C–Nu bond; reduction of $Nu^\cdot$ radicals to Nu^-(–$FE^0_{(Nu^\cdot/Nu^-)}$) is only necessary to close the thermodynamic cycle.

The $\Delta_{C–H}G^0$ y $\Delta_{C–Nu}G^0$ values can be related, according to the thermodynamic cycle (Scheme 23), by Eqs. 1 and 2. The terms, such as $\Delta_\sigma G^0$, $E^0_{(Nu^\cdot/Nu^-)}$ [91–94] and $E^0_{(\sigma^H\text{-complex})}$ [83], which are difficult for experimental access, proved to appear in both equations. Fortunately, the difference between the two $\Delta_{C–H}G^0$ and $\Delta_{C–Nu}G^0$ values (Eq. 3) depends on bond dissociation energies and standard reaction potentials, $E^0_{(\text{reaction})}$, and $E^0_{(H^+/H^\cdot)}$. The bond dissociations were taken from publications [95–97], ignoring the entropic term (it has been accepted that it can be equal to 1 meV K^{-1}, which is equivalent to 0.02 kcal mol^{-1}) [98]. Values of standard potentials have been tabulated in the papers [22–27, 94, 99]. In order for the $S_N{}^H$ process to be a favorable relative to $S_N{}^X$, it is necessary that $\Delta_{C–H}G^0 < \Delta_{C–Nu}G^0$, Eq. 4. Equation 6 shows the bond dissociation energy, $D_{C–Nu}$, which is required for the $S_N{}^H$ reaction to be a favorable one.

On substituting the $D_{C–H}$, $E^0_{(\text{reaction})}$ and $E^0_{(H^+/H^\cdot)}$ values are 111.3 kcal mol^{-1}, -0.83 V and $-1{,}53$ V, respectively. In accordance with the above mentioned references, the $D_{C–Nu}$ has to be higher than 95.2 kcal mol^{-1} (Eq. 7) in order for the $S_N{}^H$ process to be favorable.

Equations: **Thermodynamic Relationships**

$$\begin{aligned}\Delta_{C-H}G^0 = -\Delta_\sigma G^0 + D_{(C-H)} - D_{(C-Nu)} + \\ + FE^0_{(Nu^\bullet/Nu^-)} - FE^0_{(\sigma^H\text{-complex})} - FE^0_{\left(S_N{}^H\text{product}\right)} + FE^0_{(H^+/H^\bullet)}\end{aligned} \tag{1}$$

$$\Delta_{C-Nu}G^0 = -\Delta_\sigma G^0 + FE^0_{(Nu^\bullet/Nu^-)} - FE^0_{(\sigma^H\text{-complex})} \tag{2}$$

$$\Delta_{C-H}G^0 - \Delta_{C-Nu}G^0 = D_{(C-H)} - D_{(C-Nu)} - FE^0_{\left(S_N{}^H\text{product}\right)} + FE^0_{(H^+/H^\bullet)} \tag{3}$$

$$\Delta_{C-H}G^0 < \Delta_{C-Nu}G^0 \tag{4}$$

$$\Delta_{C-H}G^0 - \Delta_{C-Nu}G^0 < 0 \tag{5}$$

$$D_{(C-H)} - FE^0_{\left(S_N{}^H\text{product}\right)} + FE^0_{(H^+/H^\bullet)} < D_{(C-Nu)} \tag{6}$$

$$95.2\,\text{kcal}\,\text{mol}^{-1} < D_{(C-Nu)} \tag{7}$$

Table 6 shows experimental values of $D_{C–Nu}$ bond dissociation energies for various nucleophiles [95–97]. In accordance with the data of thermodynamic calculations, the complexes of nitroarenes with the ^-OH, ^-OR, ^-SR nucleophiles have to undergo the $S_N{}^X$-type process, since their bond dissociation energies are lower than 95 kcal mol^{-1}.

Fluorinated compounds cannot be considered because the bond dissociation energies available in the literature for aromatic fluorinated compounds are varied

Table 6 Bond dissociation energies [86–88]

	C–SR	C–OR	C–OH	C–C	C–NHR
$D_{C\text{–}Nu}$ (kcal mol^{-1})	61.7	76.0	82.0	101.8	103.2
	$S_N{}^X$ type reaction			$S_N{}^H$ reaction	

from 87 to 127 kcal mol^{-1}. Moreover, the standard potential for oxidation of the fluoride ion F^-, $E^0{}_{(F^{\cdot}/F^-)}$, is estimated to be between 2.59 and 2.62 V in DMF at 298 K.

Finally, thermodynamic study explains the operating mechanism ($S_N{}^H$ or $S_N{}^X$) in terms of standard potentials, as well as BDE values by comparison of relative stabilities of the σ^H-complex radicals.

6 Electrochemical C–H Functionalization of Heteroarenes

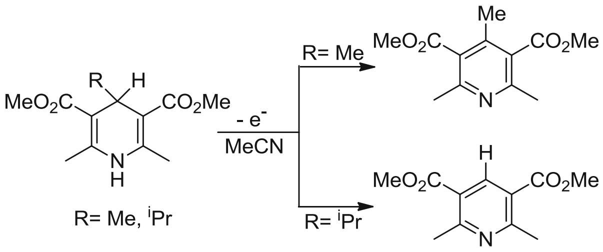
Anodic addition appears to be the main electrochemical method used for direct nucleophilic functionalization of C(sp^2)-bonds in heteroarenes. An excellent review summarizes all these studies [82]. Especially important area for the application of this methodology is preparative electrochemical oxidation of 4-alkyl-substituted 1,4-dihydropyridines (Scheme 24) [100]. Indeed, the electrolysis of 4-methyl substituted 1,4-dihydropyridine in acetonitrile in a divided cell on a platinum electrode at potential 1.2 V vs. SCE results in the formation of dimethyl 2,4,6-trimethylpyridin-3,5-dicarboxylate in 96% yield through cleavage of the C–H bond. Contrary to that, oxidation of 4-*iso*-propyl analogue of the same 1,4-dihydropyridine affords dimethyl 2,6-dimethylpyridin-3,5-dicarboxylate in 93% yield due to the elimination of the *iso*-propyl group from C-4 (cleavage of the C–C bond) (Scheme 24).

Preparative electrochemical transformations of 2,2′-bithiophene provide an original way to mono- and dipyridinyl substituted products, depending on the applied potentials (Scheme 25) [101].

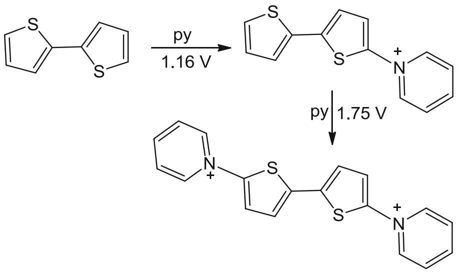
The S_NAr reactions of heteroarenes can be realized in a similar manner, as in the series of arenes [71, 82]. These nucleophilic reactions are analogous to electrochemical $S_N{}^H$ transformations of arenes [22, 24, 25]. Terrier and co-workers considered an opportunity for electrochemical methoxylation of 4,6-dinitrobenzofuroxan by action of the methoxide ion via the S_NAr mechanism [21]. The intermediate σ^H-complex formed was oxidized successfully into the corresponding substitution product. Analogously, the formation of heteroaromatic amines has been suggested to occur via intermediacy of the corresponding amino adducts, as exemplified by the oxidation of the σ^H-complex derived from the reaction of pyrimidine with $NH_2{}^-$ (Scheme 26) [3, 102–104].

Using the electrochemical methodology, we have performed cyanation of 2-nitrothiophene [22], aminations of 5-nitrothiophene-2-carbonitrile and 2-chloro-2-nitropyridine [24], and C-arylation of ketones with 2-chloro-2-nitropyridine [25] (Scheme 27).

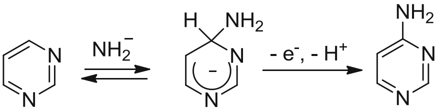
Scheme 24 Products derived from oxidation of 1,4-dihydropyridines in MeCN



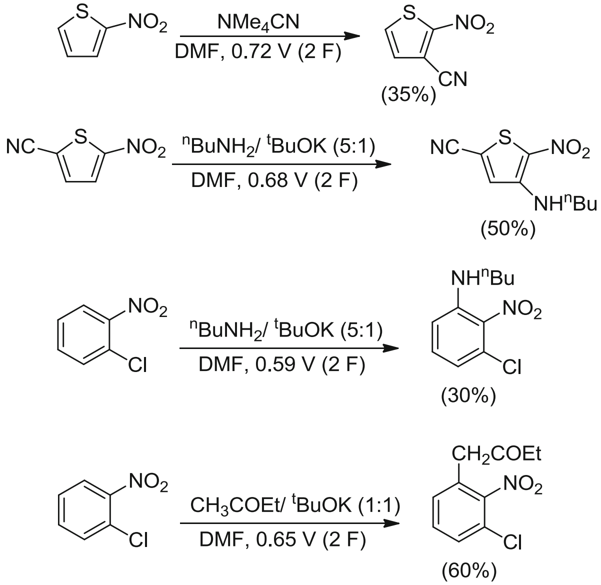
Scheme 25 Products derived from the anodic addition reactions of dithiophene in pyridine



Scheme 26 The S_N^H amination of pyrimidine



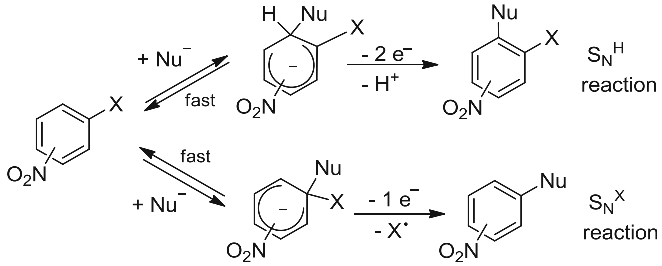
Scheme 27 Yields of products derived from electrochemical S_N^H reactions



The mechanism of these transformations is in agreement with that reported for the electrochemical S_N^H process (Schemes 5 and 19). All these reactions result in the formation of S_N^H products (yields are varied between 30 and 60%), and recover the starting aromatic compounds. The results are interesting enough to continue with a more extensive research on electrochemical S_N^H reactions of these heteroarenes.

7 Conclusion

The data in use for the electrochemical methodology in the chemistry of arenes and hetarenes allow to suggest the following general scheme for nucleophilic aromatic substitutions.



Electrochemical S_N^H and S_N^X reactions

According to this scheme the step 2 is realized by means of electrochemical oxidation of intermediate σ-complexes through the loss of one electron (S_N^X reaction) or two electrons (S_N^H reaction). These electrochemical oxidations proved to occur at different potentials (depending on the starting arene, nucleophile, and type of the intermediate σ-complex). It is worth to note that the oxidation peak potentials for σ^X-complexes are higher than those for the corresponding σ^H-complexes, and by using the correct potential one can obtain the “desired” substitution product.

In general, electrochemical C–H functionalization of arenes and heteroarenes has been developed, as a new synthetic route to structurally modified aromatics. A number of S_N^H transformations, such as cyanation, amination, C-arylation of ketones, alkylation, and phosphorylation have been performed by reacting arenes or heteroarenes with the cyanide ion, amines, ketones, RM and tetraalkylborate ions, and phosphorous compounds as nucleophiles, respectively.

In many cases electrochemistry proved to be a powerful tool to activate the S_NAr reactions. The cathodic reduction in aromatic compounds, prior to their interaction with nucleophilic reagents, is a new essential step of the S_NAr reactions. Moreover, a basic thermodynamic study explains (BDEs values of C–Nu vs. C–H), why F^-, ^-OH, ^-OR, and ^-SR nucleophiles do not react with arenes or heteroarenes.

In conclusion, it is worth to mention that several advantages of the electrochemical S_NAr reactions, such as a low cost and availability of reagents, atom economy, and high yields provide a good environmentally friendly basis for C–H functionalization of arenes and heteroarenes.

Finally, solvent is one of the important features of the S_NAr reactions. Changes in polarity of solvents, their protonation ability, electrical conductivity and other properties affect the nature of substitution products, as well as the time required to complete the reaction. The electrochemical method, which has first been used in classical organic solvents, should be extended to room temperature ionic liquids (RTILs). Recent results reported in the literature [105] show the feasibility of the $S_N{}^H$ and $S_N{}^X$ reactions in the $BMIM^+$ family of solvents. The mechanism and yields of substitution products are comparable with those obtained in the classic solvents.

References

1. Miller J (1968) Aromatic nucleophilic substitution. Elsevier, Amsterdam
2. Terrier F (1991) Nucleophilic aromatic displacement. Wiley-VCH, Welheim
3. Chupakhin ON, Charushin VN, van der Plas H (1994) Nicleophilic aromatic substitution of hydrogen. Academic, San Diego
4. Makosza M (1983) Current trends in organic synthesis. Pergamon, New York
5. Makosza M (2010) Chem Soc Rev 39:2855
6. Petrosyan VA (2011) Mendeleev Commun 21:115
7. Makosza M, Winiarski J (1987) Acc Chem Res 20:282
8. Haglund O, Nilsson M (1994) Synthesis 242
9. Terrier F, Goumont R, Pouet, MJ, Hallé JC (1995) J Chem Soc Perkin 1 1629
10. Makosza M, Wojciechowski K (1997) Liebigs Ann Chem 1805
11. Makosza M, Ziobrowski T, Serebriakov M, Kwast A (1997) Tetrahedron 53:4739
12. Makosza M (1998) Tetrahedron 54:6811
13. Makosza M, Lemek T, Kwast A (1999) Tetrahedron Lett 40:7541
14. Halama A, Kaválek J, Machacek V, Weidlich T (1999) J Chem Soc Perkin 1 1839
15. Halama A, Machacek V (1999) J Chem Soc Perkin 1 2495
16. Katrizky AR, Laurenzo KS (1986) J Org Chem 51:5039
17. Katrizky AR, Laurenzo KS (1988) J Org Chem 53:3978
18. Cervera M, Marquet J (1996) Tetrahedron Lett 37:759
19. Makosza M, Bialecki M (1998) J Org Chem 63:4878
20. Huertas I, Gallardo I, Marquet J (2000) Tetrahedron Lett 41:279
21. Moutiers G, Pinson J, Terrier F, Goumont R (2001) Chem Eur J 7:1712
22. Gallardo I, Guirado G, Marquet J (2001) Chem Eur J 7:1759
23. Gallardo I, Guirado G, Marquet J (2002) J Org Chem 67:2548
24. Gallardo I, Guirado G, Marquet J (2002) Eur J Org Chem 251
25. Gallardo I, Guirado G, Marquet J (2002) Eur J Org Chem 261
26. Gallardo I, Guirado G, Marquet J (2003) J Org Chem 68:631
27. Gallardo I, Guirado G, Marquet J (2003) J Org Chem 68:7334
28. Cruz H, Gallardo I, Guirado G (2011) Eur J Org Chem 7378
29. Gallardo I, Guirado G, Marquet J (2002) Chem Commun 2638
30. Gallardo I, Guirado G (2008) Eur J Org Chem 2463
31. Byrne WE, Fendler EJ, Fendler JH, Griffin CE (1967) J Org Chem 32:2506

32. Andrieux CP, Savéant JM (1986) Investigation of rates and mechanism of reactions. In: Bernasconi CF (ed) Techniques of chemistry, vol 6. Wiley, New York
33. Bard AJ, Faulkner LR (2001) Electrochemical methods. Wiley, New York
34. Melloni GJ (1992) J Org Chem 57:1444
35. Gallardo I, Guirado G, Marquet J (2000) J Electroanal Chem 488:64
36. Sosonkin IM, Strogov GN, Kamisnskii AY, Troshin GE, Lakomov FF (1978) Zh Org Khim 15:1895
37. Rusell CA, Chen P, Kim BH, Rajaratnam R (1997) J Am Chem Soc 119:8795
38. Amatore C, Savéant JM (1979) J Electroanal Chem 21:102
39. Machacek V, Lycka A, Nadvornik M (1985) Coll Czech Chem Commun 50:2598
40. Gallardo I, Guirado G, Marquet J, Vilà N (2007) Angew Chem Int Ed 46:1321
41. Atkins J, Gold V, Wassef WN (1983) J Chem Soc Perkin 2 1197
42. Clark JH (1980) Chem Rev 80:429
43. Huertas I, Gallardo I, Marquet J (2000) Tetrahedron Lett 43:279
44. Hamana M, Iwasaki G, Saeki S (1982) Heterocycles 17:177
45. Huertas I, Gallardo I, Marquet J (2001) Tetrahedron Lett 42:3439
46. Wrobel Z, Makosza M (1992) Pol J Chem 66:2005
47. Strauss MJ, Schran HF, Bard R (1973) J Org Chem 38:3394
48. Strauss MJ, Taylor SPB (1973) J Org Chem 38:856
49. Buncel E, Dust JM, Manderville RA (1996) J Am Chem Soc 118:6072
50. Frank H, Stadelhofer JW (1987) Industrial aromatic chemistry: raw materials, processes, and products. Springer, Berlin
51. Traynelis VJ, MacSweeney JY (1966) J Org Chem 31:243
52. Russel GA, Weiner SA (1966) J Org Chem 31:248
53. Makoska M, Winiarski J (1980) J Org Chem 45:1535
54. Buncel E, Dust JM, Terrier F (1995) Chem Rev 95:2262
55. Makosza M, Stalinski K (1990) Pol J Chem Res 73:282
56. Severin T (1958) Angew Chem Int Ed 70:164
57. Severin T, Schmitz R (1963) Chem Ber 96:3081
58. Artamkina GA, Egorov MP, Beletskaya IP (1982) Chem Rev 82:427
59. Bartoli G, Leardini R, Lelli M, Rosini G (1977) J Chem Soc Perkin 1 8:884
60. Kienzle F (1978) Helv Chim Acta 61:449
61. Bartoli G, Leardini R, Medici A, Rosini G (1978) J Chem Soc Perkin 1 7:692
62. Bartoli G, Bosco M, Baccolini G (1980) J Org Chem 45:522
63. Makosza M, Surowiec M (2001) J Organomet Chem 64:167
64. Shifman A, Palani N, Hoz S (2000) Angew Chem Int Ed 39:944
65. Taylor RP (1970) J Org Chem 35:3578
66. Amatore C, Gareil M, Savéant JM (1983) J Electroanal Chem 147:1
67. Amatore C, Pinson J, Savéant JM, Thiébault A (1981) J Am Chem Soc 103:6930
68. Amatore C, Gareil M, Oturan M, Pinson J, Savéant JM, Thiébault A (1986) J Org Chem 51:3757
69. Fleish H (2002) Breast Cancer Res 4:30
70. Andujar Sánchez CM, Iglesias MJ, García López J, Pérez Álvarez IJ, López Ortín F (2006) Tetrahedron 62:3648
71. Makosza M, Wojciechowski K (2004) Chem Rev 104:2631
72. Makosza M, Sulikowski D (2009) J Org Chem 74:3827
73. Onys'ko PP, Gololobov YG, Prokopenko VP (1977) Dokl Akad Nauk SSSR 237:105
74. Onys'ko PP, Gololobov YG (1979) Z Obshch Khim 49:39
75. Onys'ko PP, Gololobov YG (1980) Z Obshch Khim 50:729
76. Pinson J, Savéant JM (1978) J Am Chem Soc 100:1506
77. Savéant JM (1994) Tetrahedron 50:10117
78. Amatore C, Pinson J, Savéant JM, Thiebault A (1982) J Am Chem Soc 104:817

79. Amatore C, Savéant JM, Combellas C, Robveille S, Thiebault A (1985) J Electroanal Chem 184:25
80. Amatore C, Savéant JM, Combellas C, Robveille S, Thiebault A (1986) J Am Chem Soc 108:4754
81. Eberson L, Schäfer H (1971) Organic electrochemistry. Springer, New York
82. Shchepochkin AV, Chupakhin ON, Charushin VN, Petrosyan VA (2013) Russ Chem Rev 82:747
83. Yoshida K (1984) Electro-oxidation in organic chemistry: the role of cation-radicals as synthetic intermediates. Wiley, New York
84. Lund H, Hammerich O (2001) Organic electrochemistry. Marcel Dekker, New York
85. Parker VD (1970) Acta Chem Scand 24:2757
86. Parker VD (1970) Acta Chem Scand 24:2775
87. Horii D, Atobe M, Fuchigami T, Marken F (2006) J Electrochem Soc 153:D143
88. Zeng CC, Ping DW, Hu LM, Song XQ, Zhong RG (2010) Org Biomol Chem 8:2465
89. Bai YX, Pinga DW, Little RD, Tian HY, Hu LM, Zeng CC (2011) Tetrahedron 67:9334
90. Andrieux CP, Savéant JM, Tallec A, Tardivel A, Tardy C (1997) J Am Chem Soc 119:2420
91. Andrieux CP, Combellas C, Kanoufi F, Savéant JM, Thiebault A (1997) J Am Chem Soc 119:9527
92. Savéant JM (1992) J Am Chem Soc 114:10595
93. Liu WZ, Bordwell FG (1996) J Org Chem 61:4778
94. Wayner DDM, Parker VD (1993) Acc Chem Res 26:287
95. Froese RDJ, Morokura K (1999) J Phys Chem 103:4580
96. Luo YR, Homes JL (1994) J Phys Chem 98:303
97. van Scheppingen W, Dorrestijn E, Arends I, Mulder P (1997) J Phys Chem 101:5404
98. Andrieux CP, Farriol M, Gallardo I, Marquet J (2002) J Chem Soc Perkin 2 985
99. Chamberlin R, Crampton MR, Stevens JA (1993) J Chem Soc Perkin 2 1:75
100. Turovska B, Gob I, Turovskis I, Grinberga S, Belyakov S, Stupnikova S, Liepinsh E, Stradins J (2008) Chem Heterocycl Comp 44:1483
101. Li E, Kamata K, Kawai T, Abe J, Iyoda T (2002) J Chem Soc Perkin 1 1135
102. Chupakhin ON, Charushin VN, van der Plas H (1988) Tetrahedron 44:1
103. van der Plas H (2004) Adv Heterocycl Chem 86:1
104. Gulevskaya AV, Pozharskii AF (2007) Adv Heterocycl Chem 93:57
105. Cruz H, Gallardo I, Guirado G (2011) Green Chem 13:2531