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Cathodically activated nucleophilic aromatic substitution of hydrogen: a novel electrochemical mechanism†

Iluminada Gallardo,* Gonzalo Guirado and Jordi Marquet
Departament de Química, Universitat Autònoma de Barcelona, 08193-Bellaterra Barcelona, Spain.
E-mail: Iluminada.Gallardo@uab.es; Fax: 00 34 935812920; Tel: 00 34 935812137

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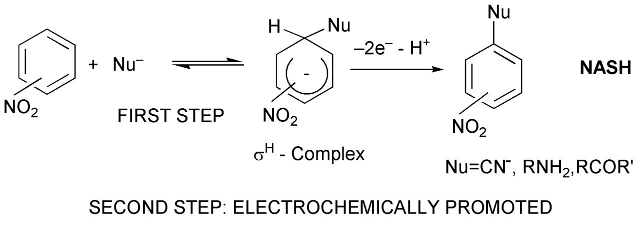
Cathodically activated nucleophilic aromatic substitution of hydrogen (S_NAr^H) is reported for the first time; the 1,3,5-trinitrobenzene radical anion reacts with the nucleophile *N*-methylformamide leading to high yields of the σ^H-complex radical anion; this intermediate can be easily oxidised electrochemically by means of a three-electron mechanism giving rise to the nucleophilic aromatic substitution product (NASH product) in good yield.

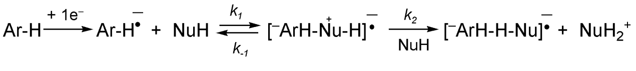
The development of new synthetic routes to produce chemicals of great interest requires not only atomically efficient chemical reactions but also environmentally favourable routes. According to these two premises recently we have focussed our attention on the anodically activated nucleophilic aromatic substitution of hydrogen reaction (Scheme 1)[1,2] NASH reactions require the replacement of a hydride ion (H^-) by a nucleophile, and for many years, the main drawbacks associated with the non-activated synthetic procedures were low yields and lack of generality. Activation of NASH reactions has been achieved by the use of chemical oxidants,[2–3] but the their range of potential is narrow, and some of them are inherently hazardous.[2–4] Hence, the use of electrochemical techniques is very attractive. The electrochemical anodical approach resulted in high yields, when cyanide,[5] alkylamines[6a] and ketones[6b] were used as nucleophiles. (Scheme 1).

Electrochemical oxidations activate as well as improve the decomposition of the σ-complexes. This was previously denoted electrochemical activation.[7] In this communication the activation is based on an alternative mechanism, that we denote cathodically promoted activation. The generation of a radical anion by means of electrochemistry is the novel concept of activation that we propose in this report. A related mechanism has been proposed in our group for some special S_NAr reactions,[8,9] denoted as reductively activated 'polar' mechanism.

As far as we are aware this is the first report of a S_NAr^H cathodically promoted process. In this case the electrochemical activation appears to correspond to the second step of the $S_{RN}2$ mechanism.[10] This is the key step of the mechanism, where a radical anion reacts with a nucleophile. The present study aims : (a) to establish the mechanism for the cathodically activated S_NAr^H and to demonstrate that the $S_{RN}2$ mechanism[10] is operating in its key step (the nucleophilic attack on the radical anion, step 2) (Scheme 2). (b) To develop a new electrochemical approach to the synthesis of nitroaromatic amides.



Scheme 1



$$\mathrm{Ar\text{-}H} \xrightarrow{+1e^-} \mathrm{Ar\text{-}\overset{-}{H^{\bullet}}} + \mathrm{NuH} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [^-\mathrm{ArH\text{-}\overset{+}{N}u\text{-}H}]\overset{-}{^{\bullet}} \xrightarrow[\mathrm{NuH}]{k_2} [^-\mathrm{ArH\text{-}H\text{-}Nu}]\overset{-}{^{\bullet}} + \mathrm{NuH_2^+}$$

" First Cathodically Activated Step "

Scheme 2

We tested the reaction between certain radical anions of nitroaromatic compounds and neutral nucleophiles. The choice of the reactants appears to be crucial. Thus, 1,3,5-trinitrobenzene[11] **1**, as a nitroaromatic substrate, and *N*-methylformamide[6,12] (nucleophile/solvent), were initially choosen as the most suitable reactants.

Cyclic voltammetry (CV) and controlled potential electrolysis linked with CV experiments were carried out. The first voltammogram (Fig. 1a) shows the electrochemical behaviour of **1** in DMF. Note that no oxidation waves are found in the initial anodic scan, whereas a chemically[13] irreversible one-electron wave appears at −0.53 V. In the reverse anodic scan an oxidation peak appears at 0.27 V. It has been demonstrated that this wave is associated with the reactivity of **1** radical anion.[13] Cyclic voltammetric experiments shown in Fig. 1b, c and d were performed using *N*-methylformamide as solvent. Fig. 1b shows, starting with a cathodic scan, a partially reversible one-electron wave ($E° = -0.50$ *vs.* SCE) corresponding to the formation of the radical anion of **1**. In the oxidation scan, two peaks appear at 0.27 and 1.12 V. The first should correspond to the own reactivity of the anion radical of **1**, while the second must correspond to the oxidation of a σ^H-complex[14] formed by the addition of *N*-methylformamide to **1**. A similar behaviour is obtained when the first scan is an anodic scan (Fig. 1c) , an

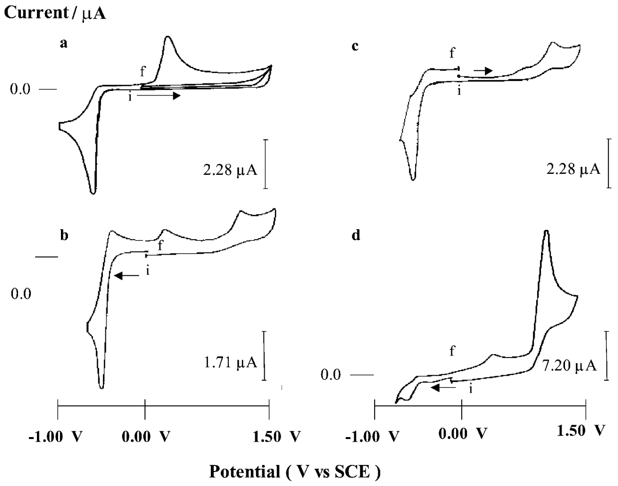


Fig. 1 (a) Cyclic voltammetry (CV) of **1** (10.0 mM) in DMF–0.1 M *n*-Bu_4NBF_4 at 10 °C. The scan potential range is: 0.00/1.50/−1.00/0.00 V (two cycles). (b) CV of **1** (10.0 mM) in *N*-methylformamide–0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan range: 0.00/−0.70/+1.50/0.00 V. (c) CV of **1** (10.0 mM) in *N*-methylformamide–0.1 M *n*-Bu_4NBF_4 at 10 °C. Scan range: 0.00/+1.50/−0.70/0.00 V. (d) CV of a solution of **1** (20.0 mM) in DMF–0.1 M *n*-Bu_4NBF electrolysed at −0.70 V after the passage of 1 F. Scan range: 0.00/−0.70/+1.50/0.00 V *vs.* SCE. Scan rate 1 V s^{-1}. Working electrode: glassy carbon electrode (0.05 mm diameter).

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† Electronic supplementary information (ESI) available: Table S1. See http://www.rsc.org/suppdata/cc/b2/b207168a/

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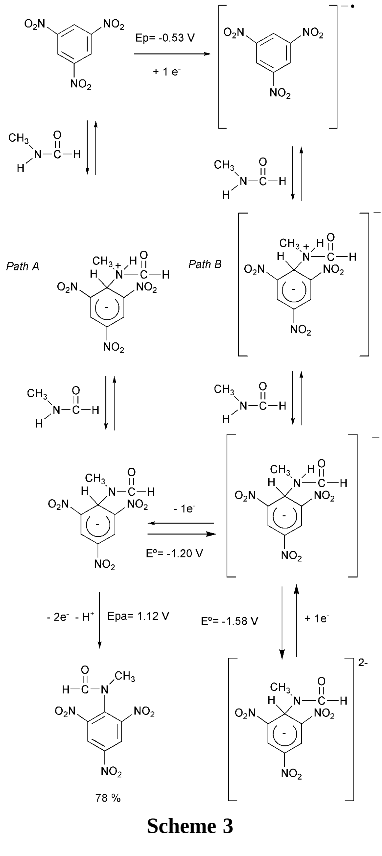
irreversible two-electron oxidation wave is obtained at the same potential value (E_{pa} = 1.12 V). A controlled potential electrolysis of this solution at 1.3 V leads to 20% of the nucleophilic aromatic substitution of hydrogen (NASH) product after the passage of 2 F. These results can be easily rationalised taking into account the thermal process described in Scheme 3 (Path A). A reversible addition of *N*-methylformamide to **1** leads to the σ^H-complex (ESI, Table S1, entry 1†). Then if an electrolysis of the σ^H-complex is performed, the NASH product will be obtained.[15] However, it is important to note that starting with a cathodic scan two one-electron reversible waves appear when the scan range reaches −2.00 V. The first at −1.20 V corresponds to reduction of σ^H-complex, whereas the second at −1.68 V corresponds to reduction of σ^H-complex radical anion (Scheme 3, Path B). In order to verify our hypothesis, a sample of **1** in *N*-methylformamide was electrolysed at −0.70 V. The controlled potential electrolysis was stopped after the passage of 1 F and a cyclic voltammogram of the mixture registered (Fig. 1d). During an oxidation scan an irreversible two-electron wave at 1.12 V was observed corresponding to the electrochemical oxidation of the σ^H-complex. After an exhaustive oxidative controlled-potential electrolysis at 1.30 V, methyl-2,4,6-trinitroanilinomethanone (NASH product) was obtained in excellent yield (80%).[16] These results undoubtedly indicate that oxidation of the main intermediate, oxidation of which leads to the NASH product, is the σ^H-complex radical anion formed initially. The formation of the σ^H-complex radical anion by direct reaction of a radical anion and a nucleophile is the key step of the elusive $S_{RN}2$ mechanism. Taking into account that there is no much difference between Fig. 1b and c as concerns to the height of the wave at 1.22 V relative to the wave at −0.53 V as well as that no electrons should be consumed to produce the radical anion of **1**, we can deduce that the attack of the nucleophile on the radical anion is very slow (even slower than the time scale of CV).

At this point, and knowing that the reaction was cathodically activated, we were ready to extend the methodology (reduction–oxidation electrolysis) to other nitroaromatic compounds (3,5-dinitrobenzonitrile (**2**), 1,3-dinitro-5-trifluoromethylbenzene (**3**), 1,3-dinitronaphthalene (**4**)). Preliminary results are gathered in Table S1.† In column 2, the results of the thermal reaction in terms of nucleophilic attack are given. Note the low percentages (near zero) in contrast to the high percentages obtained when the mixture is analysed after a reductive electrochemical activation process. In all cases, it is necessary to activate cathodically the nucleophilic attack to obtain the substituted product (NASH product) in good yields (30–80%). The synthetic approach studies seems to be very clean and chemoselective. The only product obtained is the substitution product[16] apart from the unreacted starting material, which can be easily recovered at the end of the process. In conclusion, electrochemical techniques are very useful in the field of nucleophilic aromatic substitution reactions. A new mechanism—cathodically activated S_NAr^H—has been established. Apart from the mechanistic value, it is important to remark its synthetic value. The general advantages of the method: (a) low-cost and availability of the reagents, (b) atom economy, (c) high yields, (d) environmentally favourable, (e) continuous reduction–oxidation process; makes the use of this potential synthetic electrochemical route very attractive.We are currently working in establishing the scope and limitations of this methodology. A full account will be published in the near future.



Scheme 3

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11 1,3,5-Trinitrobenzene is chosen as a nitroaromatic substrate due to its high electron deficiency and thus the radical anion will still be electron-deficient.

12 *N*-Methylformamide is chosen as a solvent/nucleophile because of its low nucleophilicity. Thus, an excess of nucleophile is necessary for promoting the nucleophilic attack (see ref. 6). In addition, the *N*-methylformamide is an appropriate solvent for carrying out electrochemical studies due to its high dielectric constant value (ε = 182), as well as for stabilizing radical anions. Connecting the characteristics of **1** radical anion (electron-deficient substract) and *N*-methylformamide (poor nucleophile), the repulsion effect should be low, thus allowing the reaction between a radical anion and a nucleophile.

13 The radical anion of **1** is not stable in DMF. It reacts following a second order reaction. A dimeric structure has been isolated and characterised: I. Gallardo, G. Guirado and J.Marquet, submitted results.

14 σ^H-Complexes have been widely studied electrochemically in our group (see refs. 3–7). The peak potential value of a TNB-σ^H-complex is around 1.1 V *vs.* SCE. Spectroscopic data (the solution became red) also indicates the presence of a TNB-σ^H-complex.

15 Electrochemical oxidation of σ^H-complexes leads to a NASH product after the passage of 2 F. [3–7] The number of Farads was calculated taking into account the percentage of nucleophilic attack to calculate the σ^H-complex concentration.

16 Apart from the substitution product and the reactant a low percentage (5–10%) of trinitroaniline was obtained (see ref. 4). The same result was obtained for the other reactions in Table S1†.