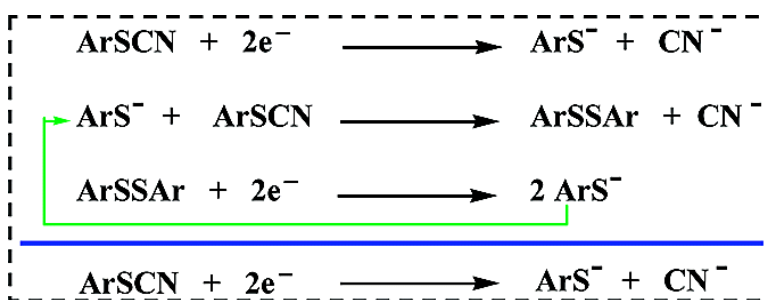


A Unique Autocatalytic Process and Evidence for a Concerted-Stepwise Mechanism Transition in the Dissociative Electron-Transfer Reduction of Aryl Thiocyanates

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A Unique Autocatalytic Process and Evidence for a Concerted-Stepwise Mechanism Transition in the Dissociative Electron-Transfer Reduction of Aryl Thiocyanates

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Abstract: Electrochemical reduction of *p*-methyl-, *p*-methoxy-, and 3,5-dinitrophenyl thiocyanates as well as *p*-methyl- and *p*-methoxyphenyl disulfides was investigated in acetonitrile at an inert electrode. This series of compounds reveals a striking change in the reductive cleavage mechanism of the S–CN bond in thiocyanates as a function of the substituent on the aryl ring of the aryl thiocyanate. With nitro substituents, a stepwise mechanism, with an anion radical as the intermediate, takes place. When electron-donating groups (methyl and methoxy) are present, voltammetric as well as convolution analyses provide clear evidence for a transition between the concerted and stepwise mechanisms based on the magnitude of the transfer coefficient α . Moreover, a very interesting autocatalytic process is involved during the electrochemical reduction of these compounds. This process involves a nucleophilic substitution reaction on the initial aryl thiocyanate by the electrochemically generated arenethiolate ion. As a result of this unusual process, the electrochemical characteristics (peak potential and peak width) of the investigated series are concentration dependent.

Introduction

The biological activity of aryl thiocyanates as antiviral, antifungal, and antibacterial agents is well-known.¹ Their activity is believed to arise from their ability to readily pass through the cell walls, consisting of loosely knit fibrils containing proteins, polysaccharides, and lipids, and then to react with intracellular species such as glutathione and cellular thiol groups, causing the disruption of the cellular metabolism.² The mechanism of the intracellular reaction has not been fully elucidated but has been shown to result in the dissociation of the S–CN bond.³ Glutathione is a good electron donor (values for the standard oxidation potential range from -0.20 to -0.26 V),⁴ and an electron transfer between arenethiolates and glutathione may be possible. Aryl thiocyanates are also good precursors for the synthesis of valuable chemicals.⁵ For instance, they were used as electrophiles in the synthesis of difluorosulfides, which show activity against HIV1.⁶ Their chemical reduction by SmI_2

has also been reported. In the presence of aryl halides, the reaction yields mixed aryl sulfides and diaryl disulfides,^{5a} while, in the presence of alkylating agents, it yields arylalkyl sulfides and diaryl disulfides.^{5b} It has been shown in both cases that the ratios of sulfides to disulfides depend on the concentration of SmI_2 . The mechanism is not fully understood in either case.

In principle, the electrochemical reduction of aryl thiocyanates should lead to the dissociation of the S–CN bond. Expecting the reduction of these compounds to be easier than that of the corresponding aryl halides and knowing that the leaving group (CN^-) has a standard oxidation potential around 2.2 V/SCE in DMF,⁷ we anticipated that these compounds would show interesting electrochemical behavior, displaying multiple reaction pathways resulting from the reductive cleavage of this bond by single electron transfer (ET).

In electrochemical studies of organic compounds, a widely investigated process is the dissociative ET where a chemical bond is broken as a result of a first electron transfer. When the one electron-transfer product is an intermediate, the ET follows a stepwise mechanism and can be described by the Hush–Marcus theory when the initial electron-transfer step is the rate-

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- (1) For example, see: Owens, R. G. In *Fungicides: An Advanced Treatise*; Torgeson, D. C., Ed. Academic Press: New York, 1967; Chapter 5, p 147.
- (2) Lukens, R. J. *Chemistry of Fungicidal Action*; Chapman and Hall: London, 1971.
- (3) Thiocyanates have been shown to liberate cyanide in the presence of enzyme bound to glutathione. (a) Habig, W. H.; Keen, J. H.; Jakby, W. B. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 501. (b) Keen, J. H.; Habig, W. H.; Jakby, W. B. *J. Biol. Chem.* **1976**, *251*, 6183. (c) Degani, Y.; Patchornick, A. *Biochemistry* **1974**, *13*, 1.
- (4) (a) Aslund, F.; Berndt, K. D.; Holmgren, A. *J. Biol. Chem.* **1997**, *272*, 30780. (b) Szajweski, R. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2011. (c) Gilbert, H. F. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1990**, *63*, 69. (d) Rost, J.; Rapoport, S. *Nature* **1964**, *201*, 185. (e) Scott, E. M.; Duncan, I. W.; Ekstrand, V. *J. Biol. Chem.* **1963**, *238*, 559.

- (5) (a) Still, I. W. J.; Toste, F. D. *J. Org. Chem.* **1996**, *61*, 7677. (b) Toste, F. D.; LaRonde, F.; Still, I. W. J. *Tetrahedron Lett.* **1995**, *36*, 2949. (c) Toste, F. D.; Still, I. W. J. *Tetrahedron Lett.* **1995**, *36*, 4361. (d) Toste, F. D.; Still, I. W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7261.
- (6) (a) Billard, T.; Langlois, B. R.; Médebielle, M. *Tetrahedron Lett.* **2001**, *42*, 3463. (b) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65 and references therein.
- (7) Gennaro, A.; Maran, F.; Maye, A.; Vianello, E. *J. Electroanal. Chem. Interfacial Electrochem.* **1985**, *185* (2), 353.

determining step.⁸ On the other hand, when the ET and the bond breaking occur in a concerted manner, Savéant⁹ proposed a model based on the Morse curve picture of bond breaking. This model gives a similar quadratic activation-free energy relationship (eq 1), the difference being the contribution of the bond dissociation energy (BDE) of the fragmented bond to the activation barrier, ΔG_0^\ddagger , which involves only the solvent (λ_0) and the inner (λ_i) reorganization energies for a stepwise mechanism (eq 2). ΔG^\ddagger (the activation free energy), ΔG° (the reaction free energy), and $\Delta G_{0,s}^\ddagger$ and $\Delta G_{0,c}^\ddagger$ (i.e., the activation energy at zero driving force) represent the intrinsic barriers for a stepwise and a concerted ET, respectively.

$$\Delta G^\ddagger = \Delta G_0^\ddagger \left(1 + \frac{\Delta G^\circ}{4\Delta G_0^\ddagger} \right)^2 \quad (1)$$

$$\Delta G_{0,s}^\ddagger = \frac{\lambda_i + \lambda_0}{4} \quad \text{and} \quad \Delta G_{0,c}^\ddagger = \frac{\lambda_0 + \text{BDE}_{\text{R-X}}}{4} \quad (2)$$

In cyclic voltammetry (CV), the peak characteristics can be used efficiently to obtain accurate mechanistic, kinetic, and thermodynamic data by application of the adequate theory. When the single ET product cannot be detected experimentally (high scan rate¹⁰ and homogeneous catalysis^{10,11}), the transfer coefficient (α), which is directly related to the intrinsic barrier (eq 3), is a sensitive probe of the mechanistic nature of the first electron transfer in dissociative processes. The transfer coefficient can be determined from the electrochemical peak characteristics (peak width, $E_p - E_{p/2}$)¹² or the variation of the peak potential, E_p , with the scan rate, ν .¹³ In a concerted mechanism, a value significantly lower than 0.5 is expected, whereas an α value close to or higher than 0.5 is expected in the case of a stepwise mechanism.

$$\alpha = \frac{\partial \Delta G^\ddagger}{\partial \Delta G^\circ} = \frac{1}{2} \left(1 + \frac{\Delta G^\circ}{4\Delta G_0^\ddagger} \right) \quad (3)$$

The dissociative ET model has been successfully tested for a number of types of organic compounds.¹⁴ Equation 3 predicts

- (8) For example, see: (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966. (b) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 979. (c) Hush, N. S. *J. Chem. Phys.* **1958**, *28*, 962. (d) Hush, N. S. *Trans. Faraday Soc.* **1961**, *57*, 557. (e) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155. (f) Marcus, R. A. *J. Chem. Phys.* **1965**, *43*, 679. (g) Marcus, R. A. Theory and Applications of Electron Transfers at Electrodes and in Solution. In *Special Topics in Electrochemistry*; Rock, P. A., Ed.; Elsevier: New York, 1977; pp 161–179. (h) Marcus, R. A. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 7. (i) Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265.
- (9) (a) Savéant, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 6788. (b) Savéant, J.-M. *Acc. Chem. Res.* **1993**, *26*, 455. (c) Savéant, J.-M. Dissociative Electron Transfer. In *Advances in Electron-Transfer Chemistry*; Mariano, P. S., Ed.; JAI Press: New York, 1994; Vol. 4, pp 53–116. (d) Savéant, J.-M. Electron Transfer. Bond Breaking and Bond Formation. In *Advances in Physical Organic Chemistry*; Tidwell, T. T., Ed.; Academic Press: New York, 2000; Vol. 35, pp 117–192.
- (10) (a) Andrieux, C. P.; Hapiot, P.; Savéant, J.-M. *Chem. Rev.* **1990**, *90*, 723. (b) Andrieux, C. P.; Hapiot, P.; Savéant, J.-M. *J. Phys. Chem.* **1988**, *92*, 5987.
- (11) Andrieux, C. P.; Savéant, J.-M. Electrochemical Reactions. In *Investigation of Rates and Mechanisms of Reactions, Techniques of Chemistry*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Vol. VI/4E, Part 2, pp 305–390.
- (12) $\alpha = (RT/F)(1.85/E_{p/2} - E_p)$.
- (13) $\partial E_p / \partial \log \nu = -29.5\alpha$ at 20 °C.
- (14) (a) Adcock, W.; Clark, C.; Houmam, A.; Krstic, A. R.; Pinson, J.; Savéant, J.-M.; Taylor, D. K.; Taylor, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 4653. (b) Savéant, J.-M. *Adv. Phys. Org. Chem.* **1990**, *26*, 1. (c) Savéant, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 6788. (d) Andrieux, C. P.; Le Gorande, A.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *112*, 6892. (e) Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 10595. (f) Bertran, J.; Gallardo, I.; Moreno, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 9576.

a linear variation of α with the driving force. However, a few experimental systems have shown a transition between concerted and stepwise mechanisms as a function of the driving force which could easily be controlled in electrochemistry by varying the electrode potential. Similar mechanism transitions have been also reported in homogeneous thermal and photochemical electron-transfer reactions.¹⁵ This behavior demonstrates that the nature of the ET process is not merely dictated by the existence of an intermediate radical anion but rather by the energetic advantage of one process over another. Analyses of the variation of the transfer coefficient with either the scan rate¹⁶ or the potential¹⁷ are the main criteria for such a mechanistic transition. In this particular case, besides the conventional voltammetric analysis, the convolution approach is a powerful tool for studying intricate details of electrode processes. Convolution analysis had been initially reported many years ago¹⁸ but has only recently been used rigorously to explore reaction mechanisms and to provide valuable kinetic and thermodynamic data for several systems.^{17,19} The great advantage with the convolution analysis is that all data points of the voltammetric curve are used in the kinetic analysis and that no assumptions on the ET rate law are made in the analysis of the experimental data. This differs from the conventional voltammetric method where a linear activation–driving force relationship is implicitly assumed.²⁰ We have investigated the electrochemical reduction of a series of aryl thiocyanates. The mechanism of this reaction has been fully elucidated and involves a unique autocatalytic process. The ET mechanism depends on the nature of the substituents on the aryl ring of the thiocyanate used. Moreover, from voltammetric analysis based on the use of the transfer coefficient α , a transition between the concerted and stepwise mechanisms, as a function of driving force, is suggested for aryl thiocyanates with electron-donating substituents. We have also applied convolution analysis to the electrochemical reduction of aryl thiocyanates and have confirmed the ET mechanism transition.

Results and Discussion

Voltammetric Behavior. The electrochemical reduction of *p*-methyl- (**1**), *p*-methoxy- (**2**), 3,5-dinitrophenyl thiocyanate (**3**), and their corresponding disulfides **4**, **5**, and **6** (Chart 1) was studied by CV in acetonitrile, in the presence of tetrabutylammonium tetrafluoroborate (TBAF 0.1 M) at a glassy carbon electrode.

Figure 1 shows cyclic voltammograms corresponding to compounds **1**, **2**, and **3** at 0.2 V/s. Compound **1** (3.26 mM)

- (15) (a) Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **2000**, *122*, 5623. (b) Pause, L.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **2001**, *123*, 4886.
- (16) (a) Andrieux, C. P.; Robert, M.; Saeva, F. D.; Savéant, J.-M. *J. Am. Chem. Soc.* **1994**, *116*, 7864. (b) Pause, L.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1999**, *121*, 7158.
- (17) Antonello, S.; Maran, F. *J. Am. Chem. Soc.* **1997**, *119*, 12595.
- (18) (a) Imbeaux, J. C.; Savéant, J.-M. *J. Electroanal. Chem.* **1973**, *44*, 169. (b) Savéant, J.-M.; Tessier, D. *J. Electroanal. Chem.* **1975**, *65*, 57.
- (19) (a) Antonello, S.; Maran, F. *J. Am. Chem. Soc.* **1999**, *121*, 9668. (b) Antonello, S.; Musumeci, M.; Wayner, D. D. M.; Maran, F. *J. Am. Chem. Soc.* **1997**, *119*, 9541. (c) Donkers, R. L.; Workentin, M. *J. Phys. Chem. B* **1998**, *102*, 401. (d) Donkers, R. L.; Maran, F.; Wayner, D. D. M.; Workentin, M. *J. Am. Chem. Soc.* **1999**, *121*, 7239. (e) Antonella, S.; Formaggio, F.; Moretto, A.; Toniolo, C.; Maran, F. *J. Am. Chem. Soc.* **2001**, *123*, 9577.
- (20) (a) Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 706. (b) Nadjo, L.; Savéant, J.-M. *J. Electroanal. Chem.* **1973**, *48*, 113. (c) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods, Fundamentals and Applications*; Wiley: New York, 1980.

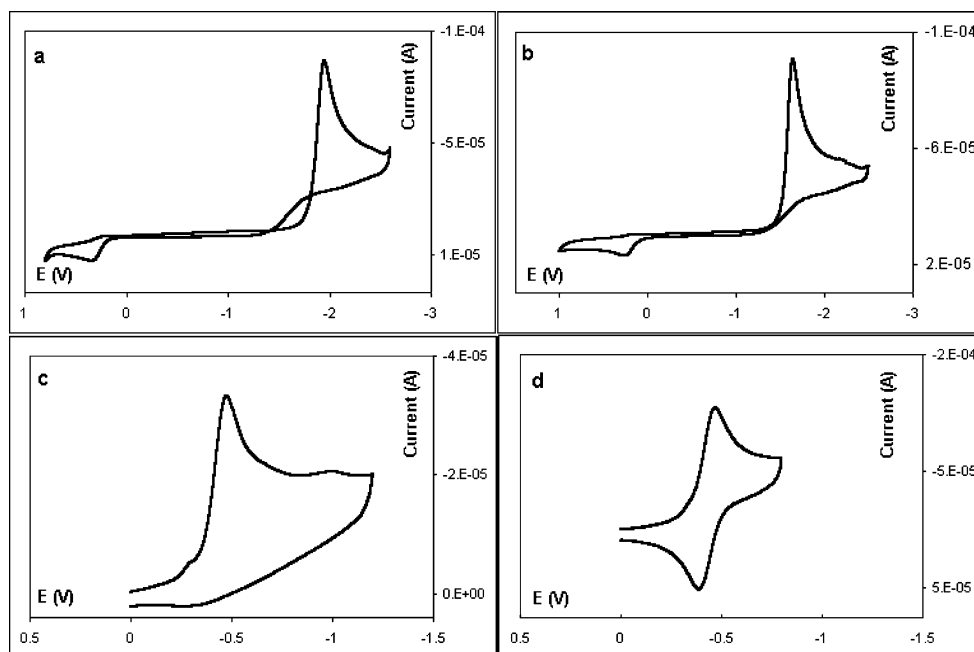
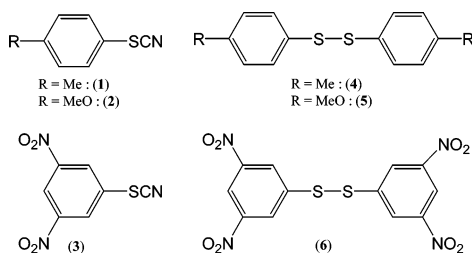


Figure 1. Cyclic voltammetry in $\text{CH}_3\text{CN}/\text{TBAF}$ (0.1 M) at a glassy carbon electrode, $\nu = 0.2$ V/s, temperature = 20°C , of (a) 4- CH_3PhSCN (**1**) 3.26 mM; (b) 4- CH_3OPhSCN (**2**) 3.45 mM; (c) 3,5-dinitroPhSCN (**3**) 2 mM; and (d) 3,5-dinitroPhSCN (**3**) 2 mM at $\nu = 2$ V/s.

Chart 1



displays (Figure 1a) an irreversible reduction peak at a potential of $E_p = -2.55$ V versus the standard oxidation potential of ferrocene ($E_{\text{Fc}/\text{Fc}^{+}}^\circ$).²¹ This reduction peak is very sharp and its width ($E_p - E_{p/2}$), where E_p is the peak potential and $E_{p/2}$ is the half-peak potential, has a value of 60 mV. Upon reversing the scan, we observe a trace crossing. By scanning toward more positive potentials, we observe an irreversible anodic peak at -0.14 V versus $E_{\text{Fc}/\text{Fc}^{+}}^\circ$, corresponding to the oxidation of toluenethiolate as verified by comparison with the cyclic voltammetry of an authentic sample. This CV is very reproducible, indicating that the crossing observed is not ascribed to the electrode material but corresponds rather to the reduction of a more reducible species formed from **1** during the anodic scan.²²

Compound **2** (3.45 M) also displays a sharp cathodic irreversible peak (Figure 1b). This peak appears at -2.27 V versus $E_{\text{Fc}/\text{Fc}^{+}}^\circ$ and is even sharper than the one corresponding to **1** ($E_p - E_{p/2} = 50$ mV). No crossing is seen with this compound, under these conditions, but it is important to note that the reduction peak appears at a potential which is 280 mV less negative than the reduction potential of **1**. This is intriguing, since **2** is expected to be reduced at a slightly more negative potential than **1**. Here again, an oxidation peak corresponding

to *p*-methoxybenzenethiolate, as verified by comparison with an authentic sample, is observed at -0.25 V versus $E_{\text{Fc}/\text{Fc}^{+}}^\circ$.

For both **1** and **2**, the reduction peaks remain irreversible upon increasing the scan rate up to 5000 V/s.

Compound **3** behaves differently in the sense that it shows a reduction peak at -1.15 V versus $E_{\text{Fc}/\text{Fc}^{+}}^\circ$ at 0.2 V/s and no trace crossing at all (Figure 1c). The reduction peak becomes reversible upon increasing the scan rate to 2 V/s (Figure 1d), indicating the intermediacy of a radical anion through a stepwise reduction mechanism. This enables us to calculate the redox potential ($3/3^{\bullet-}$) $E^\circ = -1.10$ V versus $E_{\text{Fc}/\text{Fc}^{+}}^\circ$ and to evaluate the rate constant for the decomposition of $3^{\bullet-}$ as $k = 1 \text{ s}^{-1}$.^{20a}

Trace crossing seen for **1** and **2** at low scan rates indicates the occurrence of an autocatalytic process where a species, easier to reduce than the initial substrate, is continuously produced and reduced at the electrode from the moment the initial substrate is reduced until the trace crossing disappears.^{22b} As a result of this autocatalytic process, the reduction peak is shifted to less negative potentials.^{22b} We will show later that this is the case for **1** and **2**.

Figure 2a shows successive cyclic voltammograms of **1**. While the first scan shows a CV similar to the one described earlier (Figure 1a), the second scan shows a much broader reduction peak at a less negative potential and with no trace crossing at all. The CV of this second scan is identical to the one corresponding to 4,4'-dimethylphenyl disulfide (**4**) shown in Figure 2b. This does not necessarily mean that, at the second scan, there is only disulfide **4** present at the surface of the electrode and no thiocyanate **1**, but since the aryl thiocyanates are good electrophiles and their electrochemical reduction yields the corresponding arenethiolates as seen previously, disulfide **4** will be produced as a result of a nucleophilic substitution of **1** by the arenethiolate (Scheme 1). To provide further evidence for this chemical step, a control experiment has been performed in which tetrabutylammonium phenylthiolate has been added to **1** and the reaction yielded the corresponding diaryl disulfide

(21) Ferrocene was used as an internal reference. It was added, and a run towards positive potentials was performed before each cathodic scan.

(22) (a) Amatore, C.; Pinson, J.; Savéant, J.-M. *J. Electroanal. Chem.* **1980**, *107*, 59. (b) Andrieux, C. P.; Merz, A.; Savéant, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 6097.

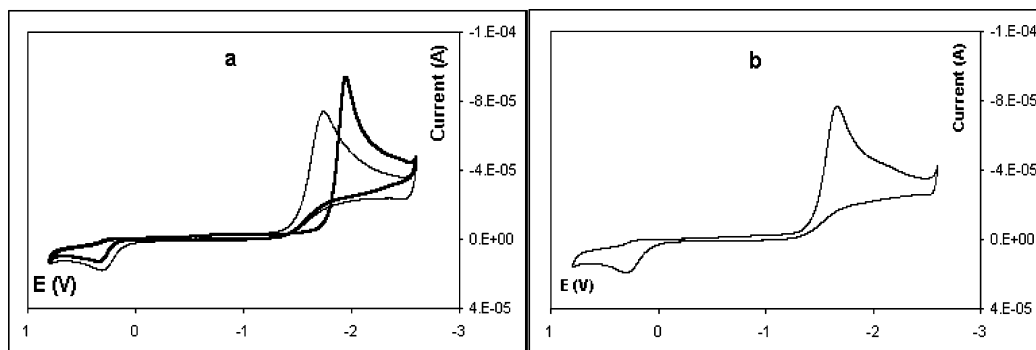
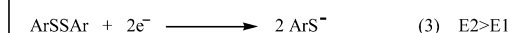
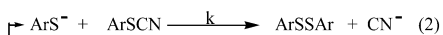
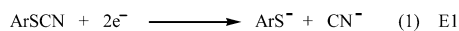


Figure 2. (a) Successive cyclic voltammograms of **1** (3.26 mM), (–) first scan and (–) second scan. (b) Cyclic voltammogram of **4** (3 mM). In CH₃CN/TBAF (0.1 M) at a glassy carbon electrode; $\nu = 0.2$ V/s.

Scheme 1



Scheme 2



4 quantitatively. In such a case, **4** will be immediately reduced, since it is easier to reduce than the corresponding aryl thiocyanate **1** and will thus induce the autocatalytic process through the generation of the thiolate. This autocatalytic process is responsible for the crossing in the CV of **1**. After the first scan, disulfide is generated at the surface of the electrode as a product of the oxidation of the thiolate. In this case, only steps 2 and 3 are taking place and all the thiocyanate **1** is consumed at the reduction peak of the disulfide. This explains the difference between the first and the second successive cyclic voltammograms. In a control reaction, adding catalytic amounts of **4** during the CV study of **1** immediately reproduces the peak shape of the second scan.

The autocatalytic mechanism reported in Scheme 1 is different from the “classical autocatalytic” mechanism, where an anion, produced at the electrode, can transfer an electron to the initial precursor (Scheme 2). This is only possible when both the radical and the anion are chemically stable and can act as a homogeneous redox catalyst system.^{11,22} In this latter case, trace crossing in cyclic voltammetry persists until the anion is oxidized, since as long as the anion is present, the autocatalytic process takes place. This is different from what is seen in Figure 1a, where the trace crossing disappears at a potential similar to the one corresponding to the reduction of the diaryl disulfide, that is, much more negative than the oxidation potential of the arenethiolate anion.

Electrolysis of **1** in CH₃CN at -2 V versus $E_{\text{Fc}^0/\text{Fc}^+}^0$ was performed and was monitored using CV and HPLC. Disulfide **4** was detected during the electrolysis but was totally consumed at the end of the electrolysis. The products of the electrolysis were *p*-toluenethiolate and cyanide anions. Two electrons per molecule of thiocyanate are consumed. The electrolysis of **2** showed similar results. The intermediate formation of **5** and its total disappearance yields *p*-methoxybenzenethiolate. Again, two electrons per molecule are consumed. When the electrolyses were stopped after consumption of the equivalent of one electron

per molecule, for both **1** and **2**, the corresponding diaryl disulfides were formed quantitatively.

These results are in good agreement with the proposed mechanism and indicate that the electrochemical reduction of **1** and **2** is not a simple ECE¹¹ process but does involve the formation of the diaryl disulfide as an intermediate. The formation of the disulfide leaves no doubt about the involvement of the autocatalytic process, as clearly shown in the control experiment described previously.

The proposed mechanism (Scheme 1) can be described by a set of dimensionless partial derivative equations, initial and boundary conditions.²³ This leads to a kinetic dimensionless parameter ($\lambda = RTkC^0/F\nu$) which represents a measure of the competition between the rate-determining step of the autocatalytic process (reaction 2 in Scheme 1) and diffusion. According to this model, the rate of the latter process is expected to be an increasing function of the sweep rate, while that of the former would increase with aryl thiocyanate concentration, since it is a second-order reaction and the autocatalytic process would shift the reduction wave of the aryl thiocyanate to the positive potentials. This is indeed what happens with the aryl thiocyanates.

Figure 3 shows voltammograms of the reduction of **1** in CH₃CN/TBAF (0.1 M) at two different concentrations (0.85 mM and 5 mM) and at different scan rates (0.2 V/s, 2.4 V/s, and 7.2 V/s). For the low concentration (0.85 mM), the crossing seen at 0.2 V/s (Figure 3a₁) is readily eliminated by increasing the scan rate to 2.4 V/s (Figure 3a₂) and to 7.2 V/s (Figure 3a₃). Reaction 2 is not taking place on the time scale of the CV scans at these scan rates for this low concentration. For the higher concentration (5 mM), a higher scan rate is needed to eliminate the crossing and to allow consumption of all the thiocyanate directly at the electrode. At 2.4 V/s (Figure 3b₂), trace crossing is still observed and the autocatalytic process is thus efficient. Moreover, one can clearly see the positive shift of the reduction potential of **1** as C_0 increases confirming again the existence of an autocatalytic mechanism. The difference in the reduction potential of **1** between 0.5 V/s and 80 V/s is about 700 mV, which is too large to be due only to the type of ET mechanism.

(23) $\partial a/\partial \tau = (\partial^2 a/\partial y^2) - \lambda ab$, $(\partial b/\partial \tau) = (\partial^2 b/\partial y^2) - \lambda ab$, $(\partial c/\partial \tau) = (\partial^2 c/\partial y^2) + \lambda ab$; $a = (C_{\text{ArSCN}}/C_{\text{ArSCN}}^0)$, $b = (C_{\text{ArS}^-}/C_{\text{ArSCN}}^0)$, $c = (C_{\text{ArSSAr}}/C_{\text{ArSCN}}^0)$, $\tau = (RTt/F\nu)$, $y = (RTx/F\nu)$, $\lambda = (RTkC_{\text{ArSCN}}^0/F\nu)$. Variables a , b , and c are the concentrations of ArSCN, ArS⁻, and ArSSAr, respectively, normalized toward the bulk concentration of ArSCN, C_{ArSCN}^0 , and y and τ are the dimensionless variables of time and surface, where t represents the time and x the distance to the electrode surface. A complete description of the mechanism will be reported shortly.

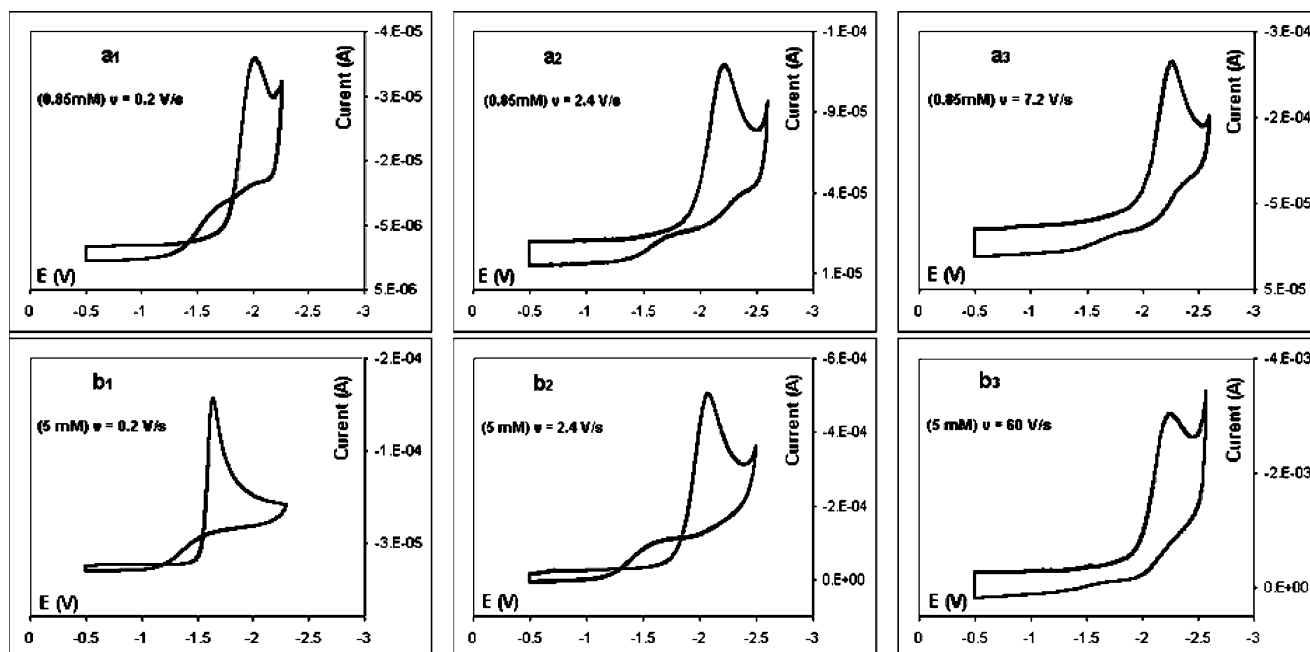


Figure 3. Cyclic voltammetry of **1**: (a₁) 0.85 mM, 0.2 V/s; (a₂) 0.85 mM, 2.4 V/s; (a₃) 0.85 mM, 7.2 V/s; (b₁) 5 mM, 0.2 V/s; (b₂) 5 mM, 2.4 V/s; (b₃) 5 mM, 60 V/s. In CH₃CN/TBAF (0.1 M) at a glassy carbon electrode. Temperature = 20 °C.

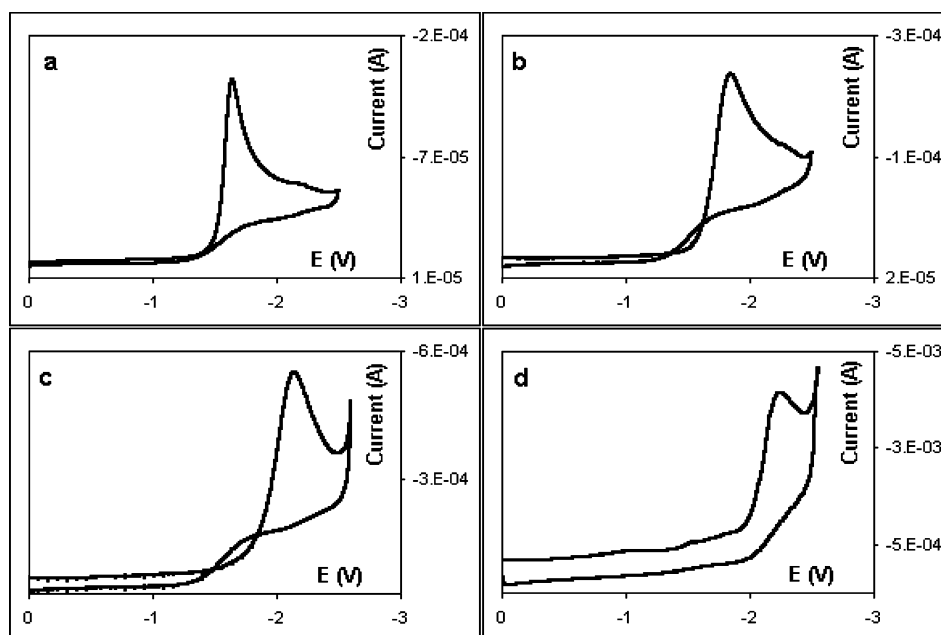


Figure 4. Cyclic voltammetry of **2** (3.45 mM): (a) $\nu = 0.2$ V/s; (b) $\nu = 1.2$ V/s; (c) $\nu = 5$ V/s, and (d) $\nu = 80$ V/s. In CH₃CN/TBAF (0.1 M) at a glassy carbon electrode. Temperature = 20 °C.

For a well behaving system reduced following a concerted mechanism with a value of 0.3, the difference would be of the order of 300 mV. This is also a consequence of the autocatalytic process. Similar behavior has also been noticed for the “traditional” autocatalytic process.^{22b}

For compound **2**, the autocatalytic process is even more efficient, as expected considering the higher nucleophilicity of *p*-methoxybenzenethiolate over the *p*-toluenethiolate ion. At low scan rates, the big shift of the reduction potential toward less negative values does not allow one to see crossing, since the reduction peak appears at the level of the reduction potential of disulfide **5** (by comparison with an authentic sample). As the scan rate is increased, the peak shifts negatively and trace

crossing appears (Figures 4b,c). Crossing disappears only at very high scan rates in this case (80 V/s), as shown in Figure 4d. A similar big shift in the reduction potential (800 mV) between 0.5 and 80 V/s is observed, again confirming the existence of the autocatalytic process and pushing the reduction potential toward less negative values.

Figure 5 shows the variation of the peak potential with the scan rate at different initial concentrations for **1** and **2**. An important feature is that the variation of the reduction peak potential with the log of the scan rate does not have the same slope over the entire studied scan rate range, and three major regions can be discerned in all cases. For the high concentrations, one can distinguish the following: at low scan rates, the

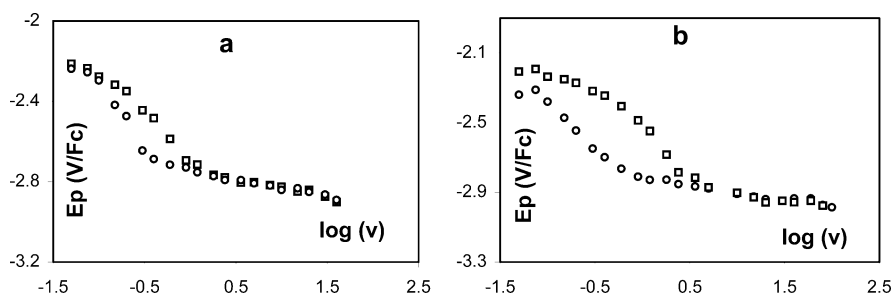


Figure 5. Variation of the reduction peak potential with the log of the scan rate ($\log(v)$) for (a) **1**, \square (3.45 mM), \circ (0.69 mM) and (b) **2**, \square (5 mM), \circ (1.25 mM).

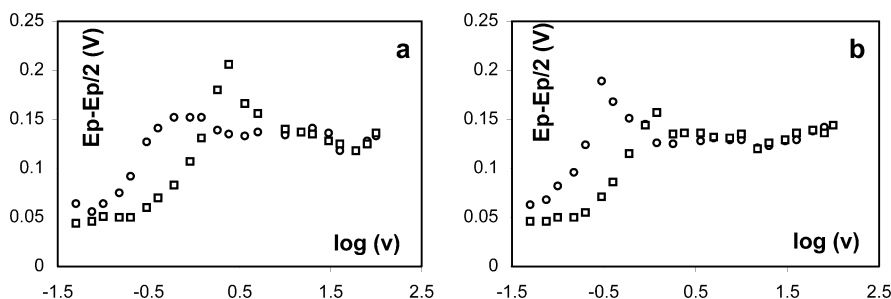


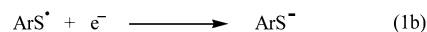
Figure 6. Variation of the reduction peak width with the scan rate v of (a) **1**, \square (3.45 mM), \circ (0.69 mM) and (b) **2**, \square (5 mM), \circ (1.25 mM).

variation of the peak potential is linear with a relatively low slope (120 and 122 mV per unit $\log(v)$ for **1** and **2**, respectively). Within this range, the crossing exists, the autocatalytic process is very efficient, and the reduction peak is consequently pushed toward more positive potentials. The intermediate region shows a much larger slope, since it corresponds to the competition between autocatalysis and diffusion (520 and 565 mV per unit $\log(v)$ for **1** and **2**, respectively), diffusion being favored as v increases. The peak potential shifts dramatically to more negative values and the higher the value of v , the less efficient the autocatalytic process. At higher scan rates (third region), where the crossing is no longer observed, the slope is much smaller (84 and 86 mV) and the autocatalysis is totally eliminated. At lower concentrations, similar behavior is seen, but competition between the autocatalytic process and direct electrochemical consumption (intermediate region) of the aryl thiocyanate at the electrode takes place at lower scan rates. An important factor is the total independence of peak potential of concentration at these high scan rates, for both compounds **1** and **2**, indicating clearly that the autocatalytic process is not involved anymore. This means that, at these high scan rates, the experimental electrochemical data correspond to the intrinsic characteristics of the direct reduction of aryl thiocyanates on the electrode, rather than a mixed process involving consumption by both reduction at the electrode and nucleophilic attack by the arenethiolate.

The α values calculated from the slope of E_p versus $\log(v)$ at the high scan rates are 0.35 and 0.34 for **1** and **2**, respectively, suggesting a slow electron transfer.

Figure 6 reports the variation of the reduction peak width ($E_p - E_{p/2}$) for **1** and **2** at two different concentrations. At high concentrations, the autocatalytic process is very efficient and the peak is very sharp (peak width around 50 mV for both **1** and **2**) at low scan rates. At higher scan rates, corresponding to more competition between diffusion and autocatalysis, the peak width increases dramatically (to higher values than 150 mV for both **1** and **2**), before settling on some more or less stable values

Scheme 3



(around 150 mV) at much higher scan rates where the autocatalysis is eliminated. At lower concentrations, similar phenomena are seen, with the difference that the competition (increase of the peak width) takes place at lower scan rates. It is important to notice here again that, at high scan rates, the peak width is independent of concentration, proving again that these values correspond to the intrinsic characteristics of the direct electrochemical reduction of **1** and **2** and not to secondary chemical reactions, that is, the autocatalysis process.

In fact, the coefficient transfer α values obtained at high scan from both the peak width and the E_p versus $\log(v)$ plots are similar, 0.32 and 0.31, respectively, that is, much lower than 0.5. In the framework of a quadratic activation–driving force relationship, which is valid for both the stepwise and the concerted reductive mechanisms, this observation means that the peak potential is more negative than the standard potential of the rate-determining reaction.^{9,11,14} This is in principle compatible with the concerted mechanism and not with the stepwise mechanism. Based on that, the initial ET to **1** and **2** is more likely concerted with the S–CN bond breaking (reaction 1a, Scheme 3), yielding a cyanide anion and a thyl radical, which is immediately reduced at the electrode to produce the *p*-toluenethiolate anion (reaction 1b, Scheme 3) whose oxidation is seen upon reversal scan.

It is important to notice here the nonlinear variation of the peak width (and consequently α) with $\log(v)$ at high scan rates (where the autocatalytic process is not involved). As shown in Figure 6a and b, the variation of the peak width is concentration independent but decreases first, reaching a minimum, and then increases again. This is exactly what has been seen in borderline cases where a transition between concerted and stepwise mechanisms has been observed. To elaborate more on this convolution, analyses for **1** and **2** were carried out.

Scheme 4



Since the reduction of disulfides is the key step in the autocatalytic process, the electrochemistry of **4** and **5** has also been investigated. The electrochemical reductions of *p*-tolyl disulfide (**4**) and 4,4'-dimethoxyphenyl disulfide (**5**) were studied under similar conditions (CH₃CN/0.1 M TBAF/20 °C). The coefficient transfers for both compounds have been determined from both the peak width and the variation of the reduction peak with log(*v*) and have values ranging from 0.3 to 0.33,¹³ that is, much lower than 0.5 (and also indicating a reaction kinetically controlled by the initial electron-transfer step). These results are in good agreement with what has been recently reported for the electrochemical reduction of a series of disulfides where loose radical anions have been found to be intermediates in the reduction of these species.²⁴ The initial electron transfer yields a radical anion which dissociates rapidly, yielding a thiyl radical and a thiolate anion. The thiyl radical produced is immediately reduced at the electrode, yielding the *p*-toluenethiolate anion whose oxidation is seen upon reversal scan, and the total process involves 2 electrons per molecule (Scheme 4).

Convolution Analysis. The heterogeneous electron-transfer kinetics of the dissociative electrochemical reduction of **1** and **2** have been explored using convolution analysis.^{17–19} These studies have been performed at low concentrations and high scan rates to avoid autocatalysis.

The resulting α_{app} versus *E* plots for **1** and **2** are shown in Figure 7, definitively showing that the electrode process is not ruled by a simple ET mechanism. α_{app} is related to α through the double-layer correction²⁵ whose properties, to the best of our knowledge, are yet unknown for the glassy carbon electrode. However, it has been previously shown that uncorrected transfer coefficient values provide a reasonable representation of the process, as these values do not differ much from the true ones.²⁶ The wavelike dependence of α is very similar to those previously reported when a transition between the concerted and stepwise ET mechanisms is taking place.¹⁶ For compound **1**, the analysis was performed for scan rates ranging from 7.2 to 80 V/s. The α_{app} versus *E* plots are characterized by a maximum at ca. -2.14 V, corresponding to an average α value of 0.31, and it is important to notice that the same maximum was obtained within only 20 mV at any of the scan rates providing α data in the appropriate range (Figure 7a). This ensures that the observed behavior reflects a real dependence of α , beyond experimental error or the effect of artifacts (mainly IR compensation).

A similar behavior is seen for compound **2** (Figure 7 b) with a maximum at ca. -2.08 V, corresponding to an average α value

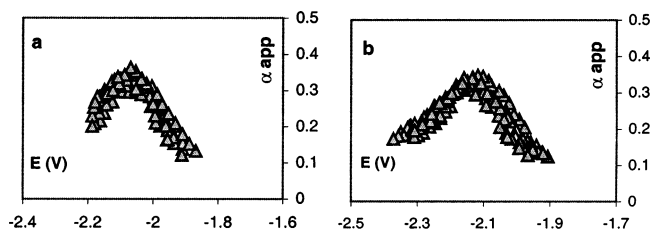


Figure 7. Variation of α_{app} with *E* for (a) **1** (0.85 mM) at scan rate $\nu = 7.2, 10, 20, 30, 40, 60,$ and 80 V/s and (b) **2** (0.69 mM) at scan rate $\nu = 7.2, 10, 20, 30, 40, 60,$ and 80 V/s.

of 0.33. Such nonlinear behavior reflects clearly a change of the electrode mechanism as a function of the potential. Such a mechanism transition favors the occurrence of the autocatalytic process at low scan rates and its inefficiency at higher scan rates. At low scan rates, the electrochemical reduction of the aryl thiocyanate yields the arylthiyl radical at the electrode, through a concerted process (reaction 3a), and this radical is immediately reduced, yielding the arenethiolate (reaction 3b).

Conclusion

Important aspects of the electrochemical reduction of the studied aryl thiocyanates were investigated. A striking change in the reductive cleavage mechanism as a function of the substituent on the aryl ring of the aryl thiocyanate is observed. A similar behavior has been reported for benzyl halides.^{14a} This is different from what is widely reported for aryl halides where a stepwise mechanism is taking place regardless of the nature of the substituents on the aryl group.²⁷ With nitro substituents, a stepwise mechanism involving the intermediacy of the radical anion takes place. With electron-donating substituents (methyl and methoxy), a transition between the concerted and stepwise mechanisms is observed on the basis of the analysis of the transfer coefficient (α). A nonlinear potential dependence of α is seen in this case, using both voltammetric and convolution analyses. Moreover, a very interesting autocatalytic process takes place during the electrochemical reduction of aryl thiocyanates. This results in the dependence of the reduction potential, as well as the peak width, on the scan rates. For low values of the kinetic competition parameter λ , small C_0 's and high sweep rates, the autocatalytic process has practically no effect and the reduction peak reflects the intrinsic characteristics of the direct reduction of the aryl thiocyanate. When the kinetic competition parameter λ increases, that is, high concentration and low scan rates, the autocatalytic process interferes more and more and the appearance of trace crossing is a characteristic feature of the efficiency of this process. As a result of this autocatalytic process, the reduction of the aryl thiocyanates takes place at negative potentials less than expected. This means that ET reactions may be involved in the bioactivity of aryl thiocyanates, since glutathione is a good electron donor. Moreover, aryl thiocyanates with electron-withdrawing substituents, which are easier to reduce, have been shown to be more active.²⁸ The autocatalytic process involves a nucleophilic substitution. This is different from the "classical" autocatalytic process involving an electron transfer between an anion produced at the electrode and the starting substrate.

(24) (a) Antonello, S.; Benassi, R.; Gavioli, G.; Taddei, F.; Maran, F. *J. Am. Chem. Soc.* **2002**, *124*, 7529. (b) Maran, F.; Wayner, D. D. M.; Workentin, M. S. *Adv. Phys. Org. Chem.* **2001**, *36*, 85. (c) Christensen, T. B.; Daasbjerg, K. *Acta Chem. Scand.* **1997**, *51*, 307. (d) Daasbjerg, K.; Jensen, H.; Benassi, R.; Taddei, F.; Antonello, S.; Gennaro, A.; Maran, F. *J. Am. Chem. Soc.* **1999**, *121*, 1750.

(25) α is related to α_{app} by the equation $\alpha = \alpha_{\text{app}} / (1 - \partial\phi^{\#} / \partial E)$, where $\theta^{\#}(E)$ is the difference between the potential of the bulk solution and the potential at which the substrate is located when the electron transfer takes place.

(26) For the mercury electrode, where the double-layer correction is better defined, α_{app} has been shown to be smaller than α by only 3%.^{17,19b}

(27) Savéant, J.-M. Single Electron Transfer and S_N2 substitution. In *Advances in Physical Organic Chemistry*; Bethel, D., Ed.; Academic Press: London, 1990; Vol. 26, pp 1–130.

(28) Morley, J. O.; Naji, M. *J. Chem. Soc., Perkin Trans. 2*, **1992**, 1301.

Finally, the reported mechanism helps to explain the results of the chemical reduction of aryl thiocyanates in the presence of electrophiles.^{5a,b} With 1 equiv of SmI₂, a single dissociative ET takes place, leading to a thiyl radical and a cyanide anion. The thiyl radical dimerizes, yielding the corresponding disulfide. In the presence of 2 equiv of SmI₂, the aryl thiocyanates yield the corresponding thiolate and cyanide anions in a two-electron reduction process, as shown in the electrolyses. The thiolate ions then attack the electrophile present, yielding the observed substitution products.

A more expanded series of aryl thiocyanates is presently under investigation, and kinetic data such as the rate constants of the nucleophilic reactions, as well as thermodynamic data such as the standard potentials and the BDEs, will be determined.

Experimental Section

Cyclic Voltammetry. Electrochemical measurements were conducted in three electrode glass cells, thermostated at 25 °C, and under dry nitrogen. The working electrode is a 2 mm diameter glassy carbon electrode (Ekochemie). The electrode was carefully polished and ultrasonically rinsed with ethanol before each run. The reference electrode was a homemade electrode consisting of a silver wire in a solution of CH₃CN/TBAF (0.1 M) separated from the main solution by a fine porosity glass frit. Its potential was calibrated in situ against the ferrocene/ferrocenium couple. The counter electrode was a platinum wire. The electrochemical instrument used is an Autolab PGSTAT30 especially configured to carry high scan rate CV experiments. A feedback correction was applied to minimize the Ohmic drop between the working and reference electrodes. For all the convoluted linear voltammograms, ferrocene was added and a run toward positive potentials was performed before each cathodic scan. The voltammetric behavior of ferrocene was thus used to judge the confidence in the positive feedback. The agreement between the different sets of kinetic data provided an a posteriori test, as described in the text. Transformation of the voltammetric current to the convoluted current was performed using the Autolab software. The other transformations of the convolution analysis were performed using Microsoft Excel.

Electrolyses. The electrolyses were carried out in 20 cm³ cells with a glassy carbon (Electrosynthesis) rectangular plate working electrode of 4 cm². The counter electrode was a platinum grid, separated from the cathodic compartment by means of a glass frit. The reference electrode was the same as that for CV. The cell was thermostated at 25 °C, and the solution was kept under a nitrogen stream during the whole electrolysis. The disappearance of the starting material and the formation of the products were followed by in situ cyclic voltammetry. The supporting electrolyte, tetramethylammonium tetrafluoroborate (TMAF), was extracted, and chromatographic analyses (HPLC and GCMS) were performed by comparison with authentic samples of the product.

Chemicals. Acetonitrile, the supporting electrolytes, TBAF, and TMAF (Fluka, *puriss*), and Di-*p*-tolyl disulfide (**4**) (Aldrich) were used as received. *p*-Methylphenyl thiocyanate (**1**), *p*-methoxyphenyl thiocyanate (**2**), and 3,5-dinitrophenyl thiocyanate (**3**) were prepared from the corresponding thiols following the previously reported procedure.²⁹ 4,4'-Dimethoxyphenyl disulfide (**5**) and di-(3,5-dinitrophenyl) disulfide (**6**) were synthesized following literature procedure.³⁰ *p*-Toluenethiolate, *p*-methoxybenzenethiolate, and 3,5-dinitrobenzenethiolate were prepared in situ by electrolysis of the corresponding disulfides.

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Supporting Information Available: Cyclic voltammetry of *p*-methylphenyl thiocyanate (**1**) in the absence and presence of 4,4'-dimethylphenyl disulfide (**4**), cyclic voltammetry of **4** and the variation of its reduction peak width and peak potential with the scan rate, and convolution analysis for **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA028542Z

- (29) Harpp, D. N.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, 181.
(30) Krishnamurthy, S.; Aimino, D. *J. Org. Chem.* **1989**, *54*, 4458.