Cryovoltammetrically probing functional group reductive cleavage: alkyl–sulfur *versus* aryl–sulfur bond cleavage in an alkyl naphthyl thioether under single electron-transfer is temperature switchable†

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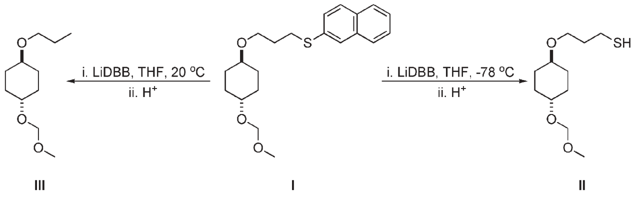
A series of single electron-transfer (SET) reactions on a naphthyl thioether have shown that the reductive cleavage mechanism changes at low temperatures and this selectivity is proved using an electrochemical analysis that mimics the SET reaction conditions.

The reductive cleavage of functional groups (FGs) using single electron-transfer (SET) reactions is widely employed in synthetic organic chemistry. Typical reaction conditions involve the use of an electron-transfer reagent (*e.g.* naphthalene or 4,4′-di-*tert*-butylbiphenyl (DBB)) and lithium metal, often resulting in synthetically useful anionic intermediates that can be utilized for the construction of complex organic molecules.[1–4] As part of a synthetic study, we report reactions involving the naphthyl thioether: 2-[(3-{[*trans*-4-(methoxymethoxy)cyclohexyl]oxy}propyl)thio]naphthalene, **I**, at 20 °C, 0 °C and −78 °C in tetrahydrofuran (THF) that show a change in the cleavage mechanism based solely upon temperature control of the SET reaction. At 20 °C or 0 °C, *alkyl*–sulfur bond fission was favoured whilst at −78 °C, *aryl*–sulfur bond cleavage was the major pathway (Scheme 1).

With a desire to understand the exact mechanism of reductive cleavage following electron-transfer (ET) we used electrochemistry, specifically cyclic voltammetry (CV), in a method designed to mimic the conditions of the SET reaction at 20 °C and −78 °C. Following the pioneering work by Van Duyne and Murray *et al.* which has shown that electrochemistry may be conducted at low temperatures, we have recently extended the use of cryoelectrochemical methodologies to a range of functionally activated organo-sulfur compounds with a view to investigating their mechanism of reactivity at −78 °C.[5–10] At this temperature, a significant improvement in the resolution of voltammetric waves and peaks is observed, *vide infra*. In general, there is much literature concerning the organo-electrochemistry of sulfur compounds at 20 °C and a number of reviews provide excellent overviews of the field.[11] However, few reports on low temperature electrochemistry of such compounds exist to date.



Scheme 1

As part of a synthetic study, the thioether **I** was treated with lithium and DBB at different temperatures; the result was surprising, and showed a clear switch in behaviour based upon temperature. The results of the SET reactions are summarized in Table 1.

The mechanism of reductive cleavage was proved by a detailed electrochemical analysis using platinum electrodes in THF and controlled-potential bulk-electrolyses at 20 °C and −78 °C. A preliminary electrochemical analysis of **I** was carried out at 20 °C using a platinum microelectrode to record the voltammetric (steady-state) response as shown in Fig. 1 (a). A reduction wave, poorly resolved from the solvent decomposition, was observed and an estimate of the half-wave potential, $E_{1/2}$, is given in Table 2 which summarizes all following electrochemical data obtained at

Table 1 Percentage yield(s) of product(s) following SET reduction of **I** at various temperatures

Temperature/°C	**I**/%	**II**/%	**III**/%
20	23	0	32
0	0	5	54
−78	0	45	7

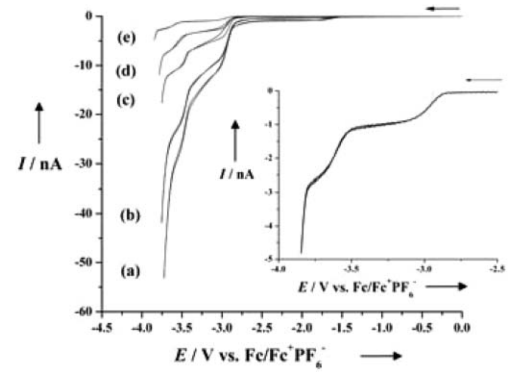


Fig. 1 Voltammetric response of **I** (3 mM) as a function of temperature: (a) 20 °C; (b) 0 °C; (c) −20 °C; (d) −50 °C; and (e) −78 °C. Inset: Magnification of steady-state response of **I** at −78 °C in the voltammetric region of interest. Electrode radius: 5.4 μm; scan rate: 10 mV s^{-1}; 0.1 M TBAP in THF.

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Table 2 Summary of electrochemical data for the reduction of **I** at 20 °C

Compound	$E_{1/2}$/V^{a}	n	D/10^{-10} m^2 s^{-1}	$E^{\mathbf{I}}_{p,c1}$/ μA^{a,b}	$E^{\mathbf{V}}_{p,c2}$/ μA^{a,b}	$E^{\mathbf{IV}}_{p,a}$/ μA^{a,b}
I	−2.93	1	21.2^{c}	−3.19	−2.35^{d}	−0.48^{d}

^{a} Potentials measured *versus* Fc/Fc^{+}PF$_6^{-}$. ^{b} Subscripts p, c, and a denote peak, cathodic, and anodic, respectively. ^{c} Obtained from ln D *vs.* T^{-1} plot. ^{d} Peak potentials (E_p) measured at 250 mV s^{-1}.

20 °C. Fig. 1 shows two important features of electrochemistry in THF: (i) voltammetry at 20 °C is affected by the electroactivity of the solvent window which 'overlaps' with the electrochemical process of interest, and (ii) voltammetry at lower temperatures leads to a significant improvement in the resolution of voltammetric waves and thus subsequent accuracy and interpretation of the electrochemical data. Highlighting this latter point is the voltammetric response shown in Fig. 1 (e), where a well-defined current plateau is seen for the first reduction wave. In addition, a second reduction wave is also observed. Therefore, analyses were possible at 20 °C; however, better resolved data could be obtained at −78 °C.

Next, microdisc chronoamperometric experiments were run at −78 °C; the procedure used is described fully in the electronic supplementary information (ESI) and the data are summarized in Table 3.

A diffusion coefficient, D, and the number of electron(s), n, for the reduction of **I** were determined. Using the first reduction-wave, steady-state data obtained at −20 °C and −50 °C, Fig. 1(c) and (d) respectively, n and D values were obtained and a plot of ln D *versus* T^{-1} allowed extrapolation to obtain a D value for **I** at 20 °C.[3]

CV of **I** was recorded at 20 °C using a platinum macroelectrode (Fig. 2), where a single, electrochemically irreversible reduction peak was observed. Anodic scanning of the potential window following reduction showed the appearance of an electrochemically irreversible oxidation peak and, with subsequent cycling of the potential, an additional reduction peak was observed. In a previous study of 1- and 2-naphthyl methyl sulfides at a glassy carbon electrode in acetonitrile a similar response was observed; however, adsorption of the electroactive species appeared to limit the voltammetry and no reports of follow-up reduction peaks were described.[12] Based upon electrochemical studies of various phenyl sulfides in aprotic media, it can be reasonably assumed that the reduction of **I** leads to the formation of a naphthyl thiolate which is readily oxidised upon reverse scanning of the potential.[13,14] Upon oxidation this then dimerises *via* a second-order chemical process to form the dimer, 2,2′-dinaphthyl disulfide, **V**, which would then undergo reduction at less negative potentials than the parent, **I**. In order to characterize these electrochemical 'fingerprints' of the species formed following reduction of **I**, a salt, tetra-*n*-butylammonium 2-thionaphtholate (nBu$_4$N^{+} NaphS^{-}), **IV**, and 2,2′-dinaphthyl disulfide, **V**, were prepared and their structures are shown in Fig. 3. For the sake of brevity, experimental details and characterization data can be found in the ESI.

Table 3 Summary of electrochemical data for the reduction of **I** at −78 °C

Compound	$E_{1/2}$/V^{a}	n^{b}	D/10^{-10} m^2 $s^{-1\,b}$
I^{c}	−2.97	1.06 (±0.03)	1.3 (±0.01)
I^{d}	−3.61	1.99 (±0.05)	—

^{a} Potentials measured *versus* Fc/Fc^{+}PF$_6^{-}$. ^{b} Data obtained from microdisc chronoamperometric experiments. ^{c} First reduction wave. ^{d} Second reduction wave.

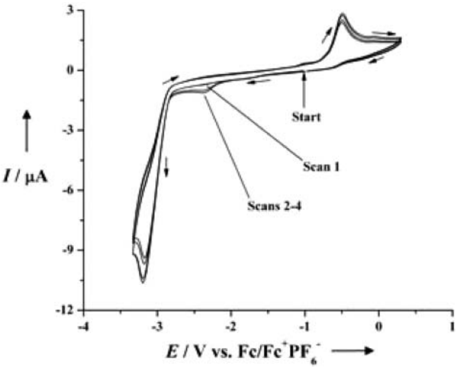
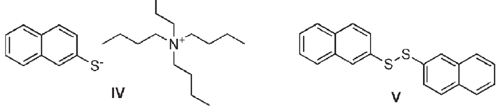


Fig. 2 Cyclic voltammograms obtained at a 1 mm platinum disc electrode for **I** (3 mM) at a scan rate of 250 mV s^{-1}. Scans 1–4. Start scan: −1.5 V, first reverse: −3.8 V, and second reverse: 0.5 V *versus* Fc/Fc^{+}PF$_6^{-}$. Electrode diameter: 1 mm; 0.1 M TBAP in THF at 20 °C.

Next, we performed an exhaustive electrolysis of **I** at constant potential to verify the SET result. Following the passage of the required number of Coulombs assuming a one electron reduction, the crude products were analysed using ^{1}H NMR in CDCl$_3$. It was shown by integral analysis of ^{1}H NMR peaks, that **III** (Scheme 1) was present in a ratio of 2.3 : 1 relative to the starting material. A full electrochemical conversion was not achieved, however (*ca.* 56%), and this was most likely due to the close proximity of the solvent window which led to inherent difficulties in defining a potential at which to perform the exhaustive electrolysis without electrolyzing the solvent.

As a function of decreasing temperature, the effect on the voltammetry of **I** was investigated and is shown in Fig. 4. In particular we wanted to observe any changes in the ET characteristics that might accompany the decrease in temperature that could explain the change in reductive cleavage mechanism.

It is evident that the electrochemical reversibility of the first reduction peak increases with decreasing temperature. Also observable is the diminished oxidative peak-current height corresponding to the oxidation of **IV**. These observations suggested to us that the formation of a radical anion, **I**$^{\bullet-}$, was probably stabilized at lower temperatures on timescales long enough to accept an additional electron before dissociating. Fragmentation of a dianion may follow a different route to that of a radical anion, thus rationalizing the synthetic results. Also seen at this temperature was an extended cathodic potential window[15,16] relative to Fc/Fc^{+}PF$_6^{-}$, within which was observed a second cathodic peak following the first (Fig. 5). At higher scan rates a single irreversible oxidation peak was seen, although no



IV **V**

Fig. 3 Structures of tetra-*n*-butylammonium thionaphtholate, **IV**, and of 2,2′-dinaphthyl disulfide, **V**.

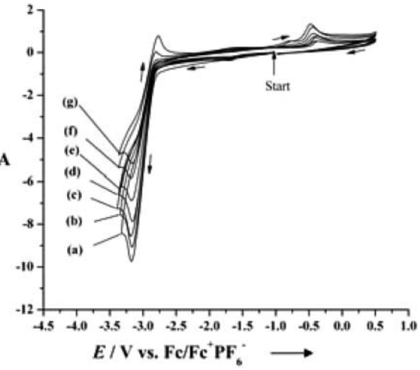


Fig. 4 Cyclic voltammograms (single scans) for **I** (3 mM) first reduction peak as a function of temperature: (a) 0 °C; (b) −20 °C; (c) −30 °C; (d) −40 °C; (e) −50 °C; (f) −60 °C; and (g) −70 °C. Start scan: −1.0 V; first reverse: −3.4 V; and second reverse: 0.5 V. Scan rate: 250 mV s^{-1}; electrode diameter: 1 mm; 0.1 M TBAP in THF.

additional reduction peaks were noticed even at a scan rate of 1 V s^{-1}. On the basis of stability arguments, one would expect a dialkyl disulfide (formed from the alkyl thiolate, RS^-, upon oxidation and then dimerisation) to be more difficult to reduce than the corresponding dinaphthyl disulfide due to delocalization of the charge in the latter molecule and so its reduction might not observed within the potential window.[17]

At −78 °C, a preparative electrolysis of **I** was performed in order to show that the reductive cleavage of **I** followed that observed under synthetic conditions. Holding the potential at −3.77 V *vs.* $Fc/Fc^+PF_6^-$ and following the passage of the required number of Coulombs assuming an $n = 2$ electron reduction, the crude product was analysed using ^{1}H NMR in $CDCl_3$. Analysis of ^{1}H NMR integrals showed the presence of **II**, **III** and **I** in a ratio of 1.8 : 0.4 : 1. This result confirmed that the reduction of **I** under electrochemical conditions at −78 °C gives the aryl–sulfur bond cleavage product, **II**, as observed in the initial SET reduction reactions. Scheme 2 outlines the possible mechanism of reductive cleavage of **I** at both 20 °C and −78 °C.

Following a series of SET reductions performed on the naphthyl thioether **I**, we have used CV to determine the mechanism of reductive cleavage. At 20 °C, we have found that **I** accepts a single electron before dissociating at the alkyl carbon–sulfur bond. The products following reductive cleavage have been characterised using known samples of the products. Using a cryoelectrochemical procedure we observed an improved resolution in the voltammetry (peaks and waves) that allowed accurate determinations of electrochemical parameters such as $E_{1/2}$, E_p, *etc*. At −78 °C, **I** is stabilized at sufficiently longer timescales to accept two electrons in a stepwise fashion. The dianion then cleaves selectively at the aryl–sulfur bond forming the alkyl thiol, **II**. Selective reductive cleavage, product(s) characterization and determination of the exact mechanism following SET reduction of a FG at various temperatures have been documented, *via* a cryoelectrochemical analysis.

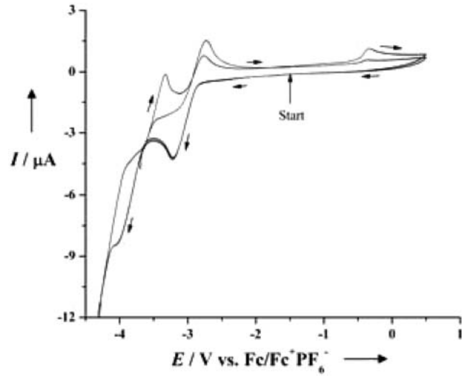
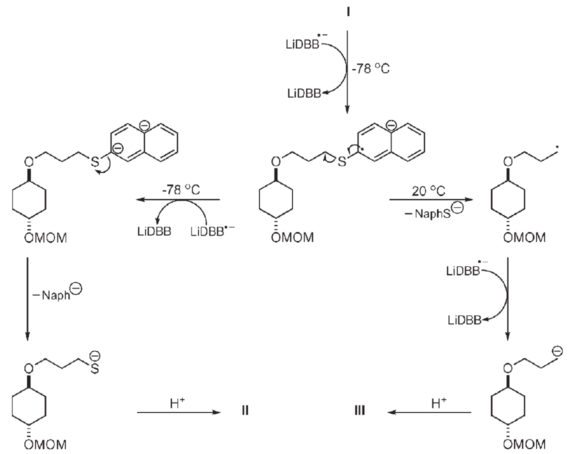


Fig. 5 Cyclic voltammograms of **I** at −78 °C. Scan rate: 250 mV s^{-1}; electrode diameter: 1 mm; 0.1 M TBAP in THF. Scans 1–4. Start scan: −1.5 V, first reverse: −4.3 V, and second reverse: 0.5 V *versus* $Fc/Fc^+PF_6^-$.



Scheme 2 Cleavage pathways following reduction of **I** under single electron-transfer (SET) conditions at 20 °C and −78 °C.

To conclude, this method of selective C–S bond cleavage, controllable by the reducing conditions applied, provides the ability to form either an alkyl thiolate or carbanion from the same naphthyl protected thiol and may have uses in synthetic organic chemistry.

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