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ANODIC OXIDATION OF DIALKYL AND DIARYL DITHIOACETALS

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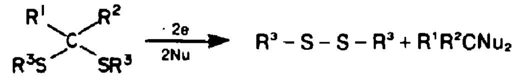
Abstract—The mechanism of the anodic oxidation of dithioacetals is discussed, taking into account new results concerning both mixed electrolyses and oxidations in super-dried solvents. In the case of the oxidation of aryldithioacetals, the formation of the -S-S- linkage is involved with a bond cleavage followed by a dimerisation. On the other hand, in the case of aliphatic starting materials the mechanism looks more consistent with the existence of a dicationic intermediate which is scavenged by nucleophiles.

The chain contraction by anodic means already reported by us[1] for 1-(alkylthio)alkyl sulphides (i.e. dithioacetals) may occur in good yields.[2] Therefore this method has been applied as an electrochemical removal of 1,3-dithian protecting groups.[3] The oxidation of bis(phenylthio) methane ($R^3 = C_6H_5$, $R^1 = R^2 = H$) has also been reported.[4] It has been demonstrated that this reaction totally excludes the formation of a sulphoxide as by-product.



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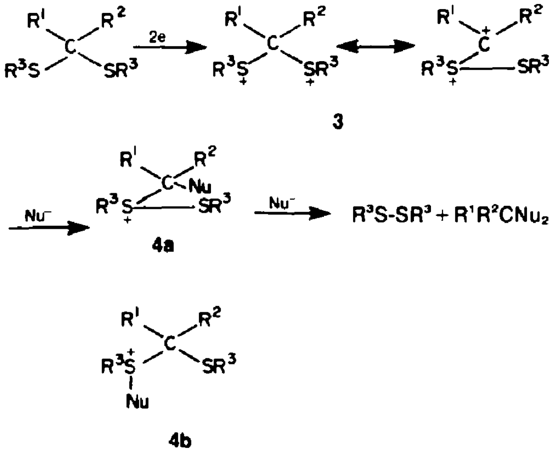
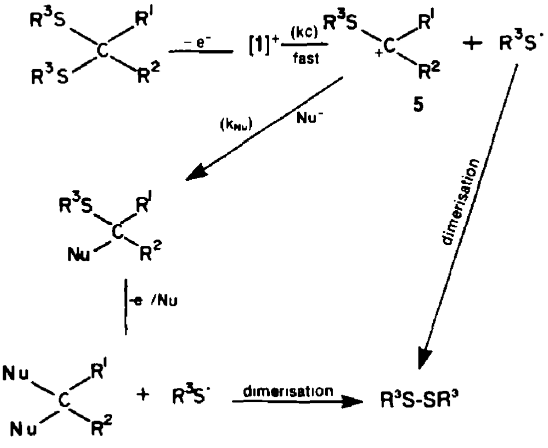
However, the work cited concerning this unusual (and anodically specific) reaction for dithians did not prove the mechanism of the cleavage of C-S bond. Two mechanisms were proposed:



Scheme 1.

One[1,2] takes account of dicationic intermediate undergoing a double nucleophilic attack, and the other one supposes[4] the fast cleavage of the radical cation after the first charge transfer, further electro transfer being counteracted by attack by nucleophiles on the intermediate cations.

In fact, it may be observed that the main difference between Schemes 1 and 2 is possibly the occurrence of a chemical reaction (here a C-S bond cleavage) following the first charge transfer (as mentioned in Scheme 2). However, formation of the dication 3 (Scheme 1) should probably occur in two electrochemical steps whereas (Scheme 2) the transfer of the second electron is subordinated to the rate of the nucleophilic attack (solvent and/or residual water). Consequently, the electrochemical analysis (in the absence of nucleophiles) as well as the product distribution after macroelectrolysis in well-defined conditions may be used as criteria in order to discriminate between the two proposed mechanisms and reveal effect of substituents R on the mechanism.



Scheme 2.

Electrochemical data should take into account recent results by Musker *et al.*[5,6] describing the isolation of stable dications from mesocyclic and acyclic dithioethers when oxidized either by chemical agents such as the nitrosyl cation NO^+ or by electrochemical means.[9] New results on oxidation of the series of the $-S-CR^1R^2-S-$ linkage are discussed in order to elucidate the way in which the -S-S- linkage is formed.

EXPERIMENTAL

Cyclic voltammetries (CV) and electrolyses were performed as previously described.[10] The microanode used for CV was a carefully burnished planinum electrode ($A = 0.8\ mm^2$) and the anode assigned for macroelectrolyses was a sheet of platinum ($A = 12\ cm^2$). After every electrolysis this electrode was burnished and cleaned with concentrated nitric acid. The counter electrode was a graphite rod.

All the experiments were carried out in acetonitrile-$LiClO_4$. Acetonitrile was purified according to the method given in Ref. 7

and dried *in situ* with neutral alumina (Woelm) activated under vacuum at 350° during 4–5 h.

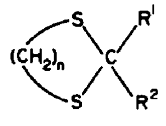
After the electrolysis, the anolyte solution was neutralized by adding Na_2CO_3 and extracted by ether. Products were separated by the usual thin layer and column chromatographic techniques and then identified by NMR and IR spectroscopies, microanalysis, and by comparison with authentic samples. The sulphonium salt 7 formed during the oxidation of the 1,3-dithiacyclohexane was isolated by evaporating under vacuum and purified by methanol. It should be noted that the reaction is not oriented to the formation of sulphoxides which were not detected from the products mixture after work up.

The gem polythioethers were synthesized by the procedures given in literature[11] except for 1,3-dithian which is available commercially from Fluka.

DISCUSSION

Aliphatic dithioethers

Acyclic disulphides possessing the structure 6 are



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easily oxidized on a burnished platinum working electrode. Results are summarized in Table 1. So, in "neutral" and commonly dried acetonitrile, it may be noticed that the electricity consumption is 2 Faradays per mole. In the presence of water of pyridine (here acting probably as nucleophile) an increase of both voltammetric currents (first anodic peak as shown in Fig. 1) and coulometric measurements were observed only for 1,3-dithiacyclohexane. Repetitive sweeps in acetonitrile with water or pyridine show beside the main peak Ox_1 an other step Ox_2 located at less anodic potentials. In comparison with an authentic sample, it has been shown that the step Ox_2 corresponds to the oxidation of 1,2-dithiacyclopentan formed at the anodic interface. This step does not occur in carefully dried solvent.

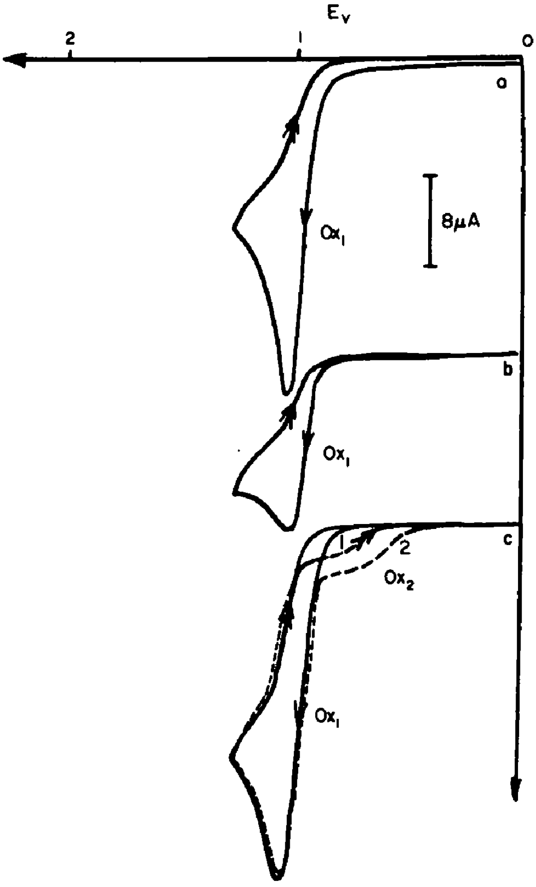
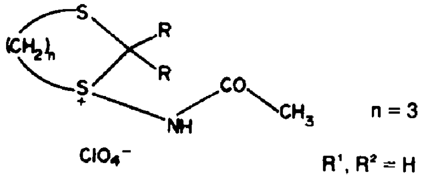


Fig. 1. Voltammogramms at platinum electrode in acetonitrile of 1,3-dithiacyclohexane (1). Concentration (5×10^{-3} M). Supporting electrolyte: 0.1 M $LiClO_4$. Sweep rate: 100 mV/s^{-1}. Electrode area: 0.8 mm^2. Reference electrode: Ag/Ag^+ (0.1 M). (a) i-E curve in "purified" acetonitrile; (b) i-E curve in dried acetonitrile with activated alumina; (c) i-E curve with pyridine (10^{-2} M). First (1) and second (2) sweep.

Fixed potential electrolysis in the couple acetonitrile-$LiClO_4$ (absence of sodium carbonate) allows the isolation[2] of salt (yield 35%), which is very hygroscopic and sensitive to the action of bases and/or nucleophiles. Microanalysis and IR spectrum agree with the formula 7. However, NMR in polar (and nucleophilic) deuteriated solvents (such as DMSO) shows the decomposition *in situ* of the salt into formaldehyde ($R^1 = R^2 = H$), 1,2-dithiacyclopentan and amide. The electrochemical reduction of the salt leads to the dithiane, in agreement with the reversible formation of the S–N linkage.



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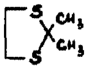
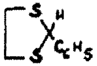
Attempts for the isolation of the cation 7 by direct action of $BrNHCOCH_3$ were unsucessful (n = 3, R^1, $R^2 = H$ and n = 2, $R^1 = CH_3$ and $R = C_6H_5$) since the reagent may be considered as an oxidant; the reaction leads nearly exclusively to the carbonyl compound through dethioacetalization.

Anodically this salt is not electroactive, but sensitive to the action of a nucleophile and then readily destroyed to lead to neutral electroactive species (possessing the S–S linkage), oxidized either at the same potential as the dithiane (increase of the height of the peak Ox_1) or at less anodic values (appearance of the prepeak Ox_2 during further sweeps in the CV of 1 in the presence of pyridine). With substituents R^1 and R^2 being alkyl or phenyl groups (e.g. compounds 3 and 4, Table 1), the absence of an increase in currents when adding water or pyridine may be related with a larger stability of electrochemically generated intermediates.

It is probably worth mentioning here that intermediates formed by anodic oxidation are electrochemically readily reducible. This appears evident from cyclic voltammetries of which the sweep in potential covers both sufficiently large anodic and cathodic range. A preparative electrolysis ($E_{ox} = +1.2$ V) on 1,3-dithiacyclohexane (in $Bu_4N^+BF_4^-$-acetonitrile) allows a total decay of the current after 2 Faradays per mole. The anolyte solution is then *immediately* reduced on a mercury cathode ($E_{red} = -1.0$ V). The reduction current integration gives 0.6 F/mole^{-1} calculated on the basis of the starting material before oxidation. Extraction of the solution with ether allows the recovery of 30% of the initial 1,3-dithian which is actually the only chemical extractable under these conditions. It can be shown, then, that the oxidation is *chemically* reversible (at least

Table 1. Voltammetric and coulometric data for some alicyclic thioacetals in acetonitrile ($LiClO_4$ 0.1 M). Platinum anode. Reference: Ag/Ag^+ 0.01 M. Sweep rate 0.4 V/s^{-1}

	Substrates ($c = 5.10^{-3}M$)	Neutral Solvent			Basic Solvent (Pyridine [(a)])		
		$E_{(V)}$	$i_{\mu A}$	coulometry ($F.mol^{-1}$)	$E_{(V)}$	$i_{\mu A}$	coulometry ($F.mole^{-1}$)
1		1:10	24	2.25	1.20	36	3.4
2		1.24	30	2.2	1.30	40	-
3		1.30	28	2.8	2.40	24	2.9
4		1.32	28	1.9	1.47	26	1.8
5	$CH_3 - S - S - CH_3$	1.12	32	–	1.40	34	-
		0.70	25	–	–	–	–

(a) Pyridine concentration: 10^{-2} M.

partially) with regeneration of the thioacetal. Simultaneously, a slow degradation of 7 by nucleophiles may be expected. However, no attempt in order to identify the products of this further degradation was made in this case. When R_1 and R_2 are different from H, the oxidation of 6 leads, in the aqueous acetonitrile, to the carbonyl compound. This reaction is then the anodic removal of the protecting group of the C=O function, already developed by Utley.[3]

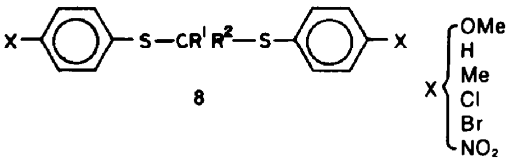
The overall deprotection reaction consumes two electrons with two nucleophilic attacks on the intermediate cations (or radicals). A mechanism according to Scheme 1 with the isolation of a sulphonoum cation of the type 4b could be proposed but the occurrence of a EEC mechanism should be reloaded to the strength and the concentration of the nucleophiles present in the electrolysis solution. Using superdry acetonitrile and very poorly nucleophilic solvents such as methylene chloride brings new information on the nature of the oxidation process. In the absence of strong nucleophiles, thioacetals 6 are oxidized through two irreversible steps (Fig. 2) when glassy carbon is chosen as anodic material. In the same conditions, the oxidation on a platinum surface exhibits only one step appearing at more anodic potentials ($\Delta E = +130$ mV). When adding some water a two fold increase of the first peak (glassy carbon) and the peak (platinum) is clearly observed. The second step no longer occurs. Very similar results are obtained in methylene chloride when adding a soluble nucleophile such as dimethylformamide.

Results obtained with the carbon anode are shown in Fig. 2. Currents are directly proportional to the substrate concentration (a self-inhibition phenomenon is then excluded). The ratio of the two currents i_1/i_2 being included between 2 and 3 may suggest that the radical cation formed during the first step disproportionates rapidly. When using steady state electrochemical analysis such as glassy carbon rotating disk electrode, only *one* wave is observed. A rather fast disproportionation rate of the radical cation is therefore expected if the two voltammetric steps correspond to two successive one-electron transfers (the distance between those two peaks is of the order of 0.2 V).

Consequently, the mechanism of the oxidation may be either a EEC C (two consecutive electrochemical steps followed by two chemical reactions) (absence of fast nucleophilic attack) or a EC EC (a sequence of electrochemical, chemical, electrochemical, and chemical steps at the interface) in the presence of water and any other reasonably strong nucleophile). It may be expected that the starting material also plays the role of a nucleophile and reacts, in the absence of a stronger nucleophile, on the intermediate dication to lead to a dicationic dimer already mentioned and isolated[9] for 1,4 and 1,5-disulphides. So the decay of the *peak* current may be explained when 6 is oxidized, e.g. on platinum with and without water (lowering of the n-value from 2 in the case of ECE process to 1 in the case of E E process, followed gy a DIM 3; the intermediate after two charge transfers reacts on the substrate to form a dimer).

Aromatic gem-dithioethers

Results with aromatic dithioethers ($R_1 = R_2 = H$, R_3 being an aromatic ring with un-reactive substituents in the para position) are listed in Table 2, with the general formula:



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Dilsulphides 8 are oxidized in several steps. The two first steps (Fig. 3) have been previously shown[1,4] to correspond to (i) oxidation of the $-S-CR^1R^2-S-$ group, and (ii) oxidation of the $-S-S-$ linkage leading to the corresponding thiosulphonate in the presence of an excess of water in the electrolysis solvent.

The other anodic steps, located at more positive potentials, probably display the ability of some intermediates formed along the two first peaks to be oxidized further. For the moment, no assumption will be made about the nature of these steps.

Data concerning the two first steps Ox_1 and Ox_2 are given in Table 2. Plotting their peak potentials (or their half-peak potentials) against the σ Hammett constants gives a rather good correlation except for (8, X = OMe) which appears to be abnormally positive. Values displayed in Table 2 also show that the Ox_1 peak current for

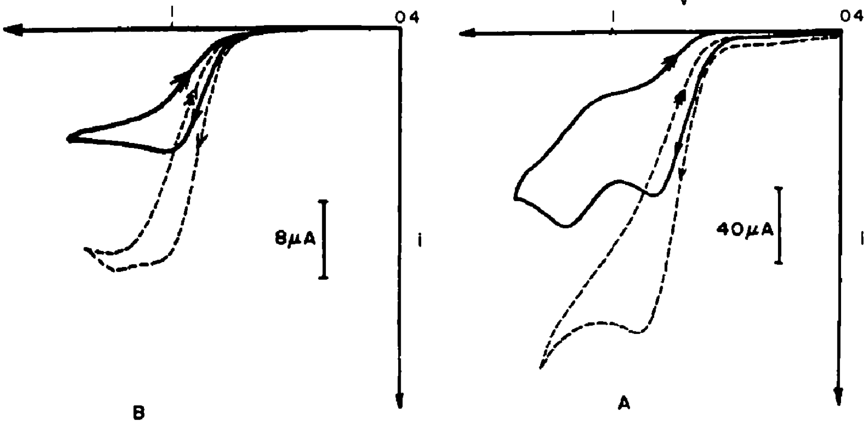
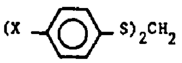


Fig. 2. Cyclic voltammetries of 1,3-dithiacyclohexane in acetonitrile/$Bu_4N^+ClO_4^-$ 0.1 M. Concentration of the substrate (5×10^{-3} M). Sweep rate 20 mV/s^{-1}. *Full line*: in super dry solvent. *Dotted line*: with water present (1.4×10^{-2} M). (A) On glassy carbon electrode; (B) on platinum electrode.

Table 2. Anodic oxidation of VIII in acetonitrile/$LiClO_4$ 0.2 M, on burnished platinum. Reference electrode: Ag/Ag^+ 0.1 M. Sweep rate: 100 mV/s^{-1}

Substrate$^{(a)}$	X	First Step		Second Sten		First step in the presence of pyridine$^{(b)}$	
		E_{p1}	i_1	E_{p2}	i_2	E'_{p1}	i'_1
	OCH_3	0.84	14.8	0.99	18.8	0.85	27.2
	CH_3	1.02	20	1.14	18.0	1.06	34
	H	1.12	25.6	1.24	8.8	1.15	35.2
	Br	1.16	21.6	1.32	14.8	1.20	36
	Cl	1.16	18.8	1.32	12	1.20	31.2
	NO_2	1.45	30.	1.57	7.2	1.46	26

(a) Bulk concentration: 5×10^{-3} M.
(b) Pyridine concentration $\sim 6.5 \times 10^{-2}$ M.

methoxy derivative is smaller. Consequently, it may be suggested that the oxidation process occurring in the case of the methoxy derivative does not obey the same scheme that this proposed below for other aromatic disulphides substituted by withdrawing groups. In the same conditions, however, coulometries and electrolyses carried out at the level of the first step do confirm that the primary oxidation consumes, in all cases, 2 Faradays per mole with formation of one equivalent of the corresponding -S-S derivative (Fig. 4).

In order to elucidate the mechanism of the formation of the S-S bond a certain number of additional experiments were carried out:

Mixed electrolyses. As shown in Table 3, mixed electrolyses were performed in order to demonstrate after the first charge transfer the more or less partial occurrence of a cleavage leading to a free radical ArS' probably adsorbed able to couple at the electrode surface. When the potential of the planinum working electrode was fixed at sufficiently anodic values (0.2 to 0.4 V beyond the peak potential values given in Table 2), it was possible to demonstrate after the work up the presence of differently substituted α disulphides either at the stage of traces (experiment 1) or with a noticeable amount (experiment 2). Yields in dissymetric dimers are probably dependent on the relative ability for the radical ArS' to be adsorbed. For a given working potential of the anode it may be expected that high superficial concentrations for *both* types of radical do increase the probability of a mixed dimerisation.

Voltammetries in "superdry" acetonitrile. When residual water is removed *in situ* by activated alumina,[8] the shape of the voltammetric curves is dramatically changed when the transfer of the second electron is subordinated to a possible attack of the nucleophile (case of the Scheme 2, summarized by a $EC_{\text{cleavage}}C_{\text{Nu}}$ mechanism whereas the total current of the first peak in the case of the Scheme 1 ($EEC_{\text{Nu}}C_{\text{Nu}}$) is probably not dependent on the nucleophile concentration. Other discrepancies are caused (at the level of the second step) by the fact that the formation of the α disulphide may be partly dependent on the rate of nucleophilic attack, and

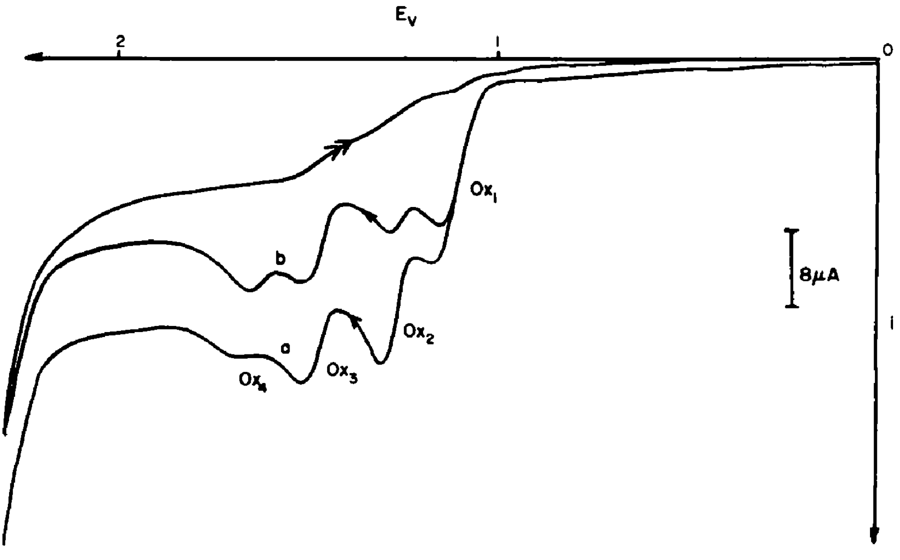
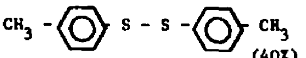
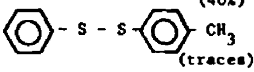
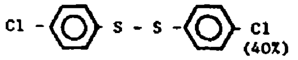
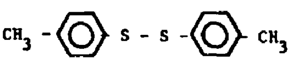
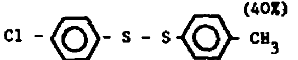


Fig. 3. Cyclic voltammetries in anodic potential range on stationary platinum in acetonitrile. Supporting electrolyte: 0.1 M Bu_4NClO_4. Reference electrode: Ag/Ag^+ (0.1 M). Sweep rate: 100 mV/s^{-1}. Electrode area: 0.8 mm^2. (a) $(ClC_6H_5S)_2CH$ (5×10^{-3} M); (b) same solution in the presence of an excess of activated alumina.

Table 3. Mixed eleectrolyses of gem dithioethers VIII in equimolecular mixture in acetonitrile–$LiClO_4$ 0.5M. Reference: Ag/Ag^+ 0.1 M. Volume of the anolyte: 60 ml. The electrolyses were performed in the presence of pyridine (4 ml)

Nature of the mixture	fixed potential	n ($F.mol^{-1}$)	Products in relative ratio
VIII , X = H (1g)	+ 1.4V	2.1	 (55%)
VIII , X = CH_3 (1.1g)			 (40%)
(Experiment n°1)			 (traces)
VIII , X = Cl (0.7g)	+ 1.4V	2.2	 (40%)
VIII , X = CH_3 (0.6g)			 (40%)
(Experiment n°2)			 (20%)

the ratio of the two peak currents i_1 and i_2 (for a given concentration of nucleophile) may give valuable information on the nature of the mechanism.

When adding activated alumina to a solution of 8 (X = Me, H, Cl, Br and NO_2) in purified acetonitrile according to conventional methods[7] we observed: (1) A new decay of the current ($n_{app} = 2 \rightarrow n_{app} = 1$) of the first step Ox_1 (Fig. 3) with a relatively more significant decrease of the current of the second step. With an excess of alumina the ratio of the two voltammetric currents tends to the value $i_2/i_1 = 0.5$, the current of i_2 for Ox_2 being however hardly known with accuracy because of the small potential difference between the two peaks. The use of platinum rotating disk electrode allows to confirm such a value for the ratio i_2/i_1. (2) The value of the current i_1 then observed corresponds to an electrochemical reaction consuming *one* electron per molecule ($n_{app} = 1$). (3) Small concentrations of water (of the same order of magnitude as depolarizer concentration) added afterwards to the solution allow then the observation of an increase of the current i_1. In these conditions, a twofold increase is seen. A similar enlargement is noticeable for i_2. In the presence of a limited amount of water (or pyridine) the current i_2 is *kinetic* and the ratio i_2/i_1 decreases when the sweep rate is made larger and larger. (4) The behaviour of disulphides Ar–S–S–Ar in the superdry acetonitrile had also been studied (Fig. 5). The careful drying of the solvent brings a decay of

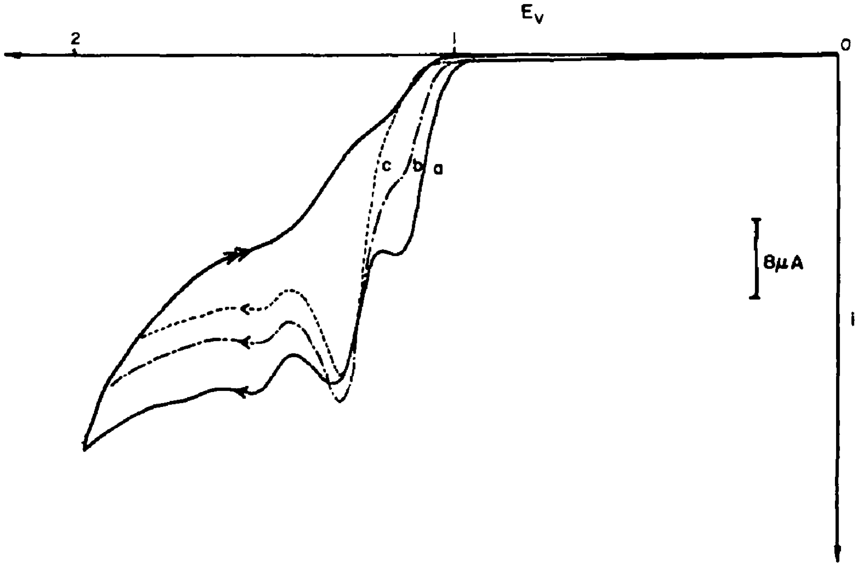


Fig. 4. Voltammogramms at a stationary platinum electrode in acetonitrile of (a) $(BrC_6H_5S)_2CH_2$ (5×10^{-3} M); (b) after coulometry at +1.1 V (consumption of 1.16 F/mol^{-1}); (c) after consumption of 1.93 F/mol^{-1}. Supporting electrolyte: 0.3 M $LiClO_4$. Sweep rate: 100 mV/s^{-1}. Electrode area: 0.8 mm^2. Reference electrode: Ag/Ag^+ (0.1 M).

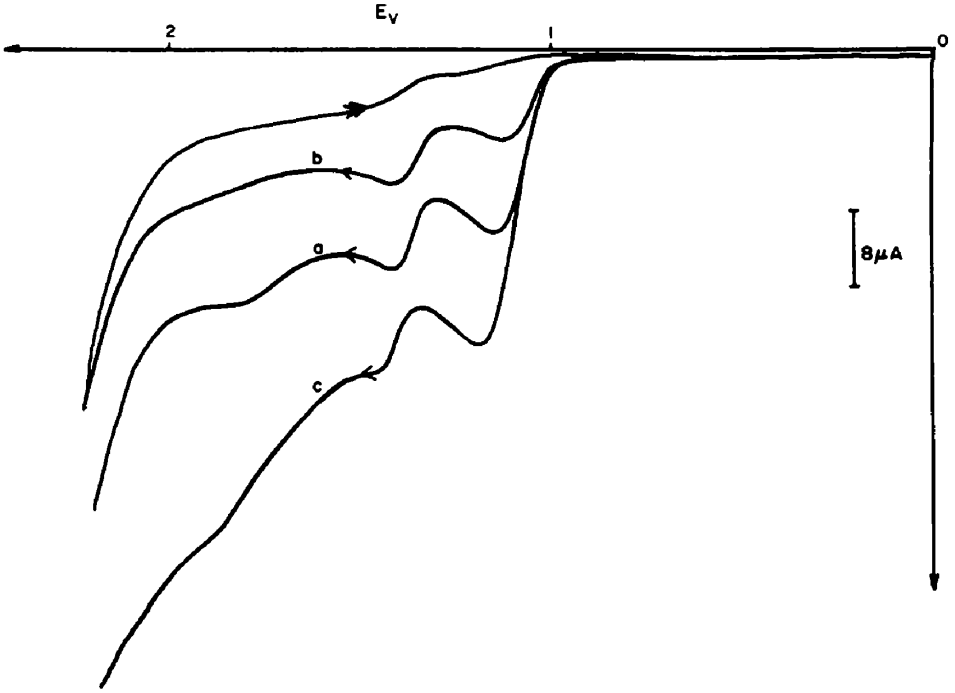
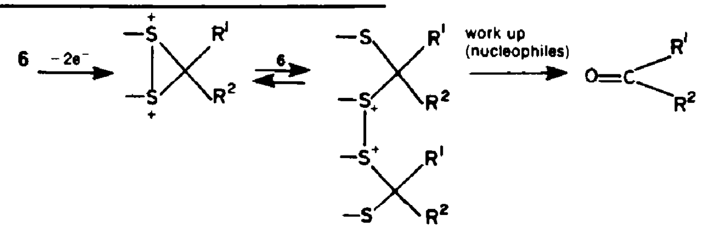


Fig. 5. Cyclic voltammetries on stationary platinum in acetonitrile. Supporting electrolyte: 0.1 M $LiClO_4$. Sweep rate: $100\,mV/s^{-1}$. Electrode area: $0.8\,mm^2$. Reference electrode: Ag/Ag^+ (0.1 M). (a) $CH_3C_6H_5S\text{-}SC_6H_5CH_3$ (5×10^{-3} M); (b) same solution with alumina added; (c) solution according to the conditions of the curve (a) with H_2O 4×10^{-3} M added.

the oxidation step up to a value of the current which corresponds to an anodic oxidation of *one* electron per molecule.

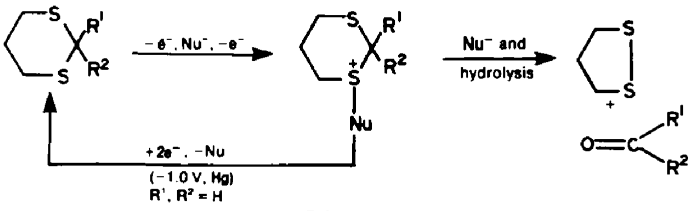
The anodic oxidation of β disulfides leading to the removal of the protecting group of the carbonyl group appears to be, till now, very unusual since neigher sulphoxides and sulphones nor sulphonium salts (resulting of the electrophilic attack by intermediates on aromatic rings) are isolated (or detected even in low yield from the products moxture after electrolysis). This anodic chain contraction, observed for any 1,3-disulphides occurs according to two mains types of processes depending on the electronic density on the sulphur atoms.

The behaviour of alicyclic thioacetals appears to be in agreement with the mechanism postulated in the Scheme 1 (EEC mechanism) only in non-nucleophilic media. However, in these conditions the dicationic form may react on the substrate to lead to a dimer ($n_{app} = 1$):



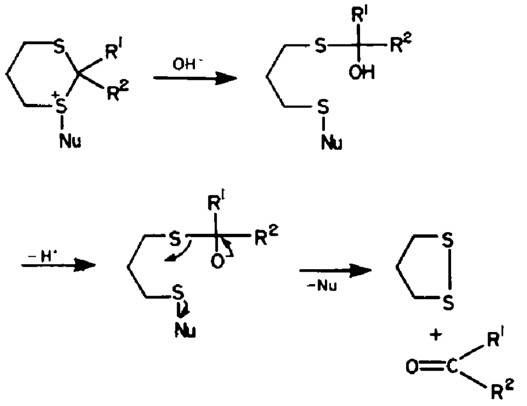
Scheme 3.

In the presence of stronger nucleophiles in large excess in the solution (water present or/and solvent of a nucleophilic character), the mechanism is of the ECE type. Consequently, the following scheme appears more suitable in order to take into account the anodic degradation of aliphatic dithianes.



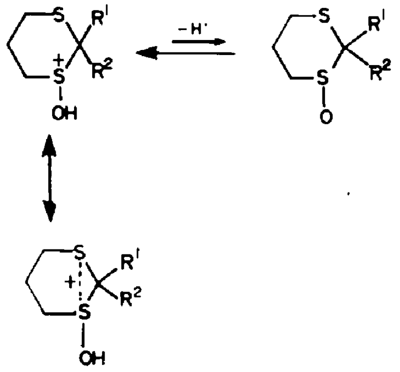
Scheme 4.

The sulphonium type intermediate is shown to be rather stable (its cathodic reduction at least partly leads back to the starting material) and is probably mainly decomposed during the work up after the macroelectrolysis. The decomposition of the monocationic intermediate may then occur according to the following mechanism:



Scheme 5.

However, the main question remains: when $Nu^- = OH^-$, why does the reaction not lead either to the sulphoxides or to the sulphones?



Scheme 6.

It seems that the proximity and the interaction of the two sulfur atoms (clearly shown by electronic[12] and photoelectronic[13] spectra) may confer[14] to the $>S^+-OH$ group a much lower acidity and consequently a larger stability to the cation. Moreover, during the anodic oxidation, the medium remains acidic. In the presence of an excess of water, the nucleophilic attack on the central carbon atom would be faster than the deprotonation rate.

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