The Anodic Oxidation of 2-(4-Nitrophenylthio)ethyl Esters in Acetonitrile

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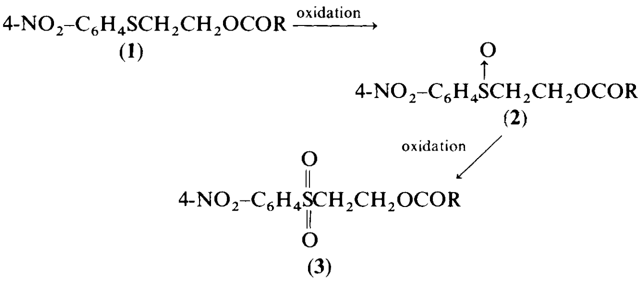
The electrochemical oxidation of 2-(4-nitrophenylthio)ethyl esters of acetic acid and of an amino acid in acetonitrile has been studied. Oxidation occurs in two steps at different potentials to the corresponding sulphoxide and then sulphone. The oxidation of the acetate ester has been investigated as a function of electrolysis conditions and the maximum yields of sulphoxide and sulphone were 90 and 65%, respectively.

The 2-(4-nitrophenylthio)ethyl group has been advocated as a protecting group for carboxylic acid functions during peptide synthesis; a common procedure for its removal involves oxidation of the sulphide to the sulphone with hydrogen peroxide in the presence of ammonium molybdate as catalyst (yield 80–95%),[1] followed by base hydrolysis.[2]

Electrochemical oxidation would be expected to be an alternative way to carry out the conversion of the substituted arylalkylsulphide to the sulphone. Despite early reports[3,4] that the oxidation of sulphides to sulphones occurs in good yield, the reaction has not been widely studied. Indeed, recent reviews[5,6] would suggest that the probability of converting the sulphide to the sulphone depends strongly on the structure of the sulphide and the reaction conditions. Three papers[7–9] are particularly relevant to the work reported here since they consider the ratio of sulphoxide/sulphone/other products as a function of electrolysis conditions in media based on organic solvents. Another review[10] concentrates on the conditions for the oxidation of sulphides to sulphoxides and this includes a section on electrochemical reactions.

As far as we are aware, no previous studies of the anodic oxidation of 2-(4-nitrophenylthio)ethyl esters have been reported. Most of this paper concerns the oxidation of the acetate ester, (**1a**). In a few experiments, the substrate was the protected amino acid (**1b**); Scheme 1.



(**a**) R = Me
(**b**) R = $C_6H_5CH_2OCONH$–CH(Me)–

Scheme 1.

Experimental

The electrochemical experiments were carried out with a Hi-Tek potentiostat, type DT 2101 and a Hi-Tek function generator type PPR1. Current–time and current–potential curves were recorded on a Philips recorder type PM 8043 and charges were measured on a Hi-Tek digital integrator, type D1BS2. Product analysis was carried out on a Shimadzu liquid chromatograph, type LC-6A with a Merck Lichrospher 100CH-18/2 (5 μm) column; the solvent was 75% CH_3CN/25% H_2O. Comparison of retention times and peak areas with those of standard samples was used to identify products and to determine yields, respectively.

Cyclic voltammograms were recorded in a three-electrode, two-compartment cell. The working electrodes used were a vitreous-carbon disc and a platinum wire. The vitreous-carbon disc electrode (Tokai Carbon Co. Ltd., type GC 30), area 0.05 cm^2, was made by sealing a rod into glass under vacuum and then polishing the exposed face with various grades of alumina powder; the electrode was always polished between experiments. The platinum electrode was a wire, sealed into glass, area 0.07 cm^2 and was initially electrochemically cleaned by cycling its potential between H_2 and O_2 evolution in 0.5 mol dm^{-3} H_2SO_4 solution; between experiments the electrode was washed with acetone and water and then dried. The counter electrode was always a Pt spiral in the same compartment. The experimental reference electrode was an Hg pool in the catholyte medium mounted in a Luggin capillary but its potential was measured *vs.* a Radiometer type K601 aqueous SCE with a Fluke digital voltmeter type 8050A and all potentials in this paper are referred to the SCE. The preparative electrolyses were carried out in a three-compartment cell with an anolyte volume of 17 cm^3 and the reference electrode was again an Hg pool. The working electrode was a Pt gauze (area 3 cm^2) and the secondary electrode was also a Pt gauze of approximately the same area separated from the anolyte by a glass frit. All solutions were deoxygenated with a fast stream of N_2 before each experiment and in preparative electrolyses the anolyte solutions were stirred with a magnetic bar.

The solvent used in all experiments, acetonitrile, was kept over CaH_2 for 24 h and distilled. The electrolytes used were Bu_4NBF_4 and $NaClO_4 \cdot H_2O$. The former was prepared from Bu_4NHSO_4 and $NaBF_4$ by precipitation in H_2O, recrystallised from ethanol–water and dried under vacuum. The latter was obtained from Merck and dried in an oven at 423 K.

The 2-(4-nitrophenylthio)ethanol was prepared by a literature procedure.[11] The 2-(4-nitrophenylthio)ethyl derivative of acetic acid was synthesised[2] by the addition of the acid to 2-(4-nitrophenylthio)ethanol and toluene sulphonic acid (catalyst) in benzene. The mixture was distilled and passed through a molecular-sieve column. The solvent was evaporated and the compound crystallised. The sulphone was prepared by the method of Amaral[2] and the sulphoxide by a similar method in the absence of molybdate. The derivative of D,L-alanine, (**1b**), was prepared in the same way.

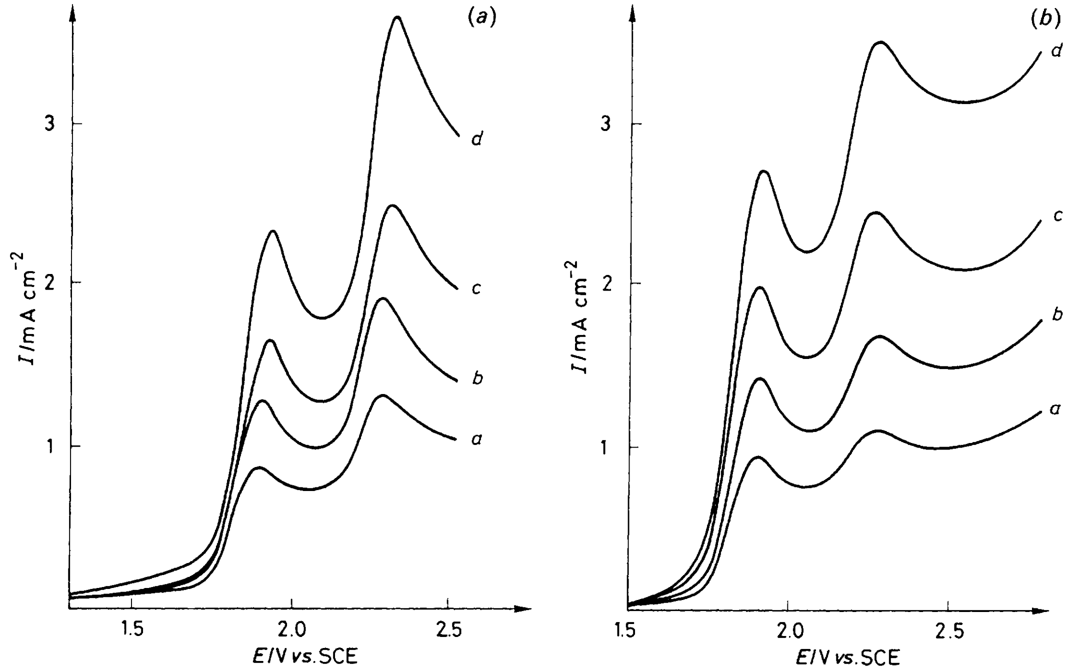


Figure. I–E curves recorded using a linear potential sweep for a vitreous-carbon disc electrode (area 0.05 cm^2) in a solution of 4-NO_2–$C_6H_4SCH_2CH_2OCOCH_3$ (2 × 10^{-3} mol dm^{-3}) in MeCN and electrolyte (0.1 mol dm^{-3}). (*a*) Bu_4NBF_4; (*b*) $NaClO_4 \cdot H_2O$. Potential sweep rates *a*, 0.02; *b*, 0.05; *c*, 0.1; *d*, 0.2 V s^{-1}.

Table. Data from controlled potential electrolyses under various conditions. All solutions 10^{-2} mol dm^{-3} 2-(4-nitrophenylthio)ethyl acetate in acetonitrile containing 0.1 mol dm^{-3} electrolyte.

			Organic yield(%)	
Electrolyte	*E*/V *vs.* SCE	*n*	**(2a)**	**(3a)**
Bu_4NBF_4	1.95	2	88	—
Bu_4NBF_4 + 5% H_2O	1.95	2	70	—
Bu_4NBF_4	2.30	4	—	15
Bu_4NBF_4	1.95 then 2.30	4	—	22
Bu_4NBF_4 + 5% H_2O	1.95 then 2.30	4	—	26
$NaClO_4 \cdot H_2O$	1.95	2	86	—
$NaClO_4 \cdot H_2O$	2.30	2.3	—	44
$NaClO_4 \cdot H_2O$	1.95 then 2.30	2.3	—	59

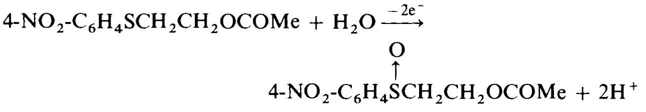
Results and Discussion

The Figure reports the I–E curves from linear potential sweep experiments for 2 mmol dm^{-3} 2-(4-nitrophenylthio)ethyl acetate, (**1a**), in acetonitrile containing 0.1 mol dm^{-3} Bu_4NBF_4 or 0.1 mol dm^{-3} $NaClO_4 \cdot H_2O$. In the Bu_4NBF_4 electrolyte, the substrate, (**1a**), shows two oxidation peaks of equal height at 1.89 and 2.27 V *vs.* SCE and cyclic voltammetry confirms that both oxidation processes are totally irreversible. Moreover, plots of I_p *vs.* $v^{\frac{1}{2}}$ are linear and pass through the origin which shows that, positive to the peaks, the oxidations are diffusion controlled; comparison of the slopes of these plots with that for the oxidation of ferrocene (a known one-electron oxidation) suggests that each oxidation reaction involves the transfer of two electrons and the same conclusion is reached if one uses the equation for the peak current density[12] assuming a value for the diffusion coefficient of 2 × 10^{-5} cm^2 s^{-1}. When the electrolyte is $NaClO_4 \cdot H_2O$, two irreversible oxidation peaks at 1.89 and 2.26 V are again observed but they are no longer of equal height. There is enhancement of the first peak at the expense of the second. A similar voltammogram can be produced in MeCN/Bu_4NBF_4 by the addition of water. Cyclic voltammograms for the corresponding sulphoxide, (**2a**), show a single oxidation peak at 2.26 V and of a height expected for a two-electron oxidation. Hence, electroanalytical experiments would suggest that (**1a**) is, indeed, oxidised in two, two-electron steps and that the product of the first step is the sulphoxide in good yield especially in the MeCN solution with low water content. The presence of water seems to lead to some over-oxidation of the sulphoxide at the potential of the first peak although there was no way of knowing whether the product of this further oxidation is the sulphone. It will be seen that this simple picture is not fully confirmed by preparative scale electrolyses.

Cyclic voltammograms for the alanine derivative, (**1b**), also showed two oxidation peaks at 1.89 and 2.34 V *vs.* SCE. Again, analysis of the I_p–$v^{\frac{1}{2}}$ plot for the first oxidation process suggests that, in dry MeCN, the current is mass transport controlled beyond the peak and that the process involves the transfer of two electrons. The presence of water leads to an enhancement of the peak height, although in all cases the more positive peak on the voltammogram is, in contrast to (**1a**), larger than the first one.

An experiment with $C_6H_5CH_2OCONHC_6H_{11}$, however, also gave a voltammogram with an oxidation peak at 2.28 V and hence it must be concluded that with compound (**1b**) both the 2-(4-nitrophenylthio)ethyl group and the benzyloxycarbonyl protected amine function are electroactive. Hence, for clean conversion of sulphide to sulphone in the protected amino acid, it would be necessary to find a protected amine function which is not oxidised electrochemically.

The Table reports data from the controlled potential oxidation of 2-(4-nitrophenylthio)ethyl acetate under various conditions. It can be seen that by electrolysis at 1.95 V, *i.e.* just positive to the first peak, it is not difficult to obtain a good yield of the corresponding sulphoxide. The highest yield was obtained under dry conditions with Bu_4NBF_4 as the electrolyte but the addition of substantial quantities of water were necessary in order to cause a significant drop in yield. Certainly the use of $NaClO_4{\cdot}H_2O$ as the electrolyte gave a yield comparable with that obtained with Bu_4NBF_4. Hence at this potential the oxidation appears to occur by the overall reaction, Scheme 2,



$$4\text{-NO}_2\text{-C}_6\text{H}_4\text{SCH}_2\text{CH}_2\text{OCOMe} + \text{H}_2\text{O} \xrightarrow{-2e^-} 4\text{-NO}_2\text{-C}_6\text{H}_4\overset{\overset{\text{O}}{\uparrow}}{\text{S}}\text{CH}_2\text{CH}_2\text{OCOMe} + 2\text{H}^+$$

Scheme 2.

where in 'dry' conditions, water is apparently still present in sufficient quantities. For the discussion below, it should be emphasised that the sulphoxide is stable in the anolyte at the end of this electrolysis. Under no conditions was any sulphone found in the electrolysis products at this potential.

The conversion into sulphone was more difficult to achieve and the yields from the electrolyses at more positive potentials were always lower. This is particularly the case with Bu_4NBF_4 as electrolyte, since yields never exceeded 30% even in the presence of water. In $NaClO_4{\cdot}H_2O$ medium, the yield of sulphone ranged from 40–65%, depending on the procedure used for electrolysis. When the electrolysis of (**1a**) was carried out at 2.30 V, it was noted that the *n*-value was only 2.3, much lower than the expected value of 4. This prompted an investigation of the oxidation of the sulphoxide. When the sulphoxide was first formed by electrolysis of the sulphide (as above), it was found that the passage of only 0.3 *F* at 2.30 V was sufficient for the consumption of all the sulphoxide and for the current to drop to the background level; the yield of sulphone was 59%. Even more remarkably, when cyclic voltammetry was carried out on the solution after electrolysis at 1.95 V, it was found that it was only possible to observe the oxidation of the sulphoxide on the first scan between 1.5 and 2.5 V. A second scan showed the absence of any sulphoxide oxidation peak and h.p.l.c. analysis confirmed that all the sulphoxide had been consumed. The yield of sulphone was 65%. It should be emphasised that: (*a*) the sulphoxide is stable in the anolyte after electrolysis at 1.9 V and, at least, a short excursion to 2.30 V is essential to produce sulphone, (*b*) the oxidation of sulphoxide in fresh $MeCN/NaClO_4{\cdot}H_2O$ did not occur in this way—apparently the presence of protons from the first oxidation step is essential to catalyse this conversion of sulphoxide to sulphone, (*c*) similar effects are not seen in $MeCN/Bu_4NBF_4$ solutions. It has, however, been shown by Miller and Mayeda[13] that $HClO_4$ is a stronger acid than HBF_4 in MeCN media. Further, they showed examples where the anodically generated $HClO_4$ (but not HBF_4) led to the acid-catalysed conversion of electrolysis products even after the electrolysis had been terminated.

It should also be noted that electrolytically initiated reactions where the complete conversion of substrate to product occurs at the expense of <0.1 *F* are a well documented phenomenon. In particular, there are many examples of electrochemically induced aromatic nucleophilic substitution[14] and of electron-transfer catalysis of ligand substitution of transition-metal complexes.[15] In these examples, however, the conversion of starting material to product involves no net oxidation or reduction. In contrast, the conversion of sulphoxide to sulphone certainly involves net oxidation. It has previously been proposed that perchlorate ion may be responsible for some oxidation[7] and in our experiments the proton may be essential to activate the perchlorate ion (or it may itself act as an oxidising agent for some readily oxidised intermediates). But we would again stress that it is essential to apply a potential at which the sulphoxide oxidises, at least for a very short period, in order to initiate such chemical oxidation. It may also be relevant to note the conclusions of Torii and Uneyama[9] who studied the oxidation of diphenylsulphoxide in $MeCN/NaClO_4$. They also found that the reaction terminated at $\leqslant 2$ *F* and that the yield of sulphone was only 50%. They postulated that the source of the second oxygen is another molecule of sulphoxide and, hence, that a type of disproportionation of the sulphoxide occurs. Unfortunately, however, the mechanism for the conversion of sulphoxide to sulphone, following the transfer of a small number of electrons, remains unclear; several of the above factors may be important.

Conclusions

Overall, it is, therefore, our conclusion that the conversion of 2-(4-nitrophenylthio)ethyl esters into the corresponding sulphoxides are facile electrolyses which occur in good yields. The further anodic oxidation to sulphone, however, is a very complex reaction and occurs in only moderate yield. Hence, although anodic oxidation provides a convenient, alternative procedure for the preparation of sulphoxide, it cannot yet be considered a useful method for the conversion of the sulphide into the sulphone as is required in the deprotection of peptides.

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