Anodic Methoxylation of 2,5-Dimethyl- and Tetramethyl-thiophene. Formation and Transformation of 2,5-Dimethoxy Adducts

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The electrooxidation of 2,5-dimethyl- and tetramethyl-thiophene in methanol containing sodium methoxide produced isomeric mixtures (in either case 40% *cis*, 60% *trans*) of the corresponding 2,5-dimethoxy adducts each in 30% yield, together with side-chain oxidation products. During GLC analysis a portion of the 2,5-dimethoxy adduct of 2,5-dimethylthiophene loses a methanol molecule to give 2,5-dihydro-2-methoxy-2-methyl-5-methylenethiophene. By contrast, the 2,5-dimethoxy adduct of the tetramethyl compound remained intact on GLC. In $CDCl_3$ solution in an NMR tube, each isomer of the 2,5-dimethoxy adducts was transformed into the corresponding 2-(methoxymethyl)thiophene. When sodium acetate was used as electrolyte, the products were the corresponding 2-(methoxymethyl)thiophenes plus thiophene-2-carbaldehydes. In order to synthesize 2-acetoxymethyl-5-methylthiophene as a reference compound, anodic acetoxylation of 2,5-dimethylthiophene was also examined.

During our investigations of the electrochemical behaviour of methylated heterocyclic aromatic compounds in methanol as solvent we observed that 2,5-dimethylthiophene (DMT) doesn't undergo the Clauson–Kaas alkoxylation,[1,2] which transforms furans into 2,5-dialkoxy-2,5-dihydrofurans. With DMT the reaction gave side-chain-substitution products instead of the expected 2,5-dialkoxy adduct.[3]

Janda and co-workers investigated the chemical and electrochemical oxidations of thiophene and substituted thiophenes in methanol and compared the results with those of furans.[4] The ring-opening reaction was common to all thiophenes tested, although substrates and oxidation agents were not always selected systematically. For example, the oxidation of DMT by means of methanolic bromine solution followed by hydrolytic work-up gave an acyclic enedione, while 2-methyl- and 3-methylthiophene were electrooxidatively converted into methyl 3-acylpropionates and their acetals. Compared with the data for acid-catalysed hydrolysis and pyrolysis of methoxylation products of furans,[5] these acyclic products may have been produced by way of 2,5-dimethoxy adducts of thiophenes and their hydro–methoxy-elimination products, 2-methoxythiophenes.

The primary purpose of the present work was to obtain the 2,5-dimethoxy adducts of thiophenes. We started by re-investigating the electrooxidation of DMT.[3] In order to avoid acid-induced secondary reactions, the oxidation reaction and the subsequent work-up were performed carefully under basic conditions. As a result, DMT gave the desired 2,5-dimethoxy adduct. Analogously, tetramethylthiophene (TMT) was converted into the expected adduct.

Results

Cyclic Voltammetric Peak Potentials (E_ps).—Methanol is, in general, not a suitable solvent for voltammetry at a platinum microelectrode. We attempted to use sodium acetate and sodium methoxide as electrolytes for cyclic voltammetry (CV) in methanol. Very large background currents were observed; addition of electroactive substrates didn't produce usable voltammetry curves. In the anodic direction, similar experiments were performed in NaCN (0.4 mol dm^{-3})–MeOH. The results were satisfactory. The CV for this electrolyte–solvent system indicated no substantial oxidation up to 1.6 V *vs.* saturated calomel electrode (SCE).[6] E_ps for DMT and TMT were 1.52 and 1.25 V *vs.* SCE (at v 0.1 V s^{-1}), respectively.

Controlled-potential Electroreaction.—The reaction was carried out at a controlled anode potential in a divided cell with a platinum anode at room temperature. The reference electrode was an SCE. The potential was set at the E_p of the thiophene. The oxidation was terminated after passage of 2 F mol^{-1} of added substrate.

Anodic reaction of DMT was carried out in methanol containing sodium methoxide. After treatment with saturated aq. sodium carbonate the crude product mixture was analysed by ^1H NMR and GLC methods. The NMR analysis showed the presence of an isomeric mixture (40% *cis*, 60% *trans*) of 2,5-dihydro-2,5-dimethoxy-2,5-dimethylthiophene **1a** in 28% yield (based on unrecovered starting material), together with 2-methoxymethyl-5-methylthiophene **3a** (35% yield) and a small amount of 5-methylthiophene-2-carbaldehyde **4a**. GLC analysis of the same mixture revealed the appearance of 2,5-dihydro-2-methoxy-2-methyl-5-methylenethiophene **2a** concomitant with a decrease in the adduct **1a**.

TMT gave the same types of products. The distribution of the resulting products, **1b**–**4b**, and the *cis*-to-*trans* ratios of the stereoisomers, *cis*-**1b** and *trans*-**1b**, coincided in both the NMR and GLC methods.

Table 1 summarizes the results of electroreaction. It also contains the results of the use of sodium acetate as an electrolyte where the products were exclusively side-chain-oxidation products.

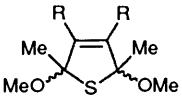
The products were isolated by preparative GLC and were identified by elemental and ^1H NMR, IR, and mass spectroscopic analyses. The result of previous NMR spectroscopic studies on geometrical isomerism in 2,5-dihydro-2,5-dimethoxyfurans[7] could be applied to the structural assignments of isomeric pairs of the relevant 2,5-dihydro-2,5-dimethoxythiophenes.† The chemical shift of a group in the 2 position of the thiophene ring is affected both by the other group at the 2 position and the magnetic influence exerted by the group at the 5 position that is *cis* to it. Thus, if a 2-methoxy group is *cis* to a

† NMR spectroscopy was also used to assign structures to the two geometric isomers of the 2,5-dicyano adduct as well as the mixed adduct of TMT (ref. 8).

Table 1 Products and yields for electrooxidation of DMT and TMT in methanol[a]

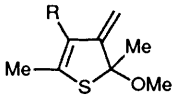
Thiophene	E_p (V *vs.* SCE)[b]	Electrolyte[c]	Conversion (%)	*n* (F mol^{-1})[d]	Product	Yield (%)[e] NMR	GLC
DMT	1.52	NaOMe	85	2.4	**1a**	28	23
					2a	0	8
					3a	35	33
					4a	*f*	*f*
		NaOAc	86	2.1	**3a**		46
					3c		5
					4a		6
TMT	1.25	NaOMe	80	2.7	**1b**	29	30
					2b	16	15
					3b	25	27
					4b	*f*	3
		NaOAc	91	2.2	**1b**		1
					2b		*f*
					3b		29
					4b		38

[a] Oxidation was performed at the peak potential of the substrate. Pt anode; SCE reference; electricity 2.0 F mol^{-1}; substrate concentration 0.1 mol dm^{-3}. [b] 0.4 mol dm^{-3} NaCN–MeOH; at *v* 0.1 V s^{-1}. [c] 0.4 mol dm^{-3}. [d] Controlled-potential coulometry. [e] Based on unrecovered starting material. [f] A small amount.

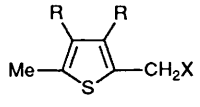


1a R = H (*cis*, 40%; *trans*, 60%)
1b R = Me (*cis*, 42%; *trans*, 58%)

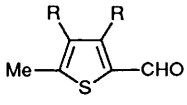
2a R = H
2ba R = Me



2bb



3a R = H, X = OMe
3b R = Me, X = OMe
3c R = H, X = OAc



4a R = H
4b R = Me

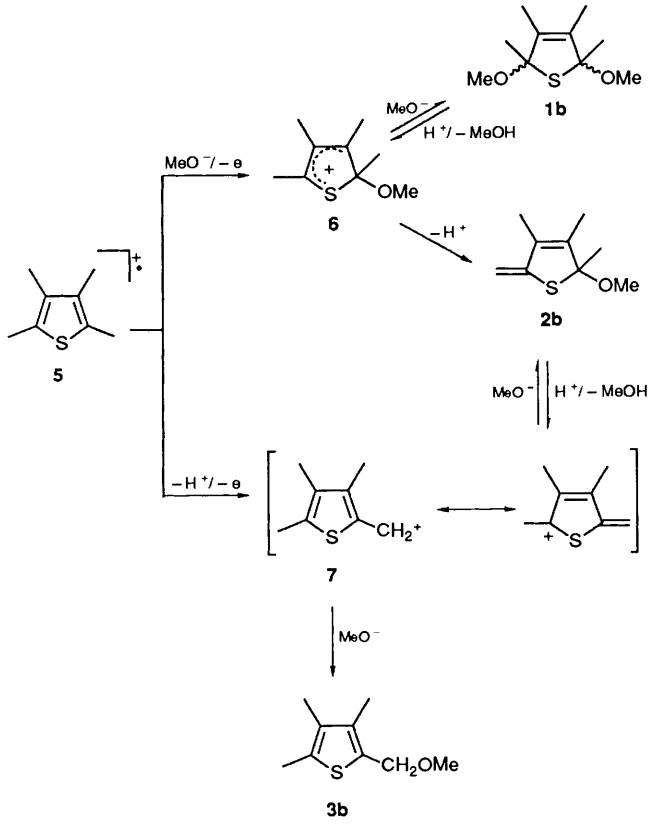
5-methoxy group it will resonate at lower field and raise the δ-value compared with the values obtained if it is *cis* to a 5-methyl group. The same reasoning can be applied to the methyl peaks and permits the indicated structural assignments for the two isomers (Table 2) to be undertaken.

Two possible structures, **2ba** and **2bb**, are conceivable for compound **2b**. The ^{1}H NMR spectrum of compound **2b** showed all three methyl groups whose greatest δ-value was 1.84 ppm. If compound **2b** has the structure **2bb**, the chemical shift of the methyl group at the 5-position will be the higher value. For reference, the methyl groups at the 2- and 5-position of DMT and TMT resonated at δ-value of 2.40 and 2.25, respectively. The structure **2ba** for the product was ascertained by acid-induced transformation of compound **2b** into the 2-methoxymethyl compound **3b** (*vide infra*). Structure **2bb** must give the 3-methoxymethyl compound.

Acid-induced Transformation of the Adducts **1** *and* **2** *into Side-chain-substitution Product* **3**.—The adducts **1** and **2** were, in the pure form, stable at room temperature for several hours. Each of them generally remained intact on GLC. However, all of them were instantaneously converted into the corresponding side-chain-substitution products **3** in solution upon treatment with even a negligible amount of acid. Therefore, addition of methanol that contains chloroform, which contains a trace amount of hydrogen chloride as an impurity, to an extract of electrooxidation products brought about the quantitative conversion of the adducts **1** and **2** into the corresponding compound **3**.

Discussion

The present paper reports the first anodic production of a 2,5-dimethoxy adduct of thiophenes. The electroreaction and subsequent work-up and refrigerated storage of the product



Scheme 1

Table 2 Physical characteristics of electrooxidation products

Product	M.p. (°C)	^{1}H NMR [δ(J/Hz)][h]	Mass m/z (M^+)	IR (ν_{max}/cm^{-1})[k]
cis-**1a**[a]	Oil	1.76 (6 H, s), 3.35 (6 H, s), 5.74 (2 H, s)	174	2800 (OMe), 1045, 1090, 1120 (C–O–C)
trans-**1a**[a]	57.5–58.0	1.85 (6 H, s), 3.24 (6 H, s), 5.64 (2 H, s)	174	2800 (OMe), 1045, 1090, 1120 (C–O–C)
2a[b]	Oil	1.83 (3 H, s), 3.20 (3 H, s), 5.10 (1 H, s[i]), 5.16 (1 H, s[i]), 5.80 (1 H, d,[i] J 6.1), 6.30 (1 H, d, J 6.1)	142	2800 (OMe), 1100 (C–O–C)
3a[c]	Oil	2.46 (3 H, s[i]), 3.34 (3 H, s), 4.50 (2 H, s), 6.57 (1 H, d[i]), 6.74 (1 H, d, J 3.4)	142	2800 (OMe), 1090 (C–O–C)
4a	Oil	2.56 (3 H, s), 6.86 (1 H, d,[i] J 3.4), 7.56 (1 H, d, J 3.4), 9.76 (1 H, s)	126	1675, 1655sh (C=O)
3c[d]	Oil	2.06 (3 H, s), 2.47 (3 H, s[i]), 5.15 (2 H, s), 6.60 (1 H, d,[i] J 3.4), 6.86 (1 H, d, J 3.4)	170	1740 (C=O)
cis-**1b**[e]	Oil	1.63 (6 H, s), 1.67 (6 H, s), 3.22 (6 H, s)[j]	202	2830 (OMe), 1100 (C–O–C)
trans-**1b**[e]	Oil	1.60 (6 H, s), 1.74 (6 H, s), 3.07 (6 H, s)[j]	202	2830 (OMe), 1100 (C–O–C)
2b[f]	Oil	1.74 (6 H, s[i]), 1.84 (3 H, m), 3.06 (3 H, s), 4.96 (1 H, s), 5.04 (1 H, s[i])[j]	170	2810 (OMe), 1095 (C–O–C)
3b	Oil	2.00 (3 H, br s[i]), 2.08 (3 H, s), 2.31 (3 H, br s), 3.33 (3 H, s), 4.46 (2 H, s)	170	2810 (OMe), 1095 (C–O–C)
4b[g]	46.5–47.5 (from hexane)	2.04 (3 H, s), 2.40 and 2.42 (6 H, ds), 9.90 (1 H, s)	154	1650 (C=O)

[a] Found (for *cis–trans* mixture): C, 55.2; H, 8.0; S, 18.6. Calc. for $C_8H_{14}O_2S$: C, 55.1; H, 8.1; S, 18.4%. [b] Found: C, 59.2; H, 6.9. Calc. for $C_7H_{10}OS$: C, 59.1; H, 7.1%. [c] Ref. 3. [d] Found: C, 56.7; H, 6.0; S, 19.0. Calc. for $C_8H_{10}O_2S$: C, 56.5; H, 5.9; S, 18.8%. [e] Found: C, 59.9; H, 8.8; S, 16.3. Calc. for $C_{10}H_{18}O_2S$: C, 59.4; H, 9.0; S, 15.9%. [f] Found: C, 63.4; H, 8.2; S, 18.6. Calc. for $C_9H_{14}OS$: C, 63.5; H, 8.3; S, 18.8%. [g] Found: C, 62.2; H, 6.7. Calc. for $C_8H_{10}OS$: C, 62.3; H, 6.5%. [h] 100 MHz; $CDCl_3$ solution; standard Me_4Si. [i] A split head. [j] Measured without delay after preparation of sample. [k] Mull for solid sample.

mixture must be conducted carefully under basic conditions. The product mixture should never be washed with brine. Part of adduct **1a** undergoes hydro–methoxy-elimination to give the secondary adduct **2a** during GLC analysis. Pure samples of adducts **1** for the elemental analysis were transformed into the corresponding side-chain-methoxylation products **3** within several hours. In $CDCl_3$ solution in an NMR tube, each isomer of **1** was converted into the corresponding compound **3**. On the other hand, the secondary adducts **2** were chemically and thermally more stable.

In consideration of the voltammetric characteristics and coulometry and by analogy with the anodic functionalization of various aromatic compounds,[9] the ECEC mechanism involving a cation-radical intermediate would be reasonable to account for the competitive reaction of the anodic ring addition and the side-chain substitution of methylated thiophenes. The cation-radical mechanism is shown in Scheme 1, illustrated for TMT. Two competitive pathways for reaction of TMT cation radical are considered. The anodically generated cation radical **5** undergoes nucleophilic attack by a powerful nucleophile, MeO^- ion, and further anodic oxidation to give the cation **6**, which is attacked by MeO^- ion (or the solvent MeOH) to produce the adduct **1b**. The cation radical **5** can also lose a proton to afford an analogue of a benzylic radical intermediate, which would sequentially undergo anodic oxidation to give a cation **7**, followed by nucleophilic attack by MeO^- ion (or the solvent).

The mechanism presented in Scheme 1 can also account for the acid-induced transformation of the 2,5-dimethoxy adduct **1b** into side-chain-methoxylation product **3b**. The adduct **1b** would undergo protonation at a methoxy group and successive methoxy group release to give the cation **6**, which would undergo deprotonation to afford diene **2b**. The adduct **2b** would analogously undergo protonation and subsequent loss of methanol to produce the cation **7**, which would eventually give rise to side-chain-oxidation products.

Electrooxidations were also performed in methanol containing sodium acetate in order to study the influence of electrolyte anion on the type of product obtained. It is seen from Table 1 that, with this electrolyte, anodic oxidation does not occur on the ring but rather on the side-chain. Incidentally, it was ascertained that the adduct **1a** is not transformed into compound **3a** in methanol containing sodium acetate. According to the proposed mechanism, in the absence of a powerful nucleophile, that is, the MeO^- ion, the electrogenerated cation radical **5** undergoes predominantly deprotonation to give a benzylic intermediate, which should eventually afford side-chain-methoxylation products.

With sodium acetate as electrolyte, formation of aldehydes was also observed; it was especially remarkable with TMT. They would be produced by hydrolytic work-up of the electrochemically generated dimethyl acetal. Further anodic transformation of primary side-chain-monomethoxylation products into *gem*-dimethoxylation products (*i.e.*, dimethyl acetals) and successive hydrolysis are known.[10]

Experimental

General.—Spectrometers and electrochemical equipment have been described previously.[7e]

Materials.—Methanol and analytical grade inorganic reagents were used with no purification.

DMT was prepared by reaction of acetonylacetone and phosphorus pentasulphide:[11] δ(100 MHz; $CDCl_3$) 2.40 (6 H, s) and 6.49 (2 H, s).

TMT was obtained by lithium aluminium hydride reduction of 3,4-bis(chloromethyl)-2,5-dimethylthiophene, which was prepared by chloromethylation of DMT:[12] b.p. 100 °C/37 mmHg (lit.,[12] 74–79 °C/15 mmHg); δ(100 MHz; $CDCl_3$) 1.96 (6 H, s) and 2.25 (6 H, s)

5-Methylthiophene-2-carbaldehyde **4a** was obtained commercially.

2-Acetoxymethyl-5-methylthiophene **3c**.—The electrolyte consisted of DMT (0.56 g, 5 mmol), anhydrous sodium acetate (4.10 g, 50 mmol) and glacial acetic acid (100 cm^3) containing acetic anhydride (2 cm^3). Electroreaction was carried out at the terminal voltage of ~50 V to maintain a current of 0.1 A in an undivided cell under a nitrogen atmosphere. Platinum foils having an area of 8 cm^2 were used as electrodes. During the reaction the solution was stirred magnetically and cooled externally with water. The current was terminated after the passage of 2 F mol^{-1} of substrate. To the product mixture was added an internal standard for GLC analysis, the mixture was poured into a vigorously stirred slurry of sodium hydrogen carbonate in water, and the organic material was extracted with diethyl ether. The extract was dried over anhydrous magnesium sulphate, filtered, and concentrated on a rotary evaporator. The crude product was then analysed by GLC on a PEG 6000 column at 160 °C. The product was 2-acetoxymethyl-5-methylthiophene **3c** (0.10 g, 18%), together with a small amount of 5-methylthiophene-2-carbaldehyde **4a**. The product was separated in pure form by preparative GLC. Identification was made on the basis of elemental and ^1H NMR, IR and mass spectroscopic analyses.

CV.—Voltammograms were recorded as described previously.[6,7e,8] E_ps for DMT and TMT were 1.52 and 1.25 V *vs.* SCE in methanol at a sweep rate v of 0.1 V s^{-1} (Pt anode; NaCN electrolyte).

Electroreaction.—The anolyte was made up of the thiophene (4 mmol), sodium methoxide [from sodium (0.46 g, 20 mmol)], and methanol (50 cm^3). The catholyte was the same medium in the absence of the substrate. The anode and cathode compartments were kept under nitrogen and the anolyte was stirred magnetically. The reaction was performed at the peak potential of the substrate at room temperature until 2 F mol^{-1} of added thiophene had passed through the electrolyte. To the product mixture was added an internal standard for GLC analysis, the mixture was treated with saturated aq. Na_2CO_3, and the organic material was extracted with diethyl ether. (The ethereal extract should not be washed with brine.) The solution was dried over anhydrous magnesium sulphate, filtered, concentrated under reduced pressure, and analysed by GLC on a PEG 6000 column at 160 °C. Each product was separated in pure form by preparative GLC. They were identified by elemental and ^1H NMR, IR and mass spectroscopic analyses (Table 2).

The method of electrooxidation with anhydrous sodium acetate (1.64 g, 20 mmol) as an electrolyte, work-up, and product isolation was identical with that described for sodium methoxide electrolyte.

Acid-induced Reactions of the Adducts **1** *and* **2**.—The adduct **1** (or **2**) was dissolved in $CDCl_3$–MeOH (1:1) at room temperature and the mixture was left intact overnight. GLC analysis showed only the presence of the side-chain-methoxylation product **3**.

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