The Direct Observation of Intermediates during the Oxidative Cyclization of Phenol Ethers

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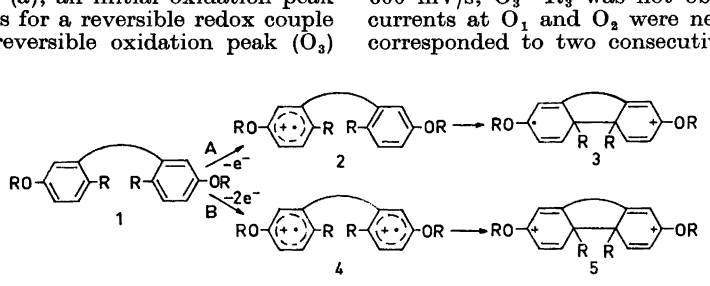
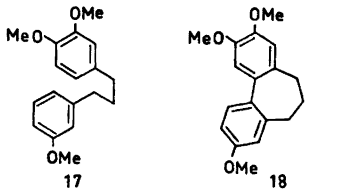
The oxidative cyclization of phenyl ethers is a topic of great current interest to organic chemists due to the importance of such coupling reactions in natural systems.[1-5] Various mechanisms, such as attack of a cation radical moiety upon an unoxidized aromatic ring (path A)[4] or initial oxidation to a dication diradical followed by coupling (path B)[2] have been proposed. The only mechanistic evidence that has been presented is voltammetric evidence for path B.[2] We now present conclusive evidence for the occurrence of path A during the oxidative cyclization of 1-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-propane (*6*).

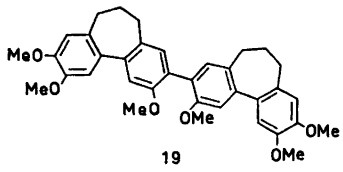
Anodic oxidation of *6* in dichloromethane-trifluoroacetic acid (TFA) (3:1) resulted in the formation of *11* which was isolated in 71 % yield. (Found: C 75.9; H 7.1. Calc. for $C_{18}H_{20}O_3$: C 76.1; H 7.0). The NMR assignment of the aromatic protons are as follows; H_A 7.14 (d, $J_{AB}=8.1$ Hz), H_B 6.79 (d,d, $J_{AB}=8.1$ Hz, $J_{BC}=2.8$ Hz), H_C 6.93 (d, $J_{BC}=2.8$ Hz), H_D 6.93 (s), and H_E 6.76 (s). Shifts are in δ values and the subscripts are those used in structure *11*. The remaining protons gave signals at δ: 3.85 (3 H, methoxy), 3.91 (3 H, methoxy), 3.93 (3 H, methoxy), 2.41 (t, 4 H, aliphatic) and 2.12 (q, 2 H, aliphatic). *M/e* 284 (M^+). An isomer of *11* was prepared by the oxidation of *17*. The isomer (*18*) showed a different NMR spectrum and did not form a dimer while *11* with an unsubstituted position *para* to the biphenyl linkage gave *19* upon further oxidation (V. D. Parker and A. Ronlán, unpublished results).

Cyclic voltammograms of *6* in the same solvent are shown in Fig. 1. At a voltage sweep rate of 31 mV/s (a), an initial oxidation peak (O_1), small peaks for a reversible redox couple (O_2-R_2), an irreversible oxidation peak (O_3) and a reduction peak (R_4) were observed on a complete cycle. The peaks O_3 and R_4 matched those observed during cyclic voltammetry of the product, *11*. The height of O_3 indicated that substrate was being oxidized nearly quantitatively to *11* at that voltage sweep rate. The effect of increasing the sweep rate is illustrated in (b) and (c).

The redox couple (O_2-R_2) became more pronounced with increasing sweep rate while the relative current at O_3 was diminished. A reduction peak (R_3) corresponding to O_3 was also observed. At 310 mV/s O_3-R_3 was very small (c). At voltage sweep rates greater than 600 mV/s, O_3-R_3 was not observed and the currents at O_1 and O_2 were nearly equal and corresponded to two consecutive one electron







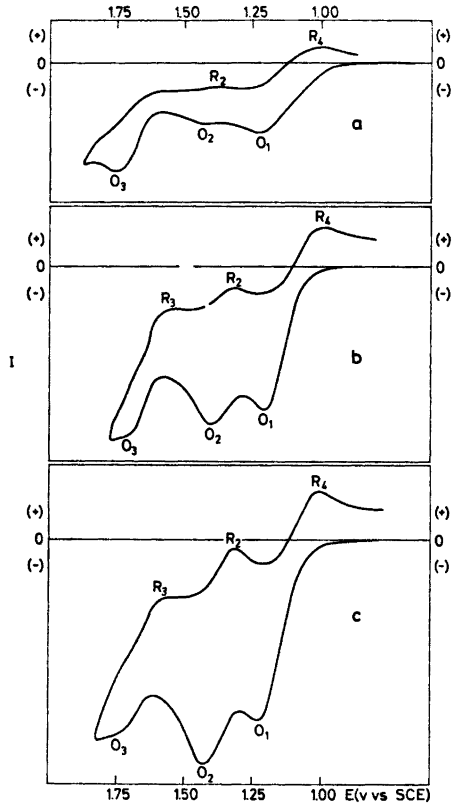


Fig. 1. Cyclic voltammograms for the oxidative cyclization of *6* in dichloromethane-TFA (3:1) containing Bu_4NBF_4 (0.2 M). Voltage sweep rate: (a) 31 mV/s, (b) 151 mV/s, (c) 310 mV/s.

transfers. Thus, it is clear that O_2-R_2 is a reversible redox couple of a short lived intermediate formed during oxidation of *6* to *11* which has a lifetime of the order of 1 s in dichloromethane-TFA (3:1) at room temperature. The reduction peak (R_4) was observed even at high sweep rates which indicates that under those conditions it corresponds to a further reduction of the species formed at R_2. Voltammetry in acetonitrile gave similar results with the height of O_2 showing a marked sweep rate dependence. On the other hand, R_2 was not observed under any conditions in acetonitrile indicating that the intermediate formed at O_2 was consumed in a rapid chemical reaction.

The sweep rate dependence for the observation of the reversible couple (O_2-R_2) suggested that the intermediate oxidized at O_2 undergoes a relatively slow chemical reaction which is outrun as the voltage sweep rate is increased. The latter suggested that it might be possible to observe different products if the chemical step was precluded by carrying out the oxidation at a potential greater than O_2. In fact, in acetonitrile *11* was formed in nearly quantitative yield when the reaction was carried out at a potential of + 1.25 V and the unrearranged dienone (*14*) was the exlusive product when the reaction was conducted at potentials greater than + 1.60 V.*

The intermediate undergoing oxidation at O_2 is a one electron oxidation product of (*6*) which reacts slow enough to be detected by slow sweep cyclic voltammetry. Mechanism B requires that the intermediate be the cation radical of *6* which is further oxidized to the dication diradical at O_2 (+ 1.42 V *vs.* SCE). We can rule out the latter mechanism on the basis that the dication diradical would not form at such a low potential** and would be a very reactive species. Mechanism A suggests that the intermediate could be a cation radical in which the cationic center and the unpaired electron are in different rings separated by saturated carbon (*8*) or the radical (*15*). On the basis of the data, we cannot definitively choose between *8* and *15* as the intermediate (Scheme). However, if *15* were the intermediate, O_2-R_2 would correspond to the couple, *15*⇌*13*. We have found that *14* oxidizes about 100 mV more easily than O_2 and this must involve oxidation of the ring containing two methoxy groups. It seems almost inconceivable that *15* should be more difficult to oxidize than *14*. Furthermore, the only product formed at potentials below O_2 is *11* which forms *via* a dienone phenol rearrangement of the intermediate and it seems much

* Compound (*14*) was isolated in 91 % yield and identified by comparison of the NMR, mass and IR spectra with that of the authentic compound prepared by either chemical [6] or electrochemical [7] oxidation of the corresponding phenol.

** The ring containing only one methoxy group in *6* would not be expected to oxidize more easily than anisole, + 1.7 V.

more likely that the cation radical (*8*) is the rearranging species rather than *15*. Two additional points favor *8* over *15* for the intermediate: At high sweep rates the cyclic voltammogram of *6* shows R_4 which must be due to reduction of the intermediate. The radical *15* would reduce at negative potentials. Also R_2 is not observed in acetonitrile, most likely due to rapid deprotonation of *12*. Thus, we favor the reaction pathway involving the cation radical (*8*) for the reactions producing both *11* and *14*.

Acknowledgement. The authors are indebted to Dr. Ulla Svanholm for advice in the interpretation of the NMR spectrum of *11*. This study was supported by a grant from the Swedish Natural Science Research Council.

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Received November 11, 1974.

Non-enzymic Oxidation of Lower Aliphatic Alcohols by Ascorbic Acid in Tissue Extracts

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It has been shown that ethanol is oxidized to acetaldehyde by ascorbic acid,[1] and since it is not oxidized further, the aldehyde accumulates. The ascorbic acid content of different tissues can vary considerably,[2] so that it can be assumed that the reaction proceeds at different speeds in different tissue extracts. As far as is known, no reports have been published on the non enzymic oxidation of other alcohols than ethanol.

Only small amounts of formaldehyde were formed from methanol when 20 mM alcohol was incubated in a citrate buffer, pH 4.0, containing 2.0 mM ascorbic acid (Table 1). The other normal and iso alcohols tested all formed more than 100 nmol aldehyde in a reaction mixture of 1 ml. With the exception of methanol the oxidation rate decreased with increasing chain length.

Table 1. Oxidation of some aliphatic alcohols by ascorbic acid. Alcohols (20 mM) in 0.1 M citrate buffer, pH 4.0, containing 2.0 mM ascorbic acid was incubated for 60 min at 65 °C. The aldehydes formed except formaldehyde were estimated gas chromatographically.[10] Formaldehyde was estimated spectrophotometrically by the Eegriwes' method.[11] The values given are the means of two experiments.

Alcohol added	Aldehyde formed	(μM)
Methanol	Formaldehyde	< 100
Ethanol	Acetaldehyde	530
Propanol	Propionaldehyde	310
Isobutanol	Isobutyraldehyde	230
Butanol	Butyraldehyde	220
Isopentanol	Isovaleraldehyde	120
Pentanol	Valeraldehyde	110

Extracts contained only a part of the ascorbic acid found in the intact tissue because of the dilution with perchloric acid (Table 2). Bovine liver has been reported to contain 1.7 mmol ascorbic acid/kg, kidney 0.7 mmol/kg, heart 0.3 mmol/kg and blood 0.1 mmol/kg.[2] Of the four tissue extracts examined the liver contained