Intramolecular Coupling of Diarylpropanes. Evidence for the Phenoxonium Ion Mechanism

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Spirodienones (cyclohexa-2,5-dienone derivatives like V) are important in biosynthesis and occur widely in nature.[1] Biosynthetically they are believed to be formed *via* coupling of a diphenolic precursor.[1] However, attempts to make spirodienones *in vitro* by oxidation of diphenols with conventional reagents have generally been unsuccessful,[1] probably due to the inability of these reagents to oxidize both phenolic moieties of the diphenol simultaneously and because free phenoxy radicals are involved in these reactions. Recently, spirodienones have been obtained from diphenolic precursors by using a vanadium oxytrichloride reagent[2] or a ferric chloride dimethylformamide complex,[3] which are able to oxidize both phenolic moieties simultaneously.

In a previous communication [4] we demonstrated that phenoxonium ions derived from hindered phenols by anodic oxidation react with anisole to give 4-(*p*-anisyl)-cyclohexa-2,5-dienones in high yield. We now report an application of the same principle to intramolecular cyclization of diarylpropanes, which gives spirodienones in high yield, and present evidence for the involvement of phenoxonium ions.

Phenols are more easily oxidized than the corresponding methyl ethers. Oxidation at the potential of the first oxidation stage of I (R = H) therefore occurs in the phenolic group without competition from oxidation of the other ring. The initial electron transfer produces the acidic cation radical (II) which deprotonates instantaneously in neutral or basic media.

In principle the cation radical (II) could also dimerize or cyclize (*via* electrophilic attack on the ether moiety or I). An investigation of the anodic oxidation of the methyl ether of I (R = OMe) has shown [5] that the stereochemistry of the diarylpropanes is in fact very favourable for the latter kind of reaction. However, on the basis of the following argument we believe that reactions other than deprotonation of the cation radical II can be ruled out. Electronically, 3-methylanisole and *p*-cresol are very similar and therefore would be expected to have similar oxidation potentials. Thus the observed difference in peak potentials (= 0.4 V)[4,8] must depend on a very rapid deprotonation of the *p*-cresol cation radical (the pK of cation radicals derived from monohydric phenols is about −5 (Ref. 6)). The deprotonation rate can be estimated [7] to be at least 10^7 times faster than dimerization of the *p*-cresol or 3-methylanisole cation radical (assuming that these two species have similar rates of dimerization). The potential of the first oxidation stage of I (R = H) is 1.30 V (standard calomel electrode) just as for *p*-cresol. This means that if cyclization is the preferred reaction for II it should be 10^7 times faster than dimerization of the *p*-cresol cation radical which is improbable (by analogy with phenol ethers,[8] we believe that the most likely reaction (next to deprotonation) of cation radicals derived from phenols is dimerization).

Any chemical reaction following electron transfer must then involve either the radical III or the phenoxonium ion IV. Reactions in which phenoxy radicals participate generally result in a mixture of products due to the delocalisation of the unshared electron over the oxygen atom and the carbon atoms of the ring. On the other hand, the positive charge of the phenoxonium ion is concentrated in the ring,[9] favouring reactions with bond formation to carbon. Thus, controlled anodic conditions ensure that the phenolic part of the molecule undergoes oxidation and an analysis of the products formed will distinguish between the phenoxonium ion and the phenoxy radical mechanisms.

The anodic oxidation of I (R = H) (0.1 mmol) in acetonitrile (50 ml) containing sodium perchlorate (0.1 M) and sodium carbonate (1 g) in a three compartment cell was monitored by peak voltammetry during constant current coulometry.[10] Precisely 2.0 Faradays per mol of I (R = H) were consumed during exhaustive electrolysis. When the oxidation was complete, the sodium carbonate was filtered off. For analysis of the product, trifluoroacetic acid (TFA) (5 ml) was added to the electrolysis mixture to convert the electro-inactive spirodienone (V, R = H) to the corresponding phenol (VII, R = H). The reaction was monitored by the appearance of an oxidation peak at 0.95 V and was complete in less than 30 min at room temperature. The height of the oxidation peak at 0.95 V indicated that the overall result of the reaction was quantitative conversion of V (R = H) to VII (R = H).

A series of preparative experiments were carried out, and the results are shown in Table 1. The formation of the compound VI represents an interesting electrochemical analogy (the reduction step in this transformation takes place at the cathode of the undivided cell) to the dienone-benzene rearrangement which is frequently encountered in alkaloid biosynthesis.[12]

While it is clear that only the phenolic ring undergoes oxidation in the case of I (R = H)

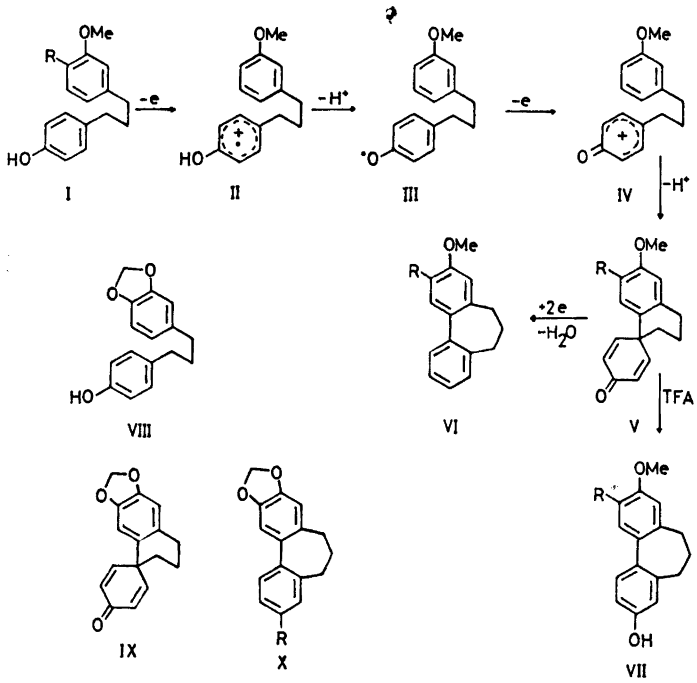

Table 1. Anodic oxidation of various diarylpropanes on a platinum anode in acetonitrile.[a]

Substrate	Products, yield (%)	TFA[b] → Phenol
I (R=H)	VI (R=H) (17): V (R=H) (68)	VII (R=H)[c]
I (R=OMe)	VI (R=OMe) (20); V (R=OMe) (73)	VII (R=OMe)[c]
VIII[d]	X (R=H) (21); IX (75)	X (R=OH)[c]

[a] These oxidations were carried out in an undivided cell (nickel cathode) on 2 mmol [0.2 mmol in case of I (R=H)] of substrate in acetonitrile (100 ml) containing sodium perchlorate (0.1 M). The potential was controlled at 1.25 V and the electrolysis was interrupted when 2 Faradays per mol of substrate had been passed. The products were isolated by chromatography on alumina and characterized by their NMR, mass spectrum and elemental analysis. [b] Compound obtained by treatment of the spirodienone with TFA. [c] Identified as its methyl ether by comparison with an authentic sample obtained from anodic coupling of the corresponding methoxylated diarylpropane.[5] [d] This compound has been oxidized to IX in 87 % yield with thallium trifluoroacetate.[11]

the same cannot be said with certainty for the oxidation of I (R=OMe) or of VIII since the additional ether group in these compounds lowers the oxidation potential of the second ring and it is expected that both aryl groups should undergo oxidation at about the same potential. Thus a dication diradical mechanism similar to that demonstrated for the anodic cyclization of methoxybibenzyls [13] cannot be ruled out for these reactions.

The absence of intermolecular coupling products and products involving carbon-oxygen bond formation from the oxidation of I (R=H) shows that the radical III is oxidized anodically as soon as it is formed. The nature of the products obtained (V and VI) strongly suggests that the phenoxonium ion IV is the result of this oxidation.

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Received January 7, 1974.

Molecular Structure of Methyl 6-*O*-Acetyl-β-D-glucopyranoside

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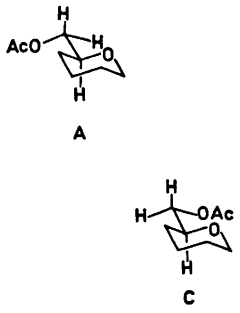
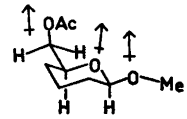
In our attempts to correlate the circular dichroism of glycoside acetates with molecular geometry, we find that the single, negative CD band observed for methyl 6-*O*-acetyl-β-D-glucopyranoside is best explained by assuming that rotamer C predominates in ethanol solution.

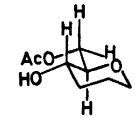


This contrasts with the results obtained for the corresponding α-anomer, for which a double CD band was observed, and which led to the suggestion that both rotamers B and C contributed to the observed CD. We suggested that for the β-anomer an unfavourable dipolar interaction for rotamer B would lead to the presence of



rotamer C only. Since this interaction is absent in the corresponding α-anomer, both rotamers B and C can be present.[1] Lemieux and coworkers have suggested, on the basis of NMR studies, as well as from considerations of optical rotation, that for D-*erythro*-hexopyranosides, rotamer C predominates over A and B.[2,3]

We have previously reported an X-ray crystallographic study on methyl 6-*O*-acetyl-β-D-galactopyranoside.[4] This showed that in the crystalline state rotamer A predominated. In the D-*gluco* series, however, this rotamer is unimportant, due to an unfavourable 1,3 interaction.



The present study, summarized in Fig. 1 and Table 1 establishes that for methyl 6-*O*-acetyl-β-D-glucopyranoside the conformation in the crystalline state corresponds to rotamer C, in agreement with the interpretation of the results from the CD investigation. The compound crystallized in space group $P2_1$, $a = 10.201$, $b = 7.239$, $c = 7.863$, $Z = 2$. The X-ray data were obtained on a Philips PW 1100 computer-controlled single-crystal diffractometer with graphite monochromatized Cu$K\alpha$ radiation. The phase

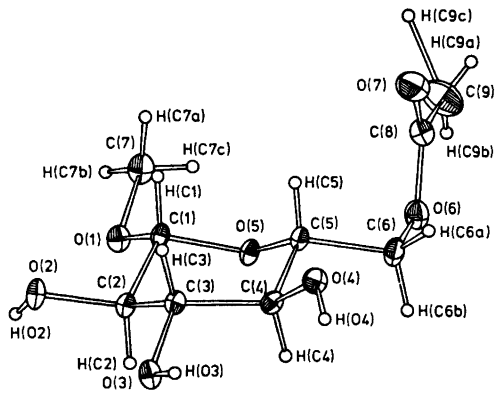


Fig. 1. Molecular structure of methyl 6-*O*-acetyl-β-D-glucopyranoside.