Cyclisation of 3-(*p*-Methylphenyl)propan-1-ol *via* its Alkoxyl Radical and Aryl Radical Cation Intermediates. A Comparison of Regioselectivities

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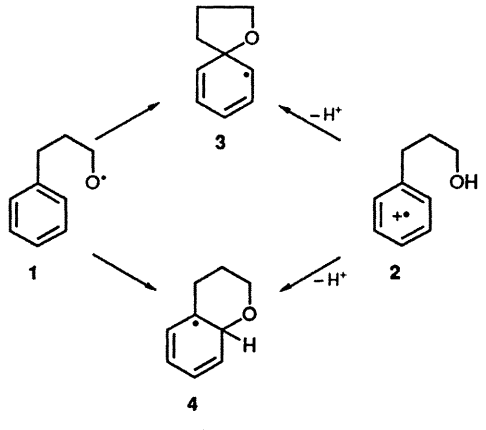
Evidence is presented that 3-(*p*-methylphenyl)propan-1-ol **5** undergoes competing 1,5- and 1,6-cyclisation *via* both its aryl radical cation **6** and alkoxyl radical **7** intermediates. Variations in both product yields and regioselectivities of cyclisation with pH are observed, with evidence of significant differences between the two intermediates.

Intramolecular radical additions in alkenyl and alkynyl systems are frequently characterised by high regioselectivity.[1] For example, ring-closure of the pent-4-en-1-oxyl radical which occurs under kinetic control, affords exclusively the *exo*-cyclised product[2] as a result of the stringent stereoelectronic constraints which govern such reactions. Analogous cyclisations onto aromatic rings are complicated by their reversibility[3,4c] and consequently only the thermodynamically-favoured *endo*-products are usually observed. However, we have reported[4] that high yields of *exo*-cyclised products may be obtained provided the intermediate spirodienyl radical is efficiently intercepted.

It is evident that the cyclised intermediates **3** and **4** resulting from *exo*- and *endo*-cyclisation, respectively, of the alkoxyl radical **1** could also be obtained from the aryl radical cation **2** as a result of intramolecular attack by the side-chain hydroxy group (Scheme 1).[5] However, the transition states for cyclisation



Scheme 1

via the radical could differ from those involving the radical cation since, in the first instance, addition of an electrophilic radical to a neutral aromatic ring is involved, and in the second, nucleophilic attack by the hydroxy group on a positively charged ring. Consequently, differences in the regioselectivities for cyclisation might be expected in the two cases. We now report on a study in which the regioselectivity of cyclisation of 3-(*p*-methylphenyl)propan-1-ol **5** *via* its aryl radical cation **6** and alkoxyl radical **7** intermediates is compared.

We have reported previously[5] that 3-phenylpropan-1-ol cyclises to chroman when oxidised to its aryl radical cation by $SO_4^{\bullet -}$. Although no products unique to 1,5-ring closure were detected in that investigation, it is possible that 1,5-cyclised intermediates could have formed but subsequently rearranged to their 1,6-analogues through migration of either carbon or oxygen (Scheme 2).

However, the introduction of a *para*-substituent onto the aryl ring should permit discrimination between the direct and indirect pathways for the formation of 1,6-cyclised products. Direct 1,6-cyclisation would afford exclusively the 7-substituted chroman **9**. In contrast, 1,5-ring closure would result in the 6-substituted isomer **12** provided carbon migration occurred in one of the spirodienyl intermediates. Oxygen migration would afford the 7-substituted isomer **9**, but migration of carbon seems more likely on energetic grounds, particularly in the case of the carbocation.

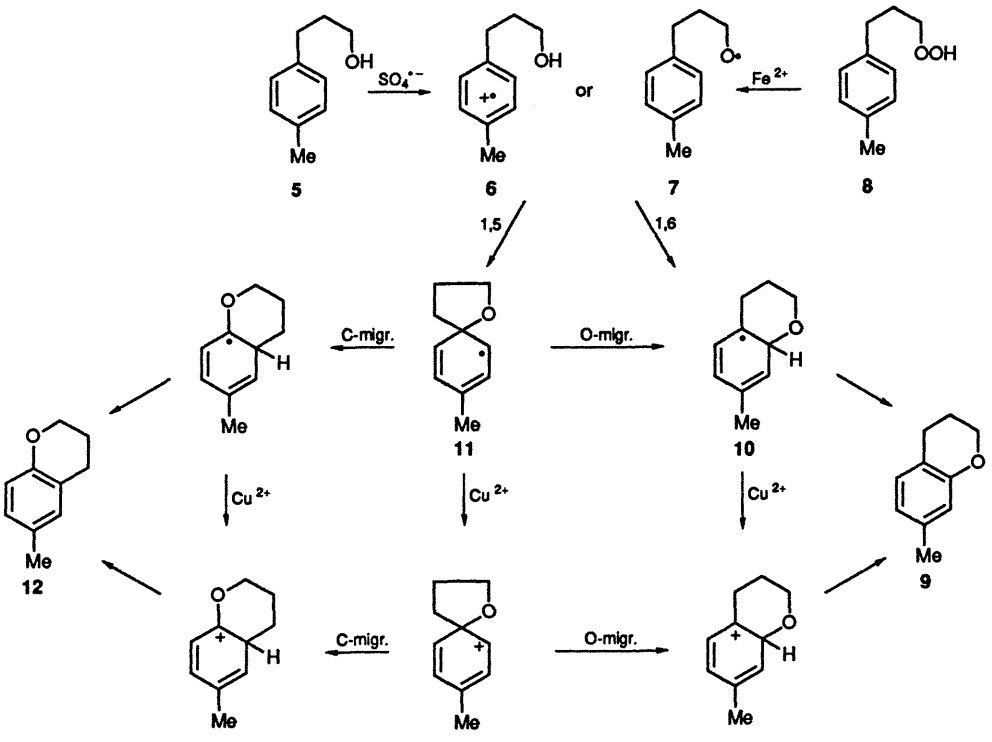
We therefore generated the aryl radical cation **6** [by oxidation of 3-(*p*-methylphenyl)propan-1-ol **5** with $SO_4^{\bullet -}$ obtained from reduction of $S_2O_8^{2-}$ with Fe^{2+}], and the alkoxyl radical **7** [by reduction of the hydroperoxide **8** with Fe^{2+}], and compared their cyclisation products. In all cases Cu^{2+} was also added to facilitate oxidation of the cyclised radical intermediates.†

The cyclisation reactions of both the aryl radical cation **6** and alkoxyl radical **7** might be expected to show some dependence on the pH of the reaction medium. In the case of the radical cation, cyclisation could be inhibited at low pH through protonation of the hydroxy group, while acid-catalysed ring-opening of the cyclised radical intermediates **10** and **11** to the radical cation could also be promoted. The latter reaction could also serve to convert the alkoxyl radical **7** to the radical cation **6**. Under highly acidic conditions, protonation of the alkoxyl radical is also possible. Such a protonated alkoxyl radical intermediate would be expected to induce electron transfer from the aromatic ring, thereby generating the radical cation **6** (*cf.* ionisation potentials[6] for toluene and ethanol of 8.82 and 10.48 eV, respectively). Cyclisation of this intermediate could also occur, probably with a similar selectivity to that of the alkoxyl radical.[2e]

Tables 1 and 2 show the effect of variations in the initial pH of the reaction mixture on the reactions of the aryl radical cation **6** and alkoxyl radical **7**, respectively. The optimum pH's for cyclisation differ significantly in the two cases, being *ca.* 5 for the radical cation and *ca.* 2 for the alkoxyl radical. In both instances the yields of the isomeric chromans decline sharply at the low end of the pH range.

There is no evidence to suggest that the alkoxyl radical **7** is converted to the radical cation **6** since 2-(*p*-methylbenzoyl)-ethanol **13**, which is afforded in high yield by the radical cation at low pH, is not observed among the products resulting from the hydroperoxide **8**. This implies that acid-catalysed conversion of the cyclised intermediates **10** and **11** to the radical cation **6** does not occur under the reaction conditions. Since the

† We have observed previously[5] that very little cyclisation occurs in the absence of Cu^{2+}. Reverse ring-opening of the cyclised radical intermediates presumably occurs, allowing competing side-chain reactions of the radical cation and alkoxyl radical to predominate.



Scheme 2

Table 1 Effect of pH on the reaction of 3-(*p*-methylphenyl)propan-1-ol **5** with $SO_4^{\bullet -}$

	Products (%)			
pH[a]	**12**	**9**	**13**	Ratio **9**:**12**
6.0 (3.1)	4.9	42.4	0	89.6:10.4
5.4 (3.1)	11.6	46.5	4.3	80.0:20.0
5.1 (2.9)	17.4	45.4	5.7	72.3:27.7
3.5 (3.1)	12.2	22.0	2.3	64.3:35.7
2.4 (3.1)	4.8	6.2	50.2	56.4:43.6
1.4 (3.2)	2.6	0.2	56.9	7.1:92.9
0.6 (2.9)	trace	trace	88.0	— —

[a] It was not possible to maintain constant pH during the reaction. Shown are the initial (and final) pH values.

Table 2 Effect of pH on the reaction of 3-(*p*-methylphenyl)propyl-1-hydroperoxide **8** with Fe^{2+}

	Products (%)				
pH[a]	**12**	**9**	**5**	**14**	Ratio **9**:**12**
6.0 (5.0)	1.8	12,9	33.0	41.0	87.8:12.2
4.9 (3.4)	4.2	17.0	32.0	39.6	80.2:19.8
3.3 (2.8)	6.1	14.1	31.9	40.1	69.8:30.2
2.1 (2.2)	6.9	16.7	36.9	31.3	70.8:29.2
1.4 (1.7)	4.3	11.6	40.3	13.4	72.9:27.1
0.5 (0.8)	0.5	1.4	47.0	2.0	73.7:26.3

[a] See footnote, Table 1.

low yields of cyclised products obtained in the $SO_4^{\bullet -}$ reaction at low pH cannot be due to inhibited formation of the radical cation, in view of the high yield of the ketone **13** obtained, this effect must consequently be ascribed to retardation of the rate of cyclisation as a result of protonation of the side-chain hydroxy group. Competing deprotonation of the side-chain at the benzylic position, which leads ultimately to the ketone **13**, therefore predominates.

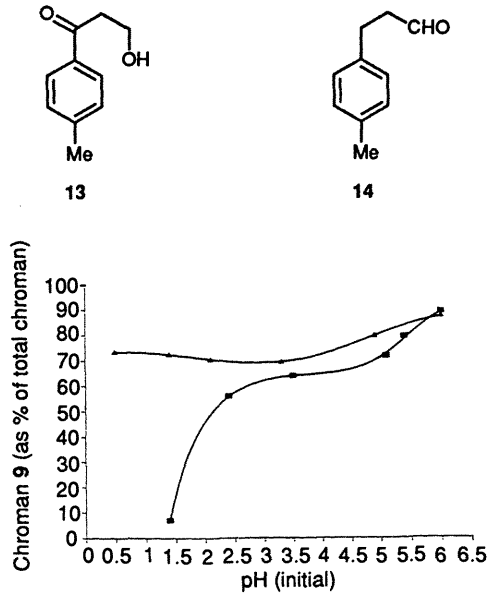


Fig. 1 Effect of pH on chroman ratio: ■, radial cation **6**; ▲, alkoxyl radical **7**

Reasons for the low yields of chromans obtained from the alkoxyl radical at low pH are less clear. It is possibly significant that the yield of the aldehyde **14**, which is thought to form from the alkoxyl radical *via* a 1,2-hydrogen shift[2c,7] with subsequent oxidation of the resulting α-hydroxyalkyl radical, also declines sharply at low pH. We therefore suggest that generation of the alkoxyl radical is inhibited at low pH.

Not only the yields, but also the ratios of the chromans **9** and **12**, show a pH dependence (Fig. 1). In both the alkoxyl radical and radical cation reactions, the 7-methylchroman **9** predominates at the upper end of the pH range and then decreases as the pH is lowered. We ascribe this effect to changes in the nature of the Cu^{2+} complexes present in solution as the pH is varied. Presumably, those Cu^{2+} species present at higher pH

are less effective at oxidising the spirodienyl radical **11** thereby allowing it to equilibrate, *via* its appropriate ring-opened precursor, to the thermodynamically favoured-intermediate **10**.

However, in contrast to the alkoxyl radical reaction where the 7-methylchroman **9** remains the major component over the entire pH range, mainly the 6-methylchroman **12** is formed from the radical cation at low pH. If it is assumed that at low pH the radical intermediates **10** and **11** are more efficiently intercepted through oxidation and the chroman ratio therefore reflects more accurately the relative rates of 1,5- and 1,6-cyclisation, a clear difference in the regioselectivities of cyclisation between the radical cation and alkoxyl radical is evident.

This report is, as far as we are aware, the first in which the regioselectivity of cyclisation of an aryl radical cation with a side-chain nucleophilic group has been investigated and compared with the related radical cyclisation. Further experimental and theoretical studies designed to elucidate the principles governing these cyclisation reactions are in progress and will be fully reported later.

Acknowledgements

Financial support from the Foundation for Research Development and Karbochem is acknowledged.

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Paper 2/06645I
Received 16*th December* 1992
Accepted 13*th January* 1993