Intramolecular Alkylation of Phenols. Part I.[1] Mechanism of Phenoxide Cyclisation

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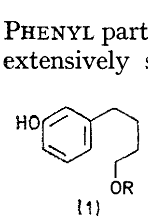
Cyclisation of 4-(*m*-hydroxyphenyl)butyl toluene-*p*-sulphonate under basic conditions is shown to occur by the hitherto unreported Ar_2^--6 mechanism. Kinetic data are presented which confirm phenyl participation under basic conditions. The corresponding 3-(*m*-hydroxyphenyl)propyl toluene-*p*-sulphonate did not cyclise and no evidence could be found for the involvement of an Ar_2^--5 mechanism.

PHENYL participation in displacement reactions has been extensively studied from both a mechanistic[2] and a synthetic standpoint.[3] However, investigation of anchimeric assistance by phenoxide ion has been confined exclusively to systems involved in geminal substitution.[2] The possibility of Ar_2^- participation presented itself and we chose 4-(*m*-hydroxyphenyl)butyl toluene-*p*-sulphonate (1; R = *p*-$CH_3C_6H_4SO_2$) as a model system. It was anticipated that phenol (1; R = *p*-$CH_3C_6H_4SO_2$) would undergo intramolecular alkylation at the *ortho*- and *para*-positions under basic conditions. The phenols (2) and (3) were the expected products.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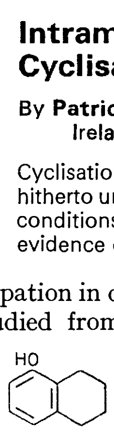
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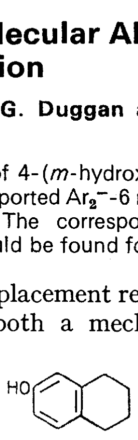
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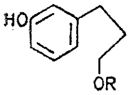
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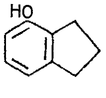
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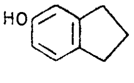
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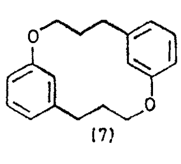
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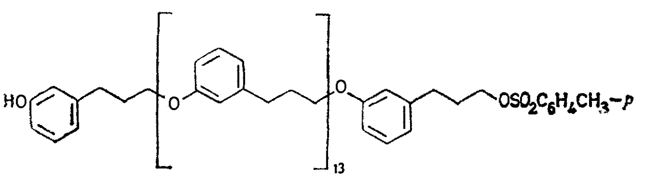
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Search for Ar_2^--6 *Participation.*—A solution of phenol (1; R = *p*-$CH_3C_6H_4SO_2$) in t-butyl alcohol–tetrahydrofuran, with a slight excess of potassium t-butoxide was heated under reflux for 10 h. The only products were (2) and (3) in the ratio 3 : 1. The benzyl ether of (1; R = *p*-$CH_3C_6H_4SO_2$) did not react under the same conditions. In boiling water, (1; R = *p*-$CH_3C_6H_4SO_2$) with five mol. equiv. of potassium hydroxide, yielded (2) and (3) in 88% combined yield in the ratio 38 : 62 with a 12% yield of the solvolysis product (1; R = H). That the Ar_2^--6 mechanism persisted under these latter conditions is indicated by the low percentage of cyclisation observed under neutral conditions (Table). To complete this preliminary investigation the cyclisation was attempted under acidic conditions. Solvolysis predominated and a decrease in the *ortho* : *para* ratio was observed (Table).

Kinetic Evidence for Ar_2^--6 *Participation.*—In search

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[1] Preliminary communication, P. G. Duggan and W. S. Murphy, *J.C.S. Chem. Comm.*, 1972, 770.

[2] For leading references see B. Capon, *Quart. Rev.*, 1964, **18**, 86.

[3] See for example S. Doring and J. Harley-Mason, *Chem. and Ind.*, 1959, 1551; S. Masamune, *J. Amer. Chem. Soc.*, 1961, **83**, 1009; J. A. Marshall and S. F. Brady, *J. Org. Chem.*, 1970, **35**, 4068; D. J. Beames, T. R. Klose, and L. N. Mander, *Chem. Comm.*, 1971, 773; W. L. Mock and K. A. Rumon, *J. Org. Chem.*, 1972, **37**, 400.

of kinetic evidence for Ar_2^--6 participation, the rate of reaction of (1; R = p-$CH_3C_6H_4SO_2$) was studied in 25% dioxan–water at 50°. The results are shown as a pH–rate profile (Figure 1). The reaction was followed spectrophotometrically and in each case studied the pH was held constant by the addition of a suitable buffer. The products (1; R = H), (2), and (3) were stable under these conditions. At each pH good first-order kinetics were observed. The observed rate constant (k_{obs}) is a composite of the rate constants leading to cyclisation (k_Δ) and to solvolysis (k_S). The magnitude of these partial rate constants at each pH were calculated from the g.l.c. data and k_{obs}. The variations of k_Δ and k_S with pH are plotted separately in Figure 2.

Solvolysis of 4-(*m*-hydroxyphenyl)butyl toluene-*p*-sulphonate

Reaction conditions [a,b]	Yield (%) [c]	*ortho* (%) [c,d]	Solvolysis (%) [c,e]
Bu^tOK–Bu^tOH	100	75	
KOH–H_2O	100	38	12
H_2O	100	38	75
H_2O–$HClO_4$; pH 1	89	23	90

[a] All reactions at 3.3×10^{-3}M. [b] All reactions at reflux temperature. [c] Determined by g.l.c. [d] Ratio with *para*-alkylation product. [e] Ratio with cyclisation.

The pK_a of (1; R = p-$CH_3C_6H_4SO_2$) was determined independently by measuring the variation of optical density as a function of pH, by spectroscopic means. Comparison with theoretical curves was made. The pK_a was found to be 9.78, which is in good agreement with the value of 9.70 determined by the same procedure from Figure 1.

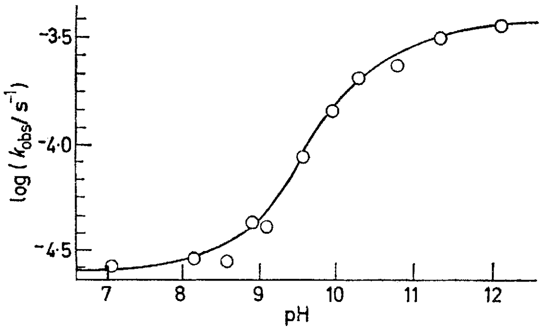

FIGURE 1 Plot of log k_{obs} against pH for solvolysis of (1; R = p-$CH_3C_6H_4SO_2$) in 25% dioxan–water at 50° (μ 0.5; $NaClO_4$). The points are experimental and the line is theoretical for pK_a 9.70

These results (Table and Figure 2) emphasise the dependence of the rate of cyclisation on pH. The rate constant (k_Δ) increased 400-fold in the pH region studied. This evidence strongly suggests Ar_2^--6 participation under basic conditions.

In contrast, under neutral or acidic conditions the low ratio of *ortho*- to *para*-alkylation coupled with the low percentage of cyclisation suggests the operation of a second process. It is probable that a slow, in relation to solvolysis, Ar_2^--6 participation is involved in this pH region. In addition, it was surprising to note that k_S was practically independent of pH. The plot of log k_S against pH (Figure 2) had a slope of 0.03 (α 0.99).

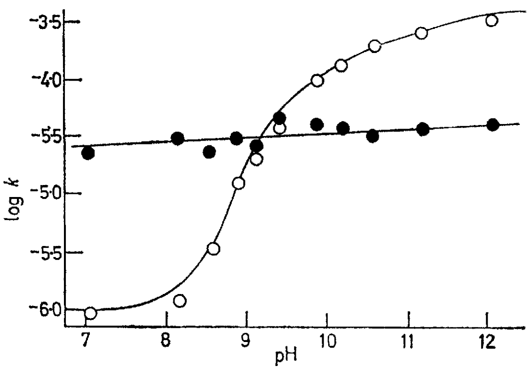

FIGURE 2 Plot of log k against pH for cyclisation (k_Δ; ○) and solvolysis (k_S; ●) of (1; R = p-$CH_3C_6H_4SO_2$) in 25% dioxan–water at 50° (μ 0.5; $NaClO_4$)

The values for k_S are of the same order as those previously observed for primary sulphonates.[4] Under these conditions at least,[5] an S_N1 mechanism seems improbable[4] since primary sulphonates are known[6] to react by an S_N2 mechanism. Although a mechanism involving solvolysis of the un-ionised phenol (1; R = p-$CH_3C_6H_4SO_2$) seems probable, further work will be required to clarify this result.

Search for Ar_2^--5 *Participation*.—This investigation was undertaken in a similar manner. Phenol (4; R = p-$CH_3C_6H_4SO_2$) was synthesised and used as a model. It was anticipated that cyclisation would result in a mixture of (5) and (6). A solution of (4; R = $CH_3C_6H_4SO_2$) (10^{-2}M) in t-butyl alcohol was heated under reflux for 24 h in the presence of a slight excess of potassium t-butoxide. This reaction yielded a crystalline product (7) in 84% yield which was insoluble in Claisen alkali. This dimeric product (7) was again obtained in essentially quantitative yield when the reaction was undertaken at 3.3×10^{-3}M. In refluxing toluene, the sodium salt of (4; R = p-$CH_3C_6H_4SO_2$) (10^{-2}M) gave 40% (7), 30% polymeric material, and 30% Claisen alkali-soluble fraction which contained (4; R = p-$CH_3C_6H_4SO_2$) and at least eight products. Microanalysis and spectroscopic data of the polymer were consistent with the structure (8).

In water, solvolysis occurred almost exclusively. When the sodium salt of (4; R = p-$CH_3C_6H_4SO_2$) (3.3×10^{-3}M) was heated under reflux for 10 h, a 93% yield of 3-(*m*-hydroxyphenyl)propan-1-ol (4; R = H) was obtained. Thus, it seems that conditions are quite unfavourable in (4; R = p-$CH_3C_6H_4SO_2$) for Ar_2^--5 participation with the result that intermolecular reactions compete successfully.

That Ar_2^--6 is much easier by comparison with Ar_2^--5

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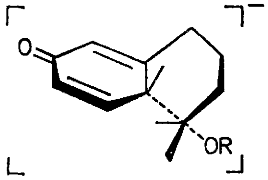
[4] S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700; P. M. Laughton and R. E. Robertson, *Canad. J. Chem.*, 1955, **33**, 1207.

[5] W. Gerrard, H. R. Hudson, and W. S. Murphy, *J. Chem. Soc.*, 1964, 2314.

[6] See for example A. Streitwieser, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 1117.

participation suggests that steric rather than electronic factors have the major influence. In the transition state an almost perpendicular approach to the ring is necessary: the actual angle depends on the extent of phenyl participation.[7] The transition states for Ar_2^{-}-6 and Ar_2^{-}-5 participation leading to *para*-alkylation can be represented by (9) and (10) respectively. Inspection of models indicates that whilst there is little, if any, strain in (9), the transition state (10) is highly strained. It is of note that the transition state of the ready Ar_1^{-}-5 participation [8] is relatively strainless.



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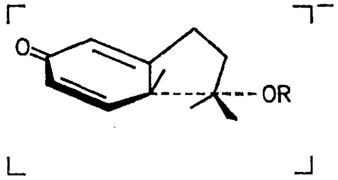
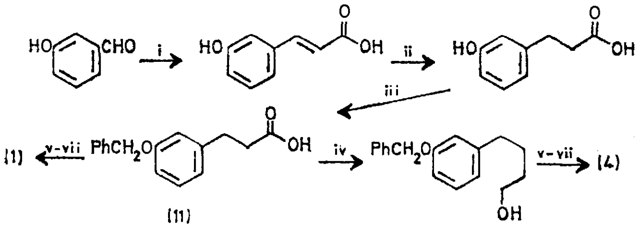


(10)

Synthesis of Starting Materials and Products.—The phenols (1 and 4; R = p-$CH_3C_6H_4SO_2$) were synthesised from the common intermediate (11) (Scheme). The solvolysis products (1 and 4; R = H) were synthesised from their corresponding benzyl ethers (see Scheme) by catalytic hydrogenation.



SCHEME Reagents: i, $CH_2(CO_2H)_2$–pyridine–piperidine; ii, Na–Hg; iii, EtOH–HCl; K_2CO_3–$PhCH_2Cl$; KOH–MeOH; H_2SO_4; iv, $SOCl_2$–CH_2N_2–Ag_2O; v, $LiAlH_4$–Et_2O; vi, p-$CH_3C_6H_4SO_2Cl$–pyridine, 0°; vii, Pd–H_2

EXPERIMENTAL

General.—Spectra were measured as liquid films for liquids and as KBr discs for solids on a Perkin-Elmer 257 spectrophotometer. U.v. spectra were measured with a Pye–Unicam SP 800 spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer R20A 60 MHz instrument. T.l.c. was undertaken on plates with Merck silica gel HF_{254} prepared according to Stahl. Preparative t.l.c. involved the use of Kieselgel PF_{254} (Merck). Dry column chromatography was carried out using silica gel (Woelm, activity 11). G.l.c. was performed with a Perkin-Elmer F11 dual column flame ionisation detector chromatograph. A copper column (8 m × 1/8 in) packed with 5% SE30 on 60—80 mesh chromosorb W was employed. Absolute percentages were obtained by reference to an internal standard, a known weight of which was added prior to injection.

Details of synthesis (see Scheme) are given in Supplementary Publication No SUP 21375 (14 pp.).*

Kinetic Measurements.—All inorganic materials used were AnalaR grade. Dioxan was B.D.H. AnalaR grade, used without further purification. Deionised water was twice distilled from alkaline potassium permanganate. The solvent, 25% (v/v) dioxan–water, was prepared at 15°.

The kinetics of solvolysis of 4-(m-hydroxyphenyl)-butyl toluene-p-sulphonate (1; R = p-$CH_3C_6H_4SO_2$) were studied in 25% dioxan–water by following the change in optical density of the substrate at a suitable wavelength. Initial repetitive scans of the u.v. region established that these held tight isosbestic points.

The reactions were buffered by the presence of hydroxide ion or by 10^{-2}M-phosphate or -borate buffers and were followed spectrophotometrically. This instrument was equipped with thermostatted multiple cell compartments and an external Unicam Ar 25 recorder. The substrate was made up as a concentrated solution (10^{-1}M) in dioxan and reaction was initiated by addition of a drop of this substrate solution to the cell containing the equilibrated reaction solution. To ensure that pH drift was absent during a kinetic experiment the pH of the solution was checked before and after reaction using a Radiometer model PHM 26 pH meter equipped with a Metrohm EA checked before and after reaction using a Radiometer 125U electrode which had been standardised using Radiometer aqueous buffer solutions. The pH values quoted for 25% dioxan–water solution are the measured values without further correction obtained using this technique.

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* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

[7] R. Heck and S. Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 3114.

[8] R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 756; 1962, **84**, 778.