Intramolecular Alkylation of Phenols. Part II.[1] *ortho*- *versus para*-Alkylation[2]

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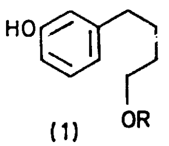
4-(*m*-Hydroxyphenyl)butyl toluene-*p*-sulphonate was used, under basic conditions, as a model for investigating the factors which affect the *ortho*- : *para*-alkylation ratio of phenols. The ratio was sensitive to the nature of the solvent, the metal cation, salt effects, and temperature. The suggested mechanism underlines the importance of the nature of the association between the metal and phenoxide ions on the orientation of the reaction.

THE factors governing *C*- *versus O*-alkylation of phenoxide ions have been the subject of many investigations.[3] Almost invariably *C*-alkylation occurred exclusively at the *ortho*-position.[4] Indeed, the then almost unique observation that *para*-alkylation occurred when alkylating agents such as diphenylmethyl chloride and triphenylmethyl chloride were used,[5] led to the suggestion [4a] that *para*-alkylation was 'diagnostic of the intermediacy of carbonium ions.' However, Kornblum and his co-workers observed that in strongly hydrogen bonding solvents appreciable *para*-alkylation of sodium phenoxide occurred.[4b] Kinetic studies ruled out the involvement of carbonium ions.[4b] Similar results in polar solvents were reported by others.[6] Later,[4b,7] it was found that alkylation could be diverted to the *para*-position by locating alkyl groups on the *ortho*-positions. Miller [7] observed an unusually high proportion of *para*-alkylation when he used cyclopropylmethyl bromide under conditions where carbonium ions were not formed.

Due to the paucity of systematic investigation, we decided to undertake the study of the factors influencing the *ortho*- : *para*-alkylation ratio of phenol anions. The phenol (1) was chosen as a model system for this purpose since (a) *O*-alkylation, an intermolecular process, could be inhibited by dilution,[1] (b) the *ortho*- : *para*-alkylation ratio, leading to (2) and (3) respectively, was very sensitive to reaction conditions, and (c) kinetic evidence had shown that under basic conditions the phenol (1) cyclised exclusively by an Ar_2^--6 mechanism.[1]



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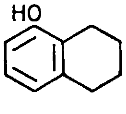

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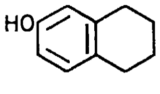

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Nature of the Solvent.—Our preliminary results [2] in both butyl alcohol–tetrahydrofuran and water suggested that the *ortho*- : *para*-alkylation ratio was solvent dependent. To test this further, the reactions of the sodium salt of (1; $R = SO_2C_6H_4Me$-*p*) were studied in a variety of solvents (Table 1). The reactions are arranged in order of increasing percentage of *para*-alkylation. Reactions were fastest in aprotic solvents and were usually complete within a week. Reactions in aprotic solvents took several weeks. Solvolysis was a competing reaction in the more polar solvents.

TABLE 1

Solvent effect on the product ratio of the sodium salt of 4-*m*-hydroxyphenylbutyl toluene-*p*-sulphonate [a] at 35° and 1×10^{-2}M

Solvent	Dielectric constant	% *ortho* [b]	% *para* [b]	% Solvolysis [b]	% Yield [b,e,g]
Bu^tOH [d]	10.9	89	11		90
Bu^tOH–THF [d]		89	11		78
THF	7	87	13		61
THF–H_2O [f]		81	19		42
EGDE [i]	7	87	13		59
Et_2O [c]	4.3	85	15		11 [h]
Pr^iOH [d]	18.3	75	15		94
Me_2NCHO	37	73	27		4
$PhCH_3$ [c]	2.4	72	28		17 [h]
EtOH	24	66	34	15	93
Me_2SO	45	55	45		5
H_2O [c]	80	54	46	21	97
MeOH	33	51	49	25	97

[a] Formed by addition of a slight excess of sodium hydride. [b] By g.l.c. [c] Heterogeneous. [d] Initially homogeneous; sodium toluene-*p*-sulphonate precipitated during reaction. [e] Reactions allowed to go to completion (t.l.c.). [f] One drop of water added to dried solvent (20 ml). [g] Yields accurate to ±5%. [h] Polymeric product also obtained. [i] EGDE = ethylene glycol dimethyl ether.

In general a decrease in the *ortho*- : *para*-alkylation ratio resulted when the polarity of the solvent was increased. For the reaction in alcohols, a linear relationship between the dielectric constant and the percentage *para*-alkylation was observed (Figure 1). Two other classes of solvents became apparent, (a) those of high dielectric constant which gave a lower percentage of *para*-alkylation than expected for an alcohol of similar dielectric constant and (b) those of low dielectric constant which gave a higher percentage of *para*-alkylation than expected for an alcohol of similar dielectric constant.

Consideration of the transition states[1] (4) and (5) will facilitate the understanding of these and other

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

[3] See for example (*a*) L. Claisen, *Z. Angew. Chem.*, 1923, **36**, 478; (*b*) L. Claisen, F. Kremers, F. Roth, and E. Tietze, *Annalen*, 1925, **442**, 210; (*c*) C. K. Ingold, *Ann. Reports*, 1926, 142; (*d*) N. Kornblum, R. A. Smiley, R. K. Blackwood, and C. Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269; (*e*) R. Gompper, *Angew. Chem. Internat. Edn.*, 1964, **3**, 568.

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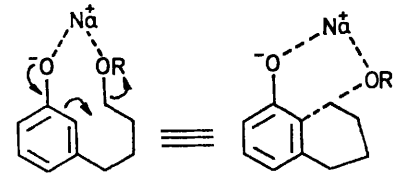
effects detailed later. Both transition states tend towards a linear arrangement[1,8] of the leaving group,



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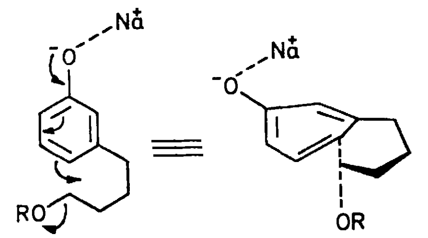

(5)

C-1 of the side-chain, and the ring position undergoing reaction. It is probable that the metal cation will lie closest to the oxygen atom.[9] We suggest that reaction at the *ortho*-position (4) involves the sodium cation which facilitates charge transfer from reactant to product. The rate of *ortho*-alkylation will therefore be relatively insensitive to the dielectric constant of the solvent as long as ion-pairing (or ion-aggregation) is not disrupted. Reaction at the *para*-position (5) cannot involve the sodium cation and charge separation becomes necessary as reaction proceeds. When ion pairs are involved, reaction will be slow at the *para*- relative to the *ortho*-position.

The effects observed (Table 1 and Figure 1) can now be interpreted. First, the effect of increasing the dielectric constant will be to make the ion pairs less tightly bound.[10] The activation energy for both *ortho*- and *para*-alkylation will decrease.[11] Faster overall rates of reaction should, and were, observed. The increasingly greater degree of solvation will affect the rate of *para*-alkylation more than that of *ortho*-alkylation.

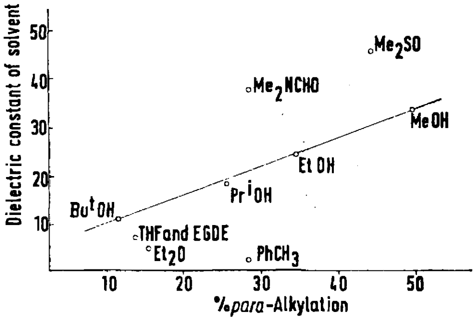

FIGURE 1 Relationship of dielectric constant of solvent with the product ratio in the reactions of the sodium salt of (1; R = $SO_2C_6H_4Me$-*p*) at 35° and 10^{-2}M. EGDE = ethylene glycol dimethyl ether

Whilst the reactions in dimethyl sulphoxide and dimethylformamide were fast, they were complex and low yields of cyclisation products were observed. In the third class of solvents, *i.e.* those with a low dielectric constant (Figure 1), ion aggregation is likely.[10,12] Here, the activation energy of *para*-alkylation will be reduced since charge transfer to the leaving group will be facilitated by neighbouring ions in the ion cluster. *ortho*-Alkylation may be slowed down by the inhibition of the formal migration of the sodium ion from oxygen to the leaving group.

Nature of the Cation.—The nature of the metal cation affects the *ortho*- : *para*-alkylation ratio (Table 2). This effect which correlates with the size of the metal cation (Figure 2) is probably associated with the strength and nature of the metal-oxygen bond.[13] Addition of one

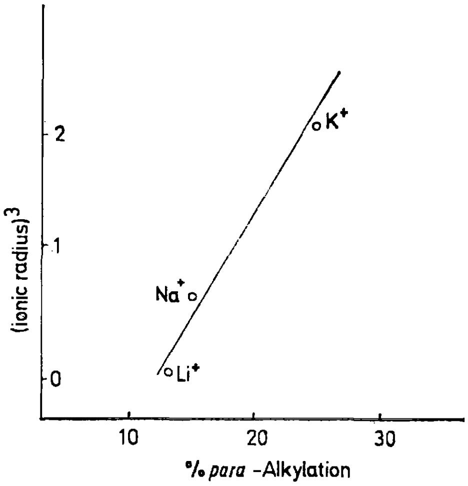

FIGURE 2 Plot of (ionic radius)^3 against % *para*-alkylation for the reaction of (1; R = $SO_2C_6H_4Me$-*p*) in t-butyl alcohol–tetrahydrofuran (5 : 1) at reflux

TABLE 2

Percentage *ortho*-alkylation [a] obtained from the reaction of alkali metal salts of 4-*m*-hydroxyphenylbutyl toluene-*p*-sulphonate at reflux temperature

Metal cation	Bu^{t}OH-THF (5 : 1) [b]	H_2O [c,e]
Lithium	87 [d]	44
Sodium	85 [d]	41
Potassium	75	38
Sodium + $(Bu)_4N^+I^-$	62	
Sodium + Na^+I^-	69	

[a] Relative to *para*-alkylation. [b] 3.3×10^{-3}M. [c] 10^{-2}M. [d] Average of repeated analyses. [e] Reaction heterogeneous.

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mol. equiv. of tetrabutylammonium iodide[4,14] had a pronounced effect on the *ortho-*:*para*-alkylation ratio. That this was not exclusively a salt effect, is shown by comparison with the result obtained by addition of a molar equivalent of sodium iodide (Table 2). Unexpectedly,[3e,4b,12b] the metal cation effect persisted in water. However, this reaction was heterogeneous.

The effect of the addition of traces of water to the reaction of the sodium salt of (1) in tetrahydrofuran deserves comment. The *ortho-*:*para*-alkylation ratio was reduced (Table 1). This probably arises by an increase in the effective size of the sodium cation.[15]

Effect of Added Salt.—The addition of a salt to the reaction increases the dielectric constant[16] and the degree of reactant ion aggregation.[17] Both of these effects, as discussed above, would be predicted to increase the rate of *para-* relative to *ortho*-alkylation. These predictions are borne out in practice (Tables 2 and 3).

TABLE 3

Effect of added sodium perchlorate on the product ratio of the sodium salt of 4-*m*-hydroxyphenylbutyl toluene-*p*-sulphonate

Solvent	% *ortho*	% *para*
Bu^tOH–THF (5 : 1), reflux	85	15
Bu^tOH–THF (5 : 1), reflux + satd. $NaClO_4$	67	33
THF, 35°	87	13
THF + satd. $NaClO_4$, 35°	69	31

TABLE 4

Temperature effect on the product ratio of the sodium salt of 4-*m*-hydroxyphenylbutyl toluene-*p*-sulphonate at 10^{-2}M

Solvent	Temp. (°C)	Yield[a]	% *ortho*[b]	% Solvolysis[a]
Bu^tOH	82	95	76	
	35	90	89	
EtOH	78	100	60	8
	35	93	66	15
MeOH	65	99	41	23
	35	97	51	25
H_2O	100	94	38	12
	35	97	54	21
Me_2NCHO	153	5	53	
	35	4	73	
$PhCH_3$	112	50	76	
	35	17	72	

[a] Absolute yield. [b] Relative to the *para*-alkylation product.

Effect of Temperature.—During the course of this investigation it seemed that the reaction temperature affected the *ortho-*:*para*-alkylation ratio. Systematic investigation (Table 4) confirmed this. Interestingly, but for reasons which are not yet clear, with the exception of toluene, in which the reaction is heterogeneous, the *ortho-*:*para*-alkylation ratio decreases with decreasing temperature.

EXPERIMENTAL

General procedures were as detailed previously.[1]

Synthesis of (1; R = $SO_2C_6H_4Me$-*p*), and phenols (1; R = H), (2), and (3) have been outlined previously.[1] The solvolysis products (1; R = Me) and (1; R = Et) were synthesised as detailed below.

4-(m-*Hydroxyphenyl)butyl Methyl Ether* (1; R = Me).—Methyl iodide (0.25 ml, 0.004 mol) was added to a solution of 4-(*m*-benzyloxyphenyl)butan-1-ol[1] (0.5 g, 0.002 mol) in dry tetrahydrofuran (5 ml). The solution was maintained under nitrogen while sodium hydride (0.055 g, 0.0023 mol) was added. The reaction was sealed and stirred for two weeks during which time additional quantities of methyl iodide and sodium hydride were added. The solvent was then removed and the residue washed, dried, and dissolved in ethanol (50 ml). This solution was treated with 5% palladium–charcoal (0.1 g) and the mixture shaken in a hydrogen atmosphere (40 lb in^{-2}) for 48 h. The crude oily product was purified by preparative t.l.c. and 4-(m-*hydroxyphenyl butyl methyl ether* (0.27 g, 77%) was obtained as an oil (Found: C, 72.9; H, 8.8. $C_{11}H_{16}O_2$ requires C, 73.4; H, 8.9%), $\nu_{max.}$ 3 290 and 1 105 cm^{-1}; τ 2.8—3.5 (m, Ph), 6.65 (t, *J* 7.0 Hz, CH_3O), overlapped by 7.4 (s, CH_2O), 7.53 (t, poorly resolved, *J* 6.0 Hz, CH_2Ph), and 8.3—8.9 (m, CH_2CH_2).

Ethyl 4-(m-*Hydroxyphenyl)butyl Ether* (1; R = Et).—This ether was synthesised (64%) in the same manner as (1; R = Me) from 4-(*m*-benzyloxyphenyl)butanol.[1] The *ether* was an oil (Found: C, 74.9; H, 9.5. $C_{12}H_{18}O_2$ requires C, 74.3; H, 9.3%), $\nu_{max.}$ 3 300 and 1 102 cm^{-1}, τ 2.6—3.5 (m, Ph), 6.5 (q, *J* 6.5 Hz, CH_2Me), 6.48 (t, *J* 6.0 Hz, CH_2O), and 8.2—9.2 (m, 3 × CH_2 and CH_3).

The following experimental details are typical of the reactions undertaken.

A solution of 4-(*m*-hydroxyphenyl)butyl toluene-*p*-sulphonate (1; R = $SO_2C_6H_4Me$-*p*) (64 mg, 0.2 mmol) in dried solvent (20 ml) under nitrogen was treated with sodium hydride (5.3 mg, 0.22 mmol). The solution (or suspension) was heated at 35° until reaction was completed (t.l.c.). For internal g.l.c. standardisation, an aliquot portion of a freshly prepared standard solution of 2,6-dimethylphenol was added. The isolated product was then treated with trimethylsilyl chloride and analysed by g.l.c.

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