426. *The Halogenation of Phenolic Ethers and Anilides. Part V. Alkyl and ω-Substituted-alkyl Ethers.*

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IN the earlier parts of this series (Bradfield and B. Jones, J., 1928, 1006, 3073; 1931, 2903) the interpretation of the Arrhenius expression, $k = \alpha e^{-E/RT}$, afforded by the kinetic activation theory, which was meeting with considerable success in the study of gaseous reactions, was applied to the benzene-substitution problem, considered as a problem of reaction rates in solution. A preliminary test of this expression, made by using Holleman's data for the relative amounts of the isomerides formed by nitration of a number of aromatic compounds, justified its application to the specific problem of the relative rates of chlorination and bromination of aromatic ethers. Two main results emerged; (i) that the term α, which includes phase and steric (geometric) or orientation factors, is constant within the error of experiment; (ii) that in compounds of the type p-RO·C_6H_4·X the groups OR and X each contribute a characteristic quota to the activation energy of further substitution. In connexion with the first conclusion, it is interesting to note that Williams and Hinshelwood (J., 1934, 1079) and Hinshelwood and Legard (this vol., p. 587) have since discovered groups of reactions in which large changes of reaction rate are attributable mainly to variations in E. Whether this will be found to be strictly true for all types of reaction is still open to question (cf., however, Evans, Morgan, and Watson, this vol., p. 1167). In the present communications the series of ethers studied has been enlarged, the additive relationships receiving further illustration.

Modifications in the group R of OR are alone dealt with, discussion of the effect of the position and nature of the group X being deferred until completion of work now in hand. A few minor departures from the " law of additivity," not greatly beyond the estimated experimental error of measurement, are discussed later, together with one or two observed anomalies where the departure is much greater.

Comparative velocities of chlorination have been determined for about twenty new ethers. The velocity coefficients are given in Table I. The relative directive powers of all the OR groups (R = alkyl) so far examined are given in Table II in the form * $100k_{\mathrm{X}}^{\mathrm{OR}}/k_{\mathrm{X}}^{\mathrm{OMe}}$, with the relative directive effects of CO_2H, Cl, and Br as p- and o-substituents in Table III. All measurements were carried out at 20°, the medium being " 99% acetic acid " (1 c.c. of water per 100 c.c. of solution).

TABLE I.

Velocity coefficients for the chlorination of substances of the types o- *and* p-C_6H_4X·OR *in* 99% *acetic acid, at* 20°.

$[Cl_2]$ = 0·0075; [ether] = 0·0225; [HCl] = 0·0375.

Group X.	Group R.	*k*.	Group X.	Group R.	*k*.	Group X.	Group R.	*k*.
p-CO_2H	CH_3	0·444	p-Cl	CH_3	1·226	p-Br	$Br[CH_2]_2$	0·266
,,	n-C_5H_{11}	0·966	,,	n-C_5H_{11}	2·755	,,	$Br[CH_2]_3$	0·819
,,	n-C_6H_{13}	0·960	,,	n-C_6H_{13}	2·770	o-CO_2H	CH_3	3·463
,,	n-C_7H_{15}	0·947	,,	n-C_7H_{15}	2·743	o-Cl	,,	4·441
,,	n-C_8H_{17}	0·919	,,	$C_{16}H_{33}$	2·663 †	,,	n-C_3H_7	10·05
,,	$C_{16}H_{33}$ ‡	1·114	p-Br	CH_3	1·256	,,	iso-C_3H_7	16·16
,,	$C_6H_5[CH_2]_2$	0·528	,,	iso-C_4H_9	2·738	,,	n-C_4H_9	10·07
,,	$C_6H_5[CH_2]_3$	0·760	,,	$C_{16}H_{33}$	2·665 †	,,	n-C_5H_{11}	9·83

† [ether] = 0·0075.

‡ [ether] = 0·0025; $[Cl_2]$ = 0·0025; *k* when R = CH_3, 0·553.

Discussion of Results.—Alkyl ethers. The variation of reaction velocity with the growth of a saturated chain of atoms has been extensively studied. With alkyl groups the effect is generally progressive up to the third or fourth carbon atom, the reactivity thereafter remaining practically constant (cf. Segaller, J., 1914, **105**, 106; Haywood, J., 1922, **121**,

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* For notation, see Bradfield and B. Jones (*loc. cit.*).

TABLE II.

Relative directive powers of the groups OR *in compounds of the types* o- *and* p-$C_6H_4X{\cdot}OR$. *Values of* $100k_X^{OR}/k_X^{OMe}$.

(a) *Alkyl ethers.*

	R= CH_3.	C_2H_5.	$C_3H_7^\alpha$.	$C_3H_7^\beta$.	$C_4H_9^\alpha$.	*iso*-C_4H_9.	$C_5H_{11}^\alpha$.	$C_6H_{13}^\alpha$.	$C_7H_{15}^\alpha$.	$C_8H_{17}^\alpha$.	$C_{16}H_{33}$.
X = *p*-CO_2H	100	198	215	444	221	211	218	216	213	207	201
p-Cl	100	199	225	439	222	220	225	226	224	—	201
p-Br	100	200	227	438	—	218	—	—	—	—	—
o-Cl	100	199	226	364	227	—	221	—	—	—	—

(b) *ω-Phenyl- and ω-bromo-alkyl ethers.*

	R = CH_3.	$[CH_2]_2Ph$.	$[CH_2]_3Ph$.	$[CH_2]_2Br$.	$[CH_2]_3Br$.
X = *p*-CO_2H............	100	119	171	—	—
p-Br	100	—	—	21	65

TABLE III.

Relative directive effects of the groups CO_2H, Cl, Br *in compounds of the types* o- *and* p-$C_6H_4X{\cdot}OR$. *Values of* $100k_X^{OR}/k_X^{CO_2H}$.

R.	X=*p*-CO_2H.	*p*-Cl.	*o*-Cl.	*p*-Br.	R.	X=*p*-CO_2H.	*p*-Cl.	*o*-Cl.	*p*-Br.
CH_3	100	276	1000	283	C_4H_9(*iso*)	100	289	—	293
C_2H_5	100	278	1011	287	$C_5H_{11}^\alpha$	100	285	1018	—
$C_3H_7^\alpha$	100	288	1051	298	$C_6H_{13}^\alpha$	100	288	—	—
$C_3H_7^\beta$	100	272	818*	279	$C_7H_{15}^\alpha$	100	290	—	—
C_4H_9	100	283	1045	—					

* See discussion (p. 1833).

1904; Bennett and Reynolds, this vol., p. **131**; Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 232, *et seq.*).

The influence of such a chain of carbon atoms on nuclear chlorination is well illustrated by the velocity ratios in Table II, the relative directive powers of *n*-alkyl groups being as follows:

$$\begin{array}{l} CH_3 : C_2H_5 : C_3H_7 : C_4H_9 : C_5H_{11} : C_6H_{13} : C_7H_{15} : C_8H_{17} : C_{16}H_{33} \\ 100 : 199 : 223 : 223 : 221 : 221 : 219 : 207 : 201 \end{array}$$

Thus, from propyl to heptyl the reactivity remains unaltered, octyl and cetyl then giving slightly lower values.

A closely parallel order of reactivity was found by Robinson and his collaborators for the nitration in acetic acid of quinol ethers of the type *p*-$RO{\cdot}C_6H_4{\cdot}OMe$ (Robinson and Smith, J., 1926, 392; Clarke, Robinson, and Smith, J., 1927, 2647; Smith, J., 1931, 251). In this series, however, of all the straight-chain alkyl ethers examined, the cetyloxy-group has the highest directive power:

$$\begin{array}{l} R{=}CH_3 : C_2H_5 : C_3H_7 : C_4H_9 : C_{16}H_{33} \\ 100 : 164 : 180 : 186 : 212 \end{array}$$

If the methyl group exerts its influence through the carbon chain, then it would seem reasonable to assume that the constant reactivity characteristic of long-chain compounds would be followed by a fall rather than a rise as the chain is lengthened (cf. Conant and Kirner, *loc. cit.*).

In calculating the relative speeds of chlorination of the different ethers it has been assumed that Z, the collision number, remains constant. Since Z involves σ, the effective molecular diameter, and M, the molecular weight, it is at once obvious that by itself an increase in molecular weight as in the higher ethers involves an appreciable alteration in Z. The effect of this increase, however, is probably balanced to some extent by a change in σ. In view of our lack of knowledge of σ, it was considered best to leave the results uncorrected.

The familiar effect of a branching chain is illustrated by the relative directive powers

$$\begin{array}{l} OCH_3 : OC_2H_5 : OC_3H_7^\alpha : OC_3H_7^\beta : OC_4H_9^\alpha : OC_4H_9\ (iso) \\ 100 : 199 : 223 : 440 : 221 : 216 \end{array}$$

The almost identical reactivities of the *n*- and the *iso*-butyl ether confirm the fact that branching on the β-carbon atom, and therefore presumably later in the chain, has little or no effect on the reactivity (cf. Orton and King, J., 1911, **99**, 1372).

The value 364 for the relative directive power of OPr^{β} in *o*-chlorophenyl *iso*propyl ether, however, presents a marked anomaly. This low reactivity is all the more unexpected since, of 14 groups examined in this series, OPr^{β} is alone abnormal. It is too early to attempt a detailed discussion of this anomaly, but it is of interest that in *p*-cymene, methyl possesses a greater *o*-directive influence than *iso*propyl (Le Fèvre, J., 1933, 980; 1934, 1501). It may well be that OPr^{β} differs from OMe and OEt in the relative proportions of *o*- and *p*-isomerides formed.

ω-Halogen ethers. General experience and several published researches have shown that the introduction of an electron-attracting atom or group into an *op*-orienting group greatly reduces the rate of substitution. The retarding influence of chlorine on both nuclear and side-chain reactivity is well illustrated by the study of *C*- and *N*-chlorination of anilides (Williams and Hughes, J., 1931, 3125; Bradfield and B. Jones, *loc. cit.*; B. Jones, J., 1934, 210).

In the present series introduction of bromine into ethyl produces a marked decrease in reactivity. As anticipated, the intervention of an additional methylene group diminishes the depressing effect, but only slightly, the values relative to the methyl ether = 100 being 21 and 65 for $[CH_2]_2Br$ and $[CH_2]_3Br$ respectively. The damping effect of intervening methylene groups is familiar from the decrease in *m*-substitution that accompanies the gradual removal from the nucleus of an electron-attracting group (Holleman and Bruyn, *Rec. trav. chim.*, 1900, **19**, 79; Baker and Ingold, J., 1926, 2462). In the present case the halogen with three carbon atoms separating it from the oxygen still exerts a considerable effect, since the rate of reaction has only reached approximately 30% of the limiting value for long-chain ethers. Progressive dissipation of the effect will undoubtedly occur as the chain is lengthened, but since there are other substituents (*e.g.*, NO_2) which have polar effects markedly stronger than those of the halogens, it seems likely from the present results that the inductive effect of one of these would be transmitted through a saturated chain of more than three carbon atoms.

ω-Phenyl ethers. That the phenyl group exerts a similar but much weaker effect than bromine is apparent from the directive powers of the methoxy-, benzyloxy-, β-phenylethoxy-, and γ-phenylpropoxy-groups :

$$\begin{array}{ccccccccccc} OCH_3 & : & OCH_2Ph & : & OC_2H_5 & : & O[CH_2]_2Ph & : & OC_3H_7 & : & O[CH_2]_3Ph \\ 100 & : & 70 & : & 199 & : & 119 & : & 223 & : & 171 \end{array}$$

Here, again, the effect diminishes as the chain is lengthened, but in spite of the inherently weaker deactivating effect of the phenyl group than of the halogens, it is, nevertheless, sufficiently potent to transmit its influence across three carbon atoms, for the γ-phenylpropoxy-group has only approximately 77% of the reactivity of the parent propoxy-group. Further increase in chain length suppresses the effect almost completely (cf. Conant and Kirner, *loc. cit.*). The phenyl group appears to exert its greatest effect, however, when attached to the β-carbon atom, for the reactivity of the β-phenylethoxy-group is only 60% of that of the ethoxy-group, whereas the benzyl and the γ-phenylpropyl ether show 70 and 77% respectively of the reactivity of the methyl and the propyl ether. This observation, although unexpected, is not unique, for Conant and his collaborators, studying the reaction of organic chlorides with potassium iodide in acetone, found that β-phenylethyl chloride showed a lower reactivity than either benzyl or γ-phenylpropyl chloride.

The effect of introducing substituents into the phenyl group is shown from the results in Part VI. Methyl increases the speed of substitution, the effect being independent of its position. Halogens, in all three positions, decrease the reactivity, with rather smaller effect in the *p*-position than in the *o*- and *m*-, which are very similar, whilst the nitro-group exerts, as anticipated, a more powerful deactivating effect, this being slightly greater in the *o*- and *p*- than in the *m*-position.

EXPERIMENTAL.

The velocity coefficients of chlorination at 20° were determined by the method described previously (Orton and Bradfield, J., 1927, 986; Bradfield and B. Jones, *loc. cit.*), the medium being purified acetic acid, stable to chlorine, and containing a total of 1 c.c. of water per 100 c.c. of reaction mixture.

Standard methods were used for the preparation of the ethers from the parent hydroxy-compounds and the alkyl or benzyl halide. As before, particular attention was paid to the freedom of the materials from impurity, especially from reactive substances, since these exert a marked effect on the rate of reaction when the proportion of ether to chlorine is 3 : 1, as in most of the measurements now recorded. Fortunately, such impurities were usually very easily detected by the appearance of a downward drift in the velocity coefficients. Whenever this occurred, the specimen was further purified by crystallisation or, if liquid, by careful distillation at 12—15 mm., until the drift was completely eliminated and further purification produced no change in the rate of chlorination. The distillations were carried out in a special vacuum-distillation flask fitted with a glass fractionating column. The constancy of the velocity coefficient rather than of the m. p. or the b. p. was taken as the criterion of purity. Each solid material was crystallised three times, usually from ethyl alcohol or glacial acetic acid, and only in exceptional cases was further crystallisation necessary.

p-*Chlorophenyl* n-*amyl ether*, prepared from *p*-chlorophenol and commercial *n*-amyl bromide in the usual manner, is a colourless liquid, b. p. 132—133°/12 mm. (Found : * C, 66·3; H, 7·6. $C_{11}H_{15}OCl$ requires C, 66·5; H, 7·6%); and the n-*hexyl ether*, a similar colourless liquid, had b. p. 172°/34 mm. (Found : C, 67·6; H, 8·0. $C_{12}H_{17}OCl$ requires C, 67·7; H, 8·0%).

p-*Chlorophenyl* n-*heptyl ether*. A commercially pure specimen of *n*-heptyl alcohol was converted into the chloride by the action of excess of thionyl chloride and pyridine, with chloroform as a diluent. The *ether*, prepared from the chloride and *p*-chlorophenol in sodium ethoxide, distils as a colourless liquid, b. p. 162°/14 mm. (Found : C, 68·8; H, 8·5. $C_{13}H_{19}OCl$ requires C, 68·8; H, 8·4%).

p-*Chlorophenyl cetyl ether*. Attempts to prepare this ether by heating together under reflux equimolecular proportions of cetyl iodide and *p*-chlorophenol were unsatisfactory owing to the difficulty of completely removing unchanged iodide. A purer specimen was obtained by using 100% excess of the phenol and adding enough acetone to the alcoholic potash to dissolve the iodide. The excess phenol was removed with aqueous potash, and on pouring into water the *ether* solidified. It was crystallised several times from alcohol and acetone; m. p. 48° (Found : C, 74·8; H, 10·4. $C_{22}H_{37}OCl$ requires C, 74·85; H, 10·6%). The corresponding p-*bromophenyl ether*, prepared similarly, crystallises from acetone as soft white crystals, m. p. 49° (Found : C, 66·4; H, 9·3. $C_{22}H_{37}OBr$ requires C, 66·5; H, 9·4%).

o-*Chlorophenyl* n-*propyl ether* distils as a colourless liquid, b. p. 119°/26 mm. (Found : C, 63·4; H, 6·4. $C_9H_{11}OCl$ requires C, 63·4; H, 6·5%), and the iso*propyl ether* as a colourless liquid, b. p. 93°/12 mm. (Found : C, 63·4; H, 6·7%). This ether behaves anomalously in that it gives an unexpectedly low velocity coefficient. The anomaly can hardly be due to impurity since two specimens, prepared at different times from different starting materials, gave the following mean values for *k* : (i) 16·18, (ii) 16·14.

o-*Chlorophenyl* n-*butyl ether*, b. p. 117°/13 mm. (Found : C, 65·0; H, 6·7. $C_{10}H_{13}OCl$ requires C, 65·0; H, 7·1%), and the n-*amyl ether*, b. p. 117°/13 mm. (Found : C, 66·5; H, 7·6. $C_{11}H_{15}OCl$ requires C, 66·5; H, 7·6%), were colourless liquids.

For the preparation of the ω-phenylalkoxybenzoic acids in good yield, it is unnecessary to convert the parent hydroxy-acid into the ester and hydrolyse this, since alkylation of the hydroxy-group is much more rapid than esterification. The general method adopted is to reflux (2—4 hours) 1 mol. of the parent acid in 2 mols. of aqueous potassium hydroxide with 1·1 mols. of the alkyl halide. Addition of concentrated hydrochloric acid to the cold solution precipitates the acid.

p-β-*Phenylethoxybenzoic acid*, m. p. 160° (Found : C, 74·0; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·3; H, 5·8%), and p-γ-*phenylpropoxybenzoic acid*, m. p. 166° (Found : C, 74·6; H, 6·3. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), both form colourless prisms from glacial acetic acid.

p-*Bromophenyl* γ-*bromopropyl ether* was prepared, together with a by-product (see below), by heating under reflux *p*-bromophenol in alcoholic sodium ethoxide with 50% excess trimethylene dibromide. On cooling, the bulk of the by-product crystallised and was filtered off. The oil which separated on pouring the alcoholic solution into twice its bulk of water was extracted with ether, dried, and distilled. A colourless liquid, b. p. 169°/12 mm., was obtained, and on standing it formed a white solid, which crystallised from alcohol as colourless prisms, m. p. 49·5° (Found : C, 36·7; H, 3·4. $C_9H_{10}OBr_2$ requires C, 36·76; H, 3·4%). The by-product,

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* Micro-determinations by Dr.-Ing. A. Schoeller.

*trimethylene glycol bis-*p*-bromophenyl ether,* crystallises from glacial acetic acid, in which it is very sparingly soluble at 20°, as long white needles, m. p. 143° (Found : C, 46·5; H, 3·66. $C_{15}H_{14}O_2Br_2$ requires C, 46·8; H, 3·66%).

p-Bromophenyl β-bromoethyl ether, similarly prepared from *p*-bromophenol and ethylene dibromide, melts at 58° after three crystallisations from glacial acetic acid (Found : C, 34·6; H, 2·9. Calc. : C, 34·4; H, 2·9%).

The *o*-methoxybenzoic acid used had m. p. 101° (Found : C, 63·1; H, 5·2. Calc. : C, 63·16; H, 5·3%). For details of the preparation and properties of the alkoxybenzoic acids, see this vol., p. 1874.

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