CXXXIII.—*The Chlorination of Anilides. Part IV. The Significance of Velocity Measurements in Relation to the Problem of Benzene Substitution.*

By ALAN EDWIN BRADFIELD and BRYNMOR JONES.

THE quantitative study of the chlorination of anilides (Orton and Bradfield, J., 1927, 986; Bradfield, this vol., p. 351) has now been extended to include certain phenolic ethers,* in which the para-position is occupied by halogen, nitro-, or carboxy-groups. The uncertainty in the interpretation of velocity measurements when two positions in the benzene nucleus are attacked is avoided by a study of compounds of this type, since chlorine enters only in the ortho-position to the group ·OR, and, further, the very high rates of reaction of the unsubstituted ethers are retarded by a *p*-substituent of this type, and become conveniently measurable at 20°. The velocity coefficients now described, except for some of the values in Table I, relate to the "99% acetic acid" medium (*i.e.*, containing 1 c.c. of water per 100 c.c. of reaction mixture) previously employed (Orton and Bradfield, *loc. cit.*) and were calculated from the ordinary expressions for bimolecular reactions (time in minutes, concentrations in g.-mols. per litre).

So far as it has yet been examined, the velocity of chlorination of phenolic ethers increases rapidly with increasing water content of the medium, the increase for an alteration from 1% to 2% of water being almost as great as for a rise of temperature of 10° (Table IA). The effect of varying the concentration of hydrochloric acid is shown in Table IB.

TABLE I.

Chlorination of *p*-chloroanisole at 20°.

Conc. of *p*-chloroanisole = 0·0075 g.-mol./litre.
,, chlorine = 0·0075 g.-mol./litre.

A. Effect of water in medium.

C.c. of H_2O per 100 c.c.	Mol. proportions of HCl.	*k*.
1	5	1·32
2	5	2·20
1	8	1·41
1·13	8	1·48

B. Effect of HCl. 99% Acetic acid.

Mol. proportions of HCl.	*k*.
1·2	1·22
1·5	1·26
5·0	1·32
8·0	1·41

It is seen from Tables II and III that the velocity coefficients are slightly altered by a change in the relative concentrations of ether and chlorine. So far as possible, standard conditions have been employed throughout, in order that the results may be comparable,

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* For a preliminary investigation, which was interrupted by the war, see Orton and D. C. Jones, *Brit. Assoc. Reps.*, 1915, 82.

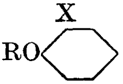
though the low reactivity of the *p*-nitro-ethers necessitated working at much higher concentrations than were required for the other substances. It is difficult to estimate the absolute order of accuracy of the measurements, but with any given substance consistently reproducible results could be obtained within about 2%. Each of the values quoted is the mean of several determinations.

Evidence was sought for a possible displacement of the carboxyl group by chlorine in the derivatives of *p*-hydroxybenzoic acid investigated (compare Francis and Hill, *J. Amer. Chem. Soc.*, 1924, **46**, 2498). Examination of the individual values of *k* for the chlorination of several compounds of this type showed that when the molecular proportion of ether and chlorine was 1 : 1, there was a slight upward drift as the reaction progressed, which was, however, within experimental error. This would be accounted for by the occurrence, to a small extent, of the successive reactions: $RO{\cdot}C_6H_4{\cdot}CO_2H \xrightarrow{Cl_2} RO{\cdot}C_6H_4Cl \xrightarrow{Cl_2} RO{\cdot}C_6H_3Cl_2$. The disturbance is almost entirely eliminated when the initial ratios are 3 : 1 or 10 : 1, and a satisfactorily constant coefficient is obtained. The agreement between the values at the two different concentrations shows that the results at the lowest concentration (1 : 1) are not seriously vitiated.

TABLE II.

Velocity coefficients for the chlorination of substances of the types

and



in 99% acetic acid, at 20°.

Conc. of chlorine throughout = 0·0075 g.-mol./litre (1 mol.).
,, hydrochloric acid throughout = 0·0375 g.-mol./litre (5 mols.).

Conc. of ether		0·0075	0·0225	0·075
Mol. propn. of ether		1	3	10
		Velocity coefficients.		
Group X.	Group R.			
Cl (*p*-)	CH_3-	1·323	1·226	—
,,	C_2H_5-	—	2·443	—
,,	*n*-C_3H_7-	—	2·756	—
,,	*iso*-C_3H_7-	—	5·377	—
,,	*n*-C_4H_9-	—	2·723	—
,,	$C_6H_5{\cdot}CH_2$-	0·8783	0·8371	0·8054
,,	*p*-$C_6H_4Cl{\cdot}CH_2$-	—	0·4834	—
,,	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$-	—	0·1742	0·1828
,,	*m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$-	—	0·2104	0·2068
Cl (*o*-)	CH_3-	—	4·441	—
,,	C_2H_5-	—	8·873	—
,,	*p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2$-	—	0·6417	0·6586
CO_2H (*p*-)	CH_3-	0·4624	0·4440	0·4389
,,	C_2H_5-	0·9084	0·8774	0·8712
,,	*n*-C_3H_7-	—	0·9563	—
,,	*iso*-C_3H_7-	2·053	1·975	—
,,	*n*-C_4H_9-	1·038	0·9633	—
,,	$C_6H_5{\cdot}CH_2$-	0·3232	0·3143	0·3002

TABLE III.

Chlorination of substances RONO_2 at 20°.

Conc. of chlorine = 0·02 g.-mol./litre (1 mol. proportion).
,, HCl = 0·05 ,, (2·5 mol. proportions).
,, ether = 0·20 ,, (10 mol. proportions).

Group R.	CH_3-	C_2H_5-	n-C_3H_7-
$k \times 10^6$	2993	5983	6612

Discussion of Results.

The Introduction of a Second Substituent into a Monosubstituted Benzene Derivative.—The success of the application of the concept of kinetic activation to bimolecular gaseous reactions (Hinshelwood, "The Kinetics of Chemical Change in Gaseous Systems," Oxford, 1926) warrants an examination of its applicability to the problem of benzene substitution, which, it has long been recognised, is essentially a problem of relative reaction rates. By analogy with the expression for simple gaseous bimolecular reactions, the equation $k = PSZe^{-E/RT}$ may be set up, where $E = E_A + E_B$ represents the energy of activation corresponding to substitution at a particular carbon atom, $Z/2$ is the number of collisions between the reacting molecules in unit time, and S is a factor (depending on the shape of the molecule) representing the probability that the molecules are oriented in a manner favourable to reaction at the moment of collision. The idea that the rate of substitution at a given point in the benzene nucleus depends on a " phase " condition of the nucleus is involved in several theories of benzene substitution, and the P term denotes the probability that the phase condition of the molecules admits of reaction.

Since, in a monosubstituted benzene derivative, there are two ortho- and two meta-positions, and one para-,

$$k_o = 2PSZe^{-E_o/RT},\ k_m = 2PSZe^{-E_m/RT},\ \text{and}\ k_p = PSZe^{-E_p/RT}.$$

In the case of a reaction yielding only *o*- and *p*-derivatives, $k_o/k_p = r_1$ represents the ratio of the total *o*-compound formed to the total *p*-compound, at a temperature T_1. If, provisionally, it be assumed that the P and S factors are identical for the two positions, $k_o/k_p = 2e^{(E_p - E_o)/RT}$, and for two temperatures, T_1 and T_2,

$$2{\cdot}303 \log_{10} (r_1/2) = (E_p - E_o)/RT_1 \quad . \quad . \quad . \quad . \quad (1)$$

and $$2{\cdot}303 \log_{10} (r_2/2) = (E_p - E_o)/RT_2$$

whence $$\log_{10} (r_1/2)/\log_{10} (r_2/2) = T_2/T_1 \quad . \quad . \quad . \quad . \quad (2)$$

Hence, if r_1 be known at a temperature T_1, r_2 for a temperature T_2 may be evaluated. In a similar manner, the ratio *o*- : *m*- : *p*-, for a reaction yielding all three isomerides, at any one temperature, can be calculated from the values at another temperature.

These relations would not be expected to hold (1) for the sulphonation of aromatic compounds, owing to the migration of the $\cdot SO_3H$ group at higher temperatures, (2) for the substitution reactions of basic substances in acid media, (3) for the nitration of phenol (which appears to be a complicated reaction: compare Martinsen, *Z. physikal. Chem.*, 1904, **50**, 385; Arnall, J., 1923, **123**, 3111), or for the chlorination of toluene, which follows an unusual course (Holleman, " Die direkte Einführung von Substituenten in den Benzolkern," Leipzig, 1910). Table IV has been constructed by taking all the data, not excluded by the above considerations, which are quoted by Holleman (*op. cit.*), mainly from investigations in his own laboratories, on the effect of temperature on the proportions of the isomerides formed by further substitution in mono- and di-substituted benzenes, and from the value of r_1 at one temperature, calculating r_2 at a higher temperature, and comparing the results with the observed values. In all cases, the alteration in the proportions of the isomerides is in the right direction, and of the correct order of magnitude. Although the accuracy of the experimental work of Holleman and his collaborators is probably unsurpassed by other workers in this field, the *exact* agreement, in some cases, between the observed and calculated values must of course be regarded as fortuitous. Nevertheless, the good general agreement appears to support the assumptions involved, and suggests the adoption of the working hypothesis that the primary factor deciding the proportions of the isomerides formed in aromatic substitution reactions is the energy of activation corresponding to the different positions available, and not the phase relationships of the molecule. The question of the retention of a " phase factor," which is the same for all the simultaneous reactions by which the isomerides are formed, remains untouched.

TABLE IV.

Isomerides formed in nitration of	Temp.	Proportions.	Temp.	Proportions.	
				Found.	Calc.
C_6H_5Cl (*o*- : *p*-)	—30°	26·9 : 73·1	0°	30·1 : 69·9	30·7 : 69·3
C_6H_5Br (*o*- : *p*-)	—30	34·4 : 65·6	0	37·6 : 62·1	37·8 : 62·2
C_6H_5I (*o*- : *p*-) *	—30	39·1 : 60·9	0	41·1 : 58·7	42·1 : 57·9
$C_6H_5\cdot NO_2$ in HNO_3 (*o*- : *m*-) †	0	6·4 : 93·2	30	8·3 : 91·0	8·2 : 91·1
$C_6H_5\cdot NO_2$ in H_2SO_4 (*o*- : *m*-) †	0	4·8 : 93·5	40	6·8 : 91·8	6·9 : 91·7
$C_6H_5\cdot CH_3$ (*o*- : *m*- : *p*-)	—30	55·6 : 2·7 : 41·7	0	56·0 : 3·1 : 40·9	56·0 : 3·8 : 40·2
$C_6H_5\cdot CH_3$ (*o*- : *m*- : *p*-)	—30	55·6 : 2·7 : 41·7	60	57·5 : 4·0 : 38·5	56·1 : 6·2 : 37·7
$C_6H_5\cdot CH_3$ (*o*- : *m*- : *p*-)	0	56·0 : 3·1 : 40·9	60	57·5 : 4·0 : 38·5	56·3 : 5·3 : 38·4
$C_6H_5\cdot CO_2H$ (*o*- : *m*- : *p*-)	—30	14·4 : 85·0 : 0·6	30	22·3 : 76·5 : 1·2	19·2 : 79·7 : 1·1
$C_6H_5\cdot CO_2Me$ (*o*- : *m*- : *p*-)	—30	23·6 : 74·4 : 2·0	30	25·7 : 69·8 : 4·5	27·5 : 69·2 : 3·3
$C_6H_5\cdot CO_2Et$ (*o*- : *m*- : *p*-)	—40	25·5 : 73·2 : 1·3	30	27·7 : 66·4 : 5·9	30·0 : 67·5 : 2·5
o-$C_6H_4Cl_2$ (1,2,3 : 1,2,5)	—30	5·2 : 94·8	0	7·2 : 92·8	7·0 : 93·0
m-$C_6H_4Cl_2$ (1,3,2 : 1,3,4)	—30	2·6 : 97·4	0	3·8 : 96·2	3·8 : 96·2
o-$C_6H_4Cl\cdot CO_2H$ (1,2,3 : 1,2,5)	—30	14·0 : 86·0	0	16·0 : 84·0	16·6 : 83·4
m-$C_6H_4Cl\cdot CO_2H$ (1,3,2 : 1,3,6)	—30	7·0 : 93·0	0	8·0 : 92·0	9·1 : 90·9
o-$C_6H_4Br\cdot CO_3H$ (1,2,3 : 1,2,5)	—30	17·1 : 82·9	0	19·7 : 80·3	19·7 : 80·3
m-$C_6H_4Br\cdot CO_2H$ (1,3,2 : 1,3,6)	—30	11·0 : 89·0	0	13·0 : 87·0	13·5 : 86·5

* Holleman, *Rec. trav. chim.*, 1913, **32**, 134.

† A small, variable amount of the *p*-isomeride has not been taken into account.

The Introduction of a Third Substituent into a Disubstituted Benzene Derivative.—The problem of calculating the resultant directive effects of two groups, present together in the nucleus, from a knowledge of their effects when present separately, can only be approached in a tentative manner. In a simple case, such as the nitration of *o*-dichlorobenzene, the nitro-group enters position 6 or 4, *o*- or *p*-, respectively, to one chlorine atom, and *m*- to the other. A simple hypothesis would be that the energies of activation of positions 6 and 4 correspond to the energies of activation of the *o*- and *p*-positions in chlorobenzene, increased (or diminished) by some quantity C due to the presence of a second chlorine atom in the nucleus. For chlorobenzene, we have equation (1) above, and for dichlorobenzene we have a similar relation qualified by the circumstance that there are now two positions ortho and two positions para to a chlorine atom :

$$2{\cdot}303 \log k'_o/k'_p = [(E_p + C) - (E_o + C)]/RT \quad . \quad . \quad (3)$$

and from (1) and (3),

$$k'_o/k'_p = k_o/2k_p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

That this relation will not hold, in general, may be seen from the table given by Holleman (*op. cit.*, p. 483), who used (4) as an empirical expression. Further, it is easily shown that analogous assumptions to those employed above are implicit in Francis's attempt to deal with the cumulative effect of groups (*J. Amer. Chem. Soc.*, 1926, **48**, 1631), which again does not always lead to satisfactory results.

Nevertheless, the velocity measurements now recorded provide some justification for this method of treatment for a series of closely related compounds. Neglecting the small variations in collision numbers due to differences in molecular weight, for the series of compounds p-X·C_6H_4·OR, where X = ·Cl, ·CO_2H, etc., and R = Me, Et, etc., and symbolising the increment in the energy of activation, due to X_1 and X_2, of the carbon atom ortho to the group OR by E_1 and E_2, we have :

$$^{*}k^{\mathrm{OMe}}_{p\cdot\mathrm{Cl}} = 2Ze^{-(E_0+E_1)/RT},\quad k^{\mathrm{OEt}}_{p\cdot\mathrm{Cl}} = 2Ze^{-(E_0'+E_1)/RT}$$

$$k^{\mathrm{OMe}}_{p\cdot\mathrm{CO_2H}} = 2Ze^{-(E_0+E_2)/RT},\quad k^{\mathrm{OEt}}_{p\cdot\mathrm{CO_2H}} = 2Ze^{-(E_0'+E_2)/RT},$$

whence $$k^{\mathrm{OEt}}_{p\cdot\mathrm{Cl}}/k^{\mathrm{OMe}}_{p\cdot\mathrm{Cl}} = e^{(E_0-E_0')/RT} = k^{\mathrm{OEt}}_{p\cdot\mathrm{CO_2H}}/k^{\mathrm{OMe}}_{p\cdot\mathrm{CO_2H}},$$

or, in general, $$k^{\mathrm{OR}}_{\mathrm{X_1}}/k^{\mathrm{OMe}}_{\mathrm{X_1}} = k^{\mathrm{OR}}_{\mathrm{X_2}}/k^{\mathrm{OMe}}_{\mathrm{X_2}}.$$

That is, the relative directive powers of two groups ·OR_1 and ·OR_2, as measured by the ratio of the velocity coefficients, should be

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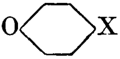
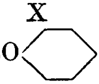
* $k^{\mathrm{OR}}_{p\cdot\mathrm{X}}$ represents the velocity coefficient for the chlorination of p-X·C_6H_4·OR.

independent of the nature of the group X. Table V, in which the ratios k_X^{OR}/k_X^{OMe} (multiplied by 100 for convenience) for the ethers are tabulated in the four series in which X = p-Cl, p-CO_2H, p-NO_2, and o-Cl, shows that the present experiments support this conclusion.

For purposes of comparison, the relative effects of the *p*-chloro-, *p*-carboxy-, and *p*-nitro-groups, and of *o*- and *p*-chloro-groups, as measured by ratios of the type $k_{X_1}^{OR_1}/k_{X_2}^{OR_1}$, are given in Tables VI and VII. Finally, from Table VIII, it may be seen that, although the velocity coefficients vary slightly with the initial molar proportions of the reactants, by taking the ratios for a pair of substances from the two values in the same vertical column of Table II, a constant is obtained which is independent of the actual initial molar proportions.

From the point of view of modern theories of benzene substitution, considerable interest attaches to these measurements of relative directing power, but further discussion is reserved, pending the completion in these laboratories of certain allied investigations.

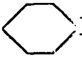
TABLE V.

Relative directive effects of the groups ·OR in compounds of the types ROX and RO. Values of $100k_X^{OR}/k_X^{OMe}$.

R =	Me.	Et.	Pr^a.	Pr$^\beta$.	Bu.	CH_2Ph.	$CH_2\cdot C_6H_4\cdot NO_2$ (p-).
X = p·CO_2H	100	198	215	444	221	70	—
p-NO_2	100	200	221	—	—	—	—
p-Cl	100	199	225	439	222	67	14·2
o-Cl	100	199	—	—	—	—	14·4

	Me.	$CH_2\cdot C_6H_4Cl$ (p-).	$CH_2\cdot C_6H_4\cdot NO_2$ (m-).
p-Cl	100	39·4	17·2

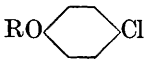
TABLE VI.

Relative directive effects of the groups ·CO_2H, ·Cl, and ·NO_2 in compounds of the type ROX. Values of $100k_X^{OR}/k_{p\text{-}CO_2H}^{OR}$.

	X = ·CO_2H.	·Cl.	·NO_2.
R = Me	100	276	0·674
Et	100	278	0·682
Pr^a	100	288	0·691
Pr$^\beta$	100	272	
Bu^a	100	283	
CH_2Ph	100	269	

TABLE VII.

Relative effects of *o*- and *p*-Cl in compounds of the types



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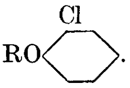

R =	Me.	Et.	CH_2Ph.
$100k^{OR}_{o\text{-}Cl}/k^{OR}_{p\text{-}Cl}$ =	362	363	364

TABLE VIII.

Effect of relative concentrations of ether and chlorine on the ratios $100k^{OR}_{p\text{-}CO_2H}/k^{OMe}_{p\text{-}CO_2H}$.

Mol. proptn., ether : Cl_2.	R = Me.	Et.	Pr^{α}.	Pr^{β}.	Bu.	CH_2Ph.
1 : 1	100	197	—	444	224	70
3 : 1	100	198	215	445	217	71
10 : 1	100	199	—	—	—	68

EXPERIMENTAL.

Reference to the earlier paper of Orton and Bradfield (*loc. cit.*) may be made for all details of the velocity measurements not now specifically mentioned. The ethers were prepared by standard methods from the corresponding hydroxy-compounds and the alkyl iodide or benzyl chloride. Small amounts of impurities (1% or less) which react slowly or not at all with chlorine do not seriously vitiate the velocity determinations, but even traces of impurities which are reactive towards chlorine exert a marked effect when the proportion of the ether to chlorine is 3 : 1 or 10 : 1. The materials were therefore repeatedly recrystallised, if solid, or, if liquid, submitted to slow fractional distillation under a pressure of 1—2 mm., until the velocity coefficient for the substance was unchanged by further purification. This was taken as our standard of purity, and was not always readily attained. Particular difficulty was met with in the case of the *p*-chloro-ethers, until a specially purified *p*-chlorophenol, supplied by Messrs. The British Drug Houses, Ltd., was used as a starting material.

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UNIVERSITY COLLEGE OF NORTH WALES,
BANGOR.

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