Some Recent Developments in the Chemistry of Free-radical Reactions in Solution.

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IT is now exactly fifty years since Lapworth [1] in this country and Noyes [2] in America put forward the view that electrolytic dissociation or ionisation played an important part in the reactions of organic compounds. In this way they provided a theoretical basis common to both inorganic and organic chemistry which helped to check the divergent paths which these two branches of the subject were tending to follow in the latter part of the nineteenth century. The subsequent introduction of the electronic theories of Lewis and Langmuir enabled the earlier hypothetical speculations to be translated into terms which were more closely related to physical reality and thereafter, very largely as a result of the work of the schools associated with the names of Robinson and of Ingold, a comprehensive theory of reaction mechanisms was developed. This theory, with but few adjustments, has now incorporated the more recent quantum-mechanical concepts of resonance which place it on a more fundamental and semi-quantitative basis. About twenty-five years ago a more intensive study of the photochemical and pyrolytic reactions of organic compounds, and in particular the experimental proof of the free existence of the simple alkyl radicals by Paneth and others, showed that in many reactions ionic dissociation was not involved and that the reacting entities were electrically neutral radicals or atoms resulting from the symmetrical fission of a covalent bond. These two types of reaction are now conveniently classified as heterolytic and homolytic reactions, respectively, according to the terminology introduced by Ingold.[3] Subsequent developments have established the existence of numerous reactions involving atoms and free radicals, both in the gaseous state and in solution, but a more complete understanding of this field, especially for reactions in solution, has hitherto been seriously hampered, except perhaps in the field of polymerisation, by a lack of accurate quantitative information.

The general pattern of free-radical reactions in solution has now become clear and the majority of such reactions can be classified as either substitution or replacement reactions, *e.g.*,

$$\text{(i)}\qquad \mathrm{R\cdot + AB \longrightarrow RA + B\cdot}$$

or addition reactions involving a chain-reaction mechanism, *e.g.*,

$$\text{(ii)}\qquad \mathrm{R\cdot + X\cdot CH{:}CH_2 \longrightarrow X\cdot \underset{|}{C}H\cdot CH_2R}$$

$$(a)\ \mathrm{X\cdot \underset{|}{C}H\cdot CH_2R + RY \longrightarrow X\cdot CHY\cdot CH_2R + R\cdot}$$

$$\text{or}\qquad (b)\ \mathrm{X\cdot \underset{|}{C}H\cdot CH_2R + X\cdot CH{:}CH_2 \longrightarrow X\cdot \underset{|}{C}H\cdot CH_2\cdot CHX\cdot CH_2R}\text{, etc.}$$

The reaction (ii, *a*), which results in the direct addition of RY to $\mathrm{X\cdot CH{:}CH_2}$ may, under favourable conditions, be replaced by an alternative course (ii, *b*), in which the intermediate free radical $\mathrm{X\cdot \underset{|}{C}H\cdot CH_2R}$ reacts with the ethylenic molecule $\mathrm{X\cdot CH{:}CH_2}$ rather than with the molecule RY and gives rise to addition polymerisation. Free-radical substitution or replacement reactions are usually characterised by a *low degree of specificity* as revealed, for example, in homolytic aromatic substitution or in the atomic chlorination of straight-chain aliphatic acids. On the other hand, free-radical addition reactions normally show a very *high degree of specificity*, similar to that shown in heterolytic addition reactions, which leads to unidirectional reaction. This is revealed, for example, in the peroxide-induced addition of hydrogen bromide to unsymmetrical ethylenic systems and in the large number of addition reactions of halogeno-alkanes studied by Kharasch.[4] The low specificity of the substitution reactions is in keeping with the electrical neutrality of the free radical R·, which reacts with the unperturbed molecule AB in the absence of long-range coulombic forces and molecular polarisation. The high specificity of the addition reactions may be attributed to the differential stabilities of the alternative intermediate free radicals, which can vary with structure within very wide limits. It is important to recognise, however, that the products formed in either type of homolytic reaction need not necessarily be different from those formed in the corresponding heterolytic reaction. An interesting example of the formation of the same product by two different mechanisms has been provided by Kharasch and Fuchs [5] in the addition of thiols to methyl acrylate. These reactions, which are catalysed by *either* a strong base *or* a free radical, may be represented as follows :

$$\text{(I)} \qquad \mathrm{RS^- + CH_2{:}CH{\cdot}CO_2Me \longrightarrow [RS{\cdot}CH_2{\cdot}CH{\cdot}CO_2Me]^-}$$

$$\mathrm{[RS{\cdot}CH_2{\cdot}CH{\cdot}CO_2Me]^- + RSH \longrightarrow RS{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me + RS^-}$$

$$\text{(II)} \qquad \mathrm{RS{\cdot} + CH_2{:}CH{\cdot}CO_2Me \longrightarrow RS{\cdot}CH_2{\cdot}\underset{|}{C}H{\cdot}CO_2Me}$$

$$\mathrm{RS{\cdot}CH_2{\cdot}\underset{|}{C}H{\cdot}CO_2Me + RSH \longrightarrow RS{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me + RS{\cdot}}$$

Product analysis by itself cannot therefore always be relied upon as a certain guide to mechanism. In the homolytic reaction (II) the product also contains compounds formed from two or more molecules of methyl acrylate for each molecule of thiol (reaction ii, *b*).

Another feature of homolytic reactions which has now become clearer is the recognition of the possibility, under suitable experimental conditions, of the *simultaneous* occurrence of homolytic and heterolytic processes. This is illustrated, for example, in the work of Wibaut [6] on the influence of temperature on the orientation of the products in the halogenation of aromatic compounds, and the same principle appears to be evident in the recent work of Klapproth and Westheimer [7] on aromatic mercuration. These workers have shown that many of the apparent anomalies in the orientation of the products in aromatic mercuration become more readily understood if a distinction is made between mercuration with ionised mercuric salts in strong acid solution on the one hand and mercuration with the largely undissociated mercuric acetate in non-polar solvents on the other. In the former case, *e.g.*, with mercuric perchlorate in aqueous perchloric acid, the usual orientation effects for electrophilic substitution are observed, as is shown in the following figures for the mercuration of nitrobenzene, whereas in the latter case the orientation effects are much less pronounced, which is one of the characteristics of a homolytic process :

Mercuration of nitrobenzene.

Experimental conditions	*o*- + *p*- Substitution, %	*m*- Substitution, %
$Hg(ClO_4)_2$ in 60% $HClO_4$ at 23°	11	89
$Hg(ClO_4)_2$ in 40% $HClO_4$ at 95°	37	63
$Hg(OAc)_2$ in excess of $Ph{\cdot}NO_2$ at 95°	52	48
$Hg(OAc)_2$ in excess of $Ph{\cdot}NO_2$ at 150°	57	43

In both of these examples there is clearly no sharp line of demarcation between the heterolytic electrophilic type, which shows the typical pronounced orientation effects, and the homolytic type in which these effects are smoothed out. This smoothing out or levelling effect has also been observed in other ways. Szwarc, Leigh, and Sehon,[8] in an investigation on the influence of aromatic substitution on the C–Br bond dissociation energy in a series of substituted benzyl bromides, have shown that substitution of a hydrogen atom in the ring by chlorine, bromine, methyl, nitro- or cyano-groups, results in comparatively small changes in the activation energy of the process $X{\cdot}C_6H_4{\cdot}CH_2Br \longrightarrow X{\cdot}C_6H_4{\cdot}CH_2{\cdot} + Br{\cdot}$, in sharp contrast to the effect of these substitutents on comparable ionic reactions.

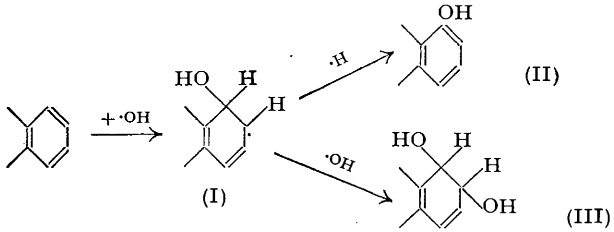
This characteristic absence of specificity in homolytic substitution or replacement reactions is nowhere more clearly demonstrated than in homolytic aromatic substitution. The well-known clearly-defined orientation effects observed in substitution by electrophilic and nucleophilic reactions are here so effectively damped down that it becomes important to redefine the terms *o*/*p*-direction and *m*-direction by reference to the statistical ratio of 60% *o*/*p*-substitution and 40% *m*-substitution. Substituent atoms or groups which give rise to more than 40% substitution at the *m*-position are termed *m*-directing; those giving less than 40% are termed *o*/*p*-directing. On this basis all the reactions which are to be found in the earlier experimental work on homolytic aromatic substitution are examples of *o*/*p*-substitution. In homolytic aromatic substitution, however, the subdivision into *o*- and *p*-substitution on the one hand, and *m*-substitution on the other, has no real justification, and these conventional terms are retained here only in order to direct emphasis to the characteristic differences between the results obtained in heterolytic and homolytic substitution. The quantitative figures available to date must be accepted only as rough approximations, but more accurate quantitative data in this field have recently become available in the work of Weiss[9—13] and his collaborators on substitution reactions with the hydroxyl radical, derived from either Fenton's reagent or the action of ionising radiations on aqueous solutions. In both cases the reactions with nitrobenzene and with chlorobenzene show that the nitro-group and the chlorine atom are *o*/*p*-directing, this term being used in the conventional sense as defined above, as shown in Table 1.

The hydroxylation of benzoic acid by means of free hydroxyl radicals produced by *X*-rays has also been reported by Stein and Weiss,[10] who recorded the formation of *o*-, *m*-, and *p*-hydroxybenzoic acids in the approximate ratio 6 : 4 : 10. The irradiation of ferric ion-pair complexes has been reported by Bates, Evans, and Uri,[14] and their reaction product was said to include *o*-, *m*-, and *p*-hydroxybenzoic acids in the approximate ratio 2 : 2 : 1.

TABLE 1. *Action of hydroxyl radical on nitrobenzene and on chlorobenzene.*

Source of radical	Aromatic compound	pH	Yield of isomerides, %: *ortho*	*meta*	*para*
$FeSO_4$–H_2O_2	$Ph\cdot NO_2$	—	25—30	20—25	50—55
$H_2O \rightsquigarrow H\cdot + \cdot OH$	,,	2	34·5	31	34·5
,, ...	,,	6	35·5	29	35·5
,, ...	,,	12	27·5	27	45·4
$FeSO_4$–H_2O_2	PhCl	—	40—45	20—25	20—25
$H_2O \rightsquigarrow H\cdot + \cdot OH$	,,	2	25—30	30—35	35—40
,, ...	,,	6	15—20	20—25	50—60
,, ...	,,	12	35—40	20—25	35—40

The process of aromatic hydroxylation by means of hydroxyl radicals is of special interest on account of its biological implications in the metabolism of drugs and toxic substances. The results of the biological hydroxylation of simple aromatic compounds have been reviewed by Smith,[15] and these show that in derivatives carrying the classical *o*/*p*-directing groups the hydroxylation is found to take place at the *o*- and *p*-positions, while with the classical *m*-directing group NO_2 hydroxylation takes place at the *o*-, *m*-, and *p*-positions.[16] While there does not appear to be any direct evidence on the biological hydroxylation of benzoic acid, it may be mentioned that Lederer [17] has reported the occurrence of *o*-, *m*-, and *p*-hydroxybenzoic acids as normal constituents of the urine of pregnant mares. These experimental observations, which reveal a close parallel with the work of Weiss, are readily explicable on the basis of a free-radical mechanism, which in biological systems involves not necessarily the free hydroxyl radical but a precursor such as the sulphate radical ion as in the Elbs reaction.[18] Smith [15] has further pointed out that with aromatic compounds in biological systems either phenol or diol formation can occur (II or III) and both can arise from a common intermediate radical (I), the stability of which would largely control whether it would eject a hydrogen atom or combine with another hydroxyl radical. The former process would be expected to take place with simple benzene derivatives, and the latter with the more complex polycyclic hydrocarbons, which would give rise to more stable intermediate radicals owing to the additional resonance energy associated with the fused aromatic structures.



Although the general characteristics and significance of homolytic aromatic substitution reactions are thus becoming clearer, the further development of the subject is restricted by the dearth of accurate quantitative data. This is particularly evident in the substitution reactions in which aryl radicals take part as a result of the reactions of certain diazo-compounds and of acyl peroxides. Many of these reactions lend themselves very well to quantitative study. In an attempt to provide such data a detailed investigation has now been initiated into the quantitative aspects of the reactions of aryl radicals on a wide range of aromatic compounds.

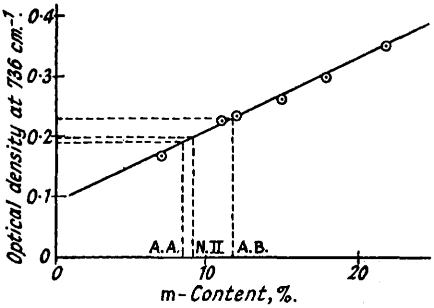
In the earlier qualitative work substitution by aryl radicals was reported to have taken place at the *o*- and *p*-positions only, but in a homolytic substitution process the occurrence of some substitution at the *m*-position might also be expected. It was necessary, therefore, to carry out a series of reactions with aryl radicals (Ar), derived from several different sources, and an aromatic compound (PhR), and to submit the products of these reactions ($Ar{\cdot}C_6H_4R$) to a method of analysis which would allow the proportion of the *m*-isomeride to be estimated. With regard to the directing influence of the nitro-group, the method first employed was based on a bromometric titration of the mixed bases formed on reduction of the mixed nitrodiphenyls.[19] Since the *m*-amine reacts with three molecular proportions of bromine, whereas the *o*- and the *p*-isomeride react with only two molecular proportions, the method provides a means of estimating the ratio $m/(o + p)$. The analytical procedure was tested with synthetic mixtures and shown to be reliable, but it was found that the aryl radical could not be phenyl because, whereas 2- and 3-aminodiphenyl react normally, 4-aminodiphenyl cannot be titrated with a bromide–bromate mixture without undergoing oxidation. The experimental work was therefore carried out with the *p*-bromophenyl and *p*-tolyl radicals, and four sources of the free radical were used in each series, namely, the diazoate, nitrosoacylarylamine, dimethyltriazen, and the acyl peroxide. The results of these reactions, summarised in Table 2, show that the *p*-bromophenyl radical enters the nitrobenzene nucleus at the *m*-position to the extent of 12·1%, while for the *p*-tolyl radical the figure is 8·6%.

TABLE 2. *Action of aryl radical on nitrobenzene.*

Source of radical, p-R·C$_6$H$_4$·	*meta*, %:		Source of radical, p-R·C$_6$H$_4$·	*meta*, %:	
	R = Br	R = Me		R = Br	R = Me
Diazoate, p-R·C$_6$H$_4$·N$_2$·ONa	12·5	9·4	Dimethyltriazen,	21·7	7·0
	12·3	8·3	p-R·C$_6$H$_4$·N$_2$·NMe$_2$	28·6	8·5
		9·1		24·5	
Nitrosoacylarylamine,	11·9	8·7	Acyl peroxide (p-R·C$_6$H$_4$·CO$_2$)$_2$	11·8	9·5
p-R·C$_6$H$_4$·N$_2$·OAc	12·7	8·0		11·6	9·2
			Average	(12·1)	(8·6)

The results are thus qualitatively in agreement with those of Weiss for the hydroxyl radical, and the figure for *m*-substitution in these reactions is substantially independent of the source of the aryl radical, which may be interpreted as evidence for a common mechanism to all four reactions involving the aryl radical as the substituting agent. The anomalous results obtained with 1-*p*-bromophenyl-3 : 3-dimethyltriazen have been shown to be due to the rearrangement of *p*-bromobenzenediazochloride, formed by the action of hydrogen chloride on the triazen, into *p*-chlorobenzenediazobromide: the bases obtained on reduction of the reaction product are thus a mixture of 4-bromo- and 4-chloro-aminodiphenyls in unknown proportions, which leads to an abnormal result in the bromide–bromate titration.

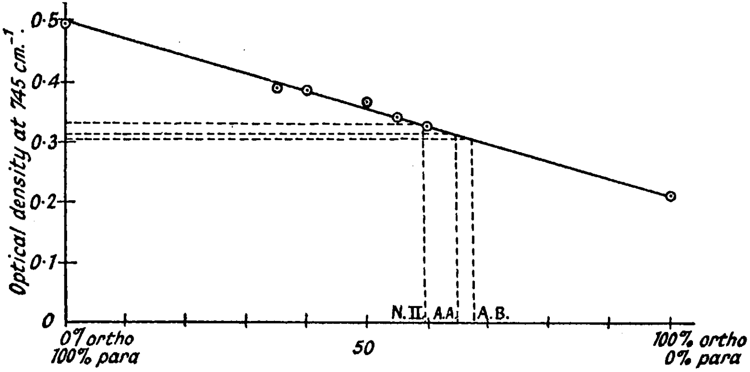
FIG. 1.



The information thus obtained, which establishes the occurrence of substitution at all three positions with reference to the nitro-group, does not provide the proportions in which all three isomerides are formed, and it gives no information on the influence of the substituent nitro-group on the activation or deactivation of the nucleus as a whole. To obtain the complete picture it is necessary to pursue two parallel lines of investigation, as was in fact done by Ingold and his collaborators [20–21] for electrophilic aromatic substitution more than twenty years ago, namely, (*a*) the determination of the proportions in which each of the three isomerides is formed, and (*b*) the determination of the rate of the total substitution reaction relatively to that of benzene. By means of infra-red spectroscopy it has now been possible to obtain an accurate assessment of the directing influence of both the chlorine atom and the nitro-group, and by means of a series of competitive reactions the activating or deactivating influences at work have been quantitatively assessed.

Infra-red spectroscopy was first applied to the reaction product obtained from the action of phenyl radicals on nitrobenzene.[19] Such a product would be expected to provide results which should be in close agreement with those already obtained by chemical analysis for the corresponding reactions with the *p*-bromophenyl and *p*-tolyl radicals. A preliminary study of the infra-red spectra of the three isomeric nitrodiphenyls in nitromethane showed that characteristic bands for each isomeride occurred within the region 710—810 cm.$^{-1}$, but that there was considerable overlapping. It was found, however, that the absorption at 736 cm.$^{-1}$ provided a direct measure of the *m*-isomeride in artificial mixtures of the three isomerides, and the variation in optical density at this wave number with the content of the 3-isomeride is shown in Fig. 1. The variation in optical density at 736 cm.$^{-1}$, due to changes in the *o*- and *p*-content, was shown to be comparatively small. By means of this graph it was possible to estimate the extent of substitution at the *m*-position with respect to the nitro-group. The proportion of substitution at the *o*- and *p*-positions was obtained in similar manner by measurement of the optical density at 745 cm.$^{-1}$, which was shown to be particularly sensitive to the *o* : *p* ratio. Fig. 2 shows the observed optical densities of the pure *o*- and *p*-isomerides and of mixtures of the two, and from this graph the *o* : *p* ratio of a mixture of unknown composition can be estimated.

FIG. 2.



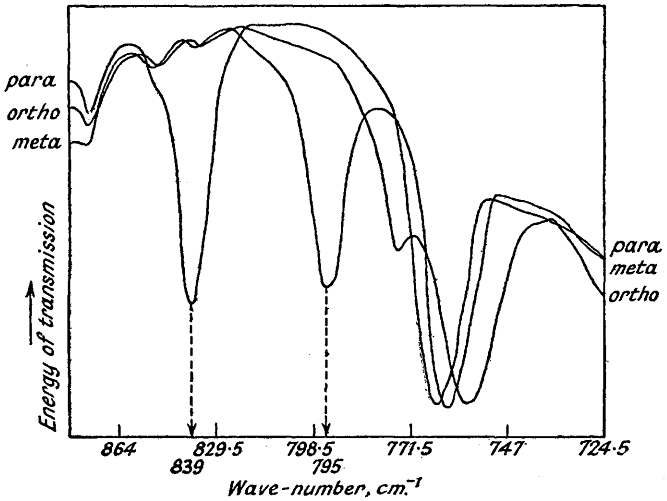
The results thus obtained for the products of the phenylation of nitrobenzene are as follows :

Source of Ph radical	Nitrodiphenyls, % :		
	ortho	*meta*	*para*
Na benzenediazoate (N.II.)	54 ± 4	9 ± 2	37 ± 4
Benzoyl peroxide (A.A.)	59·5 ± 4	8·5 ± 2	32 ± 4
,, ,, (A.B.)	59·5 ± 4	11·5 ± 2	29 ± 4

These results provide, not only confirmation of the results previously obtained by chemical analysis, but also further indication of the independence of the orientation on the source of the phenyl radical. During the course of this work, De Tar and Scheifele[22] reported results on the phenylation of nitrobenzene, using benzoyl peroxide, benzenediazohydroxide, and nitrosoacetanilide as their source of the phenyl radical and employing measurement of the ultra-violet absorption for the determination of the proportions of the isomerides formed. Their results are in general agreement with those reported above, but a comparison of the two investigations shows the superiority of the infra-red technique in this particular instance.

A similar investigation was carried out on the product obtained by the action of phenyl radicals on chlorobenzene, both the Gomberg reaction and benzoyl peroxide being used as the source of the phenyl radical.[23] In the preliminary study of the infra-red absorption of the three isomeric chlorodiphenyls in nitromethane solution it was found that the *m*- and *p*-isomerides possessed characteristic bands in the region 11—15µ, but the corresponding band for the *o*-isomeride was very close to a strong band common to all three isomerides and would probably be of little value for quantitative estimation (Fig. 3). Measurements were made in nitromethane solution, the 795 cm.$^{-1}$ and 839 cm.$^{-1}$ bands being used to estimate the *m*- and the *p*-content, respectively, the *o*-content being derived by difference. A typical curve for such an experimental mixture is shown in Fig. 4. The reliability and accuracy of the method are illustrated in Table 3, and the analytical results for a series of nine reaction products, obtained from either sodium benzenediazoate or benzoyl peroxide, are shown in Table 4.

FIG. 3.



In the parallel investigation on the determination of the activating or deactivating influence of the substituent atom or group, two lines of approach are possible, namely, the direct measurement of the velocity constants for attack on the substituted and unsubstituted compounds, and the method of competitive experiments in which the ratio of the velocity constant for attack on a pair of compounds (X and Y) is obtained by analysis of the mixed product formed when a mixture of the two compounds of known composition is allowed to react in a homogeneous medium with a limited quantity of the substituting agent. The ratio of the velocity constants k_x/k_y or ${}^x_yK$ is equal to the ratio of the amounts of the two products formed from an equimolar

TABLE 3. *Infra-red analysis of mixtures of chlorodiphenyls.*

Solution	Percentage of chlorodiphenyls : *ortho*	*meta*	*para*
(i) Found	42·36	30·57	27·07
Calc.	39·14	32·14	28·72
(ii) Found	48·80	29·47	21·73
Calc.	44·29	32·47	23·24
(iii) Found	—	62·42	37·58
Calc.	—	61·90	38·10

TABLE 4. *Phenylation of chlorobenzene.*

Reaction	Percentage of chlorodiphenyls : *ortho*	*meta*	*para*
Gomberg, (i)	64·48	21·30	14·22
,, , (ii)	65·78	20·55	13·67
,, , (iii)	63·37	22·72	13·90
,, , (iv)	64·48	22·23	13·09
Benzoyl peroxide, (v)	62·82	24·56	12·62
,, , (vi)	61·36	24·99	13·65
,, , (vii)	57·62	27·08	15·29
,, , (viii)	60·27	25·89	13·84
,, , (ix)	59·51	26·98	13·51

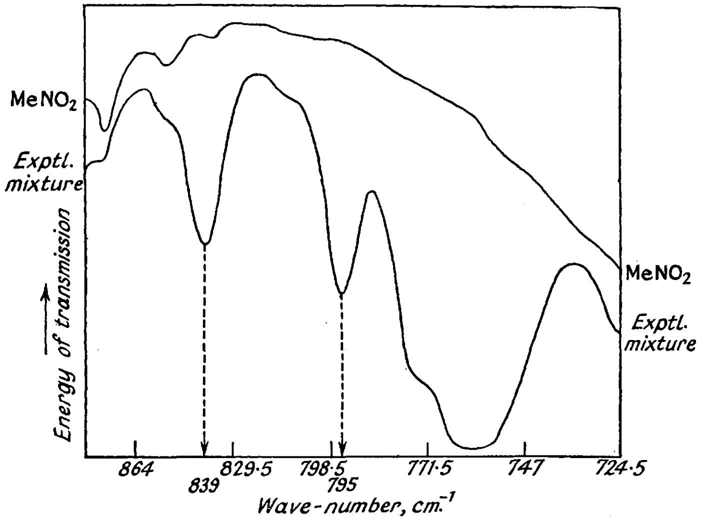
mixture of the two components X and Y provided (*a*) that the excess of the two components over the attacking reagent is large, so that the molar composition of the mixture is not appreciably disturbed by the unequal rates of disappearance of the two components, and (*b*) that the substitution reactions under investigation are of the same kinetic order.

For the reactions under investigation the method of the direct kinetic approach is of uncertain value because it is probable that in most cases it is not the actual substitution reaction which is the rate-determining stage. It is thus necessary to use the method of competitive reactions on the lines employed by Ingold and his collaborators [20, 21, 24, 25] for electrophilic substitution. The competitive method, moreover, possesses two special advantages in that (i) it allows measurements to be carried out with a solid component provided it is sufficiently soluble in the second component to give a solution of the required concentration, and (ii) by means of successive estimations with two pairs of reactants containing one reactant in common, it is possible to derive a rate ratio for a pair of components which cannot be satisfactorily compared directly. Thus, for the three reactants ArH, ArX, and ArY, we have :

$${}^{\mathrm{ArX}}_{\mathrm{ArH}}K = {}^{\mathrm{ArX}}_{\mathrm{ArY}}K \times {}^{\mathrm{ArY}}_{\mathrm{ArH}}K$$

There are several alternative reactions which can be used as a source for the aryl radical as outlined above in the parallel work on the orientation problem, but in competitive experiments it is essential to use a homogeneous or one-phase system in order to eliminate purely mechanical factors such as rate of stirring, and for the present purposes the reactions of benzoyl peroxide were chosen. These reactions, which may be represented thus :

FIG. 4.



Main reaction : $(\mathrm{Ph{\cdot}CO_2})_2 + \mathrm{ArH} \longrightarrow \mathrm{PhAr} + \mathrm{Ph{\cdot}CO_2H} + \mathrm{CO_2}$
Side reaction : $(\mathrm{Ph{\cdot}CO_2})_2 + \mathrm{ArH} \longrightarrow \mathrm{PhH} + \mathrm{Ph{\cdot}CO_2Ar} + \mathrm{CO_2}$

are usually clean and it has been generally found possible to account for about 85—90% of the reagent as identified products. In all cases it is first necessary to remove benzoic acid and benzoates, which are formed as by-products.

The experimental procedure requires a method for the quantitative analysis of the two products, PhAr and PhAr′, which result from the attack of ArH and Ar′H by the phenyl radical. Three analytical methods were evolved, nitrobenzene, chlorobenzene, or pyridine, being used as one reactant of each pair.[23, 26] The products from the reactions with nitrobenzene were analysed by quantitative reduction with titanous chloride under special experimental conditions previously developed and tested with artificial mixtures of known composition. The products from reactions with chlorobenzene were analysed for chlorine by a micro-Carius method, and the products from the reactions in which pyridine was used as one of the components were analysed by separation into neutral and basic fractions. With certain combinations of reactants, for example PhCl and $\mathrm{Ph{\cdot}NO_2}$, two independent methods of analysis are available. Time does not permit mention of certain experimental difficulties which were encountered with various pairs of reactants and subsequently overcome. Four reactants were used, namely, benzene, nitrobenzene, chlorobenzene, and pyridine, which give rise to six pairs. The experimental results are summarised in Table 5.

TABLE 5. *Direct rate ratios from competitive experiments.*

Reactants: X	Y	Expt. no.	${}^{x}_{y}K$	
$\mathrm{Ph{\cdot}NO_2}$	PhH	1	11·57	$\ngtr$ 4·17
,,	,,	2	23·27	
,,	,,	3	5·21	
,,	,,	11	4·17	
PhCl	PhH	14	1·21	1·31
,,	,,	15	1·41	

Reactants: X	Y	Expt. no.	${}^{x}_{y}K$	
PhCl	$\mathrm{Ph{\cdot}NO_2}$	12	0·358	0·361
,,	,,	13	0·364	
C_5H_5N	PhH	16—23		1·04
PhCl	C_5H_5N	24—26		1·15
$\mathrm{Ph{\cdot}NO_2}$	C_5H_5N	29—30		3·95

The direct determination of ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$, *i.e.*, the rate ratio for nitrobenzene and benzene, was not wholly satisfactory because of the comparatively high volatility of diphenyl, some of which was always lost during the removal by distillation of the excess of nitrobenzene. Modifications in the working-up procedure, designed to eliminate this loss, account for the very variable results. The results can be accepted as giving a *maximum* value for ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$. As explained above, however, it is possible to derive indirect values for ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$ by employing chlorobenzene in the first instance and pyridine in the second as a common reference compound. The rate ratios measured were therefore ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$, ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhCl}}K$, and ${}^{\mathrm{PyH}}_{\mathrm{PhH}}K$, ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PyH}}K$, whence

$${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K \times {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhCl}}K = {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K \text{ and } {}^{\mathrm{PyH}}_{\mathrm{PhH}}K \times {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PyH}}K = {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$$

The following rate ratios (Table 6) can be derived from pairs, or from groups of three, of the directly determined rate ratios in Table 5, each group of two or three providing two new values for K.

TABLE 6. *Derived rate ratios from competitive experiments.*

Reactants: X	Y	${}^{x}_{y}K$ Direct	${}^{x}_{a}K\,{}^{a}_{y}K$ Derived	${}^{x}_{a}K\,{}^{a}_{b}K\,{}^{b}_{y}K$ Derived
$\mathrm{Ph{\cdot}NO_2}$	PhH	$\ngtr$4·17	3·63	3·31
			4·11	4·50
PhCl	PhH	1·31	1·50	1·48
			1·20	1·21
PhCl	$\mathrm{Ph{\cdot}NO_2}$	0·361	0·29	0·29
			0·31	0·32

Reactants: X	Y	${}^{x}_{y}K$ Direct	${}^{x}_{a}K\,{}^{a}_{y}K$ Derived	${}^{x}_{a}K\,{}^{a}_{b}K\,{}^{b}_{y}K$ Derived
C_5H_5N	PhH	1·04	1·14	0·92
			1·05	1·30
PhCl	C_5H_5N	1·15	1·26	1·44
			1·42	1·24
$\mathrm{Ph{\cdot}NO_2}$	C_5H_5N	3·95	4·00	3·67
			3·19	3·50

The values selected for ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$ and ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$ on the basis of the above results are 4·0 and 1·44, respectively, the latter value being based on ${}^{\mathrm{PhCl}}_{\mathrm{Ph\cdot NO_2}}K = 0{\cdot}361$, which is regarded as the most reliable figure, by multiplying by 4. For electrophilic substitution (nitration) the corresponding figures are $\sim 10^{-4}$ and 0·033.

De Tar and Scheifele [22] have recently reported a qualitative competitive reaction of nitrosoacetanilide with a mixture of benzene and chlorobenzene. They, too, found that the chlorobenzene was preferentially attacked and they comment on the fact that in electrophilic substitution Bird and Ingold [25] found that benzene underwent nitration with nitric acid-acetic anhydride 30 times faster than did chlorobenzene. Nearly twenty years ago Grieve and Hey [27] allowed toluene and nitrobenzene (both in excess) to compete for phenyl radicals derived from sodium benzenediazoate, and reported that the yield of nitrodiphenyls was four times as great as the yield of methyldiphenyls.

The results outlined above have established that both the nitro-group and the chlorine atom are *activating* in homolytic aromatic substitution, but the effects shown are very much *smaller in magnitude* than those encountered in electrophilic substitution. This is in agreement with the general pattern of homolytic reactions, which are free from the powerful electrostatic forces which dominate heterolytic reactions. The neutral radical approaches the site of the reaction not only without experiencing either electrostatic attraction or repulsion, but also without causing any electronic perturbation in the molecule to be attacked.

The quantitative information thus made available enables the results to be combined and expressed more explicitly in terms of *partial rate factors.* This concept, first introduced by Ingold *et al.* in 1931 [21] for electrophilic aromatic substitution, gives a quantitative expression for the influence of a substituent atom or group on reactivity in relation to substitution at an individual nuclear carbon atom. If the rates of homolytic substitution are expressed in terms of the rate of substitution at any one position in the aromatic nucleus, the rate for benzene as a whole becomes 6 and that for nitrobenzene as a whole 24, and, provided the proportions are known in which the *o*-, *m*-, and *p*-isomerides are formed, the rates of substitution at each position in nitrobenzene can be calculated. The partial rate factors designated ${}^{\mathrm{PhX}}_{\mathrm{PhH}}F_o$, ${}^{\mathrm{PhX}}_{\mathrm{PhH}}F_m$, and ${}^{\mathrm{PhX}}_{\mathrm{PhH}}F_p$, together constitute a complete specification of the influence of the substitutent group or atom X on the reactivity of the molecule C_6H_5X towards the reagent under consideration. For the substitution of nitrobenzene and chlorobenzene by the phenyl radical the relevant experimental values may be taken as :

	Rate ratio (Benzene = 1)	Isomerides, % : *ortho*	*meta*	*para*
Nitrobenzene	4·0	58	10	32
Chlorobenzene	1·44	62	24	14

which give rise to the following partial rate factors :

$${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_o = 7{\cdot}0 \qquad {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_m = 1{\cdot}2 \qquad {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_p = 7{\cdot}9$$

$${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_o = 2{\cdot}7 \qquad {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_m = 1{\cdot}03 \qquad {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_p = 1{\cdot}2$$

Several attempts have been made to obtain a theoretical derivation of the directive influence of groups in heterolytic and homolytic aromatic substitution. From the figures given by Wheland [28] it is possible to calculate the partial rate factors for homolytic substitution in nitrobenzene and chlorobenzene; for nitrobenzene these are :

$${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_o = 2{\cdot}25 \qquad {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_m = 0{\cdot}85 \qquad {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_p = 8{\cdot}7$$

Then, since

$${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K = \tfrac{1}{6}\left(2\,{}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_o + 2\,{}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_m + {}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}F_p\right),$$

these partial rate factors lead to a value to 2·5 for ${}^{\mathrm{Ph\cdot NO_2}}_{\mathrm{PhH}}K$ for homolytic substitution without reference to the nature of the radical involved. In similar manner for chlorobenzene the calculated partial rate factors are :

$${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_o = 5{\cdot}8 \qquad {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_m = 1{\cdot}4 \qquad {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_p = 1{\cdot}9$$

from which ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$ becomes 2·7, again without reference to the nature of the radical involved. Although numerical agreement is not close, the over-all picture is satisfactory in that it predicts predominant *o*/*p*-substitution in both nitrobenzene and chlorobenzene, and it also indicates mild activation in both cases. These results are the more remarkable since they are based on theoretical derivations made nearly ten years ago at a time when the experimental facts were unknown.

A new experimental method has been developed for the determination of partial rate factors which is *independent* of any knowledge of the proportions in which the isomerides are formed.[23] In this method, which is illustrated by application to the action of the phenyl radical on chlorobenzene, the assumption has to be made that the frequency factor, or the entropy of activation, remains constant throughout the series of reactions investigated, and that the energy contributions for the reaction at any one position in a polysubstituted benzene derivative are additive, or nearly so. This is not an unlikely assumption and is one for which there is some experimental support in the work of Ingold *et al.*[21] and in that of Bradfield and Brynmor Jones [29] on heterolytic substitution reactions of phenolic ethers. The experimental values required are the relative rates of substitution with reference to benzene for (*a*) chlorobenzene, (*b*) *p*-dichlorobenzene, and (*c*) *s*-trichlorobenzene. These were found to be :

$${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K = 1{\cdot}44 \qquad {}^{p\text{-}\mathrm{C_6H_4Cl_2}}_{\mathrm{PhH}}K = 2{\cdot}69 \qquad {}^{s\text{-}\mathrm{C_6H_3Cl_3}}_{\mathrm{PhH}}K = 5{\cdot}02$$

which, for benzene = 6, become PhCl = 8·64, p-$C_6H_4Cl_2$ = 16·14, s-$C_6H_3Cl_3$ = 30·12. These values give rise to three equations involving three unknowns, which lead to a cubic equation in any one of the three partial rate factors chosen. For the reaction with chlorobenzene we have :

$$8{\cdot}64 = 2F_o + 2F_m + F_p \quad . \; . \; . \; . \; . \; . \; . \; . \; . \tag{1}$$

For *p*-dichlorobenzene, in which there are four identical positions each influenced by one *o*- and one *m*-chlorine atom, we have :

$$4F_oF_m = 16{\cdot}14 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \tag{2}$$

whereas for *s*-trichlorobenzene, in which there are three identical positions each influenced by two *o*- and one *p*-chlorine atom, we have :

$$3F_o^2F_p = 30{\cdot}12 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \tag{3}$$

From (2) $F_m = 4{\cdot}035/F_o$ and from (3) $F_p = 10{\cdot}04/F_o^2$

Then $\qquad 2F_o + 8{\cdot}07/F_o + 10{\cdot}04/F_o^2 = 8{\cdot}64$

therefore $\qquad 2F_o^3 + 8{\cdot}07F_o + 10{\cdot}04 = 8{\cdot}64F_o^2$

i.e., $\qquad F_o^3 - 4{\cdot}32F_o^2 + 4{\cdot}035F_o + 5{\cdot}02 = 0$

The solution of this equation shows no real positive root, but if a relatively small allowance is made for experimental error and/or a slight divergence from the additive relationship on which the method is based, a positive root for ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_o$ of 2·3 is obtained, which in turn gives ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_m = 1{\cdot}75$ and ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_p = 1{\cdot}9$.

The partial rate factors for homolytic substitution in chlorobenzene based on the three methods outlined above are summarised in Table 7. Each method indicates a predominance of substitution at the *o*- and *p*-positions, together with mild activation at all three positions. For purposes of comparison the partial rate factors for the nitration of chlorobenzene [25] are also included.

By means of the methods described above it has thus been possible to obtain for the first time a complete definition in quantitative terms of the influence of a substituent atom or group on a homolytic substitution reaction in the aromatic nucleus. It has been shown that both the nitro-group and the chlorine atom are *ortho-para*-directing substituents, the term being used in the conventional sense defined above, and that both substituents have an activating influence. The characteristic picture thus revealed is in close agreement with that obtained by theoretical deduction. What has already been achieved with the nitro-group and the chlorine atom can be applied to other substituent groups or atoms, and in this way useful new information should result which will be of value in the wider fields of chemistry as a whole. The results so far obtained have a special personal significance in that they seem to provide a satisfactory, consistent, and rigid experimental vindication of some rather speculative ideas which were first put forward nearly 20 years ago.

TABLE 7. *Partial rate factors for substitution in chlorobenzene.*

Reaction and method	${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_o$	${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_m$	${}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_p$
Phenylation by infra-red analysis and competitive experiments	2·7	1·03	1·2
Calculation for Wheland's figures for homolytic substitution	5·8	1·4	1·9
Cubic method for phenylation	2·3	1·75	1·9
Nitration by HNO_3–Ac_2O	0·03	0·00	0·139

It is customary on these occasions for the lecturer to thank those who have helped to contribute to the subject under discussion. In following precedent I do so not as a formal duty, but rather in a spirit of humble gratitude to all those who over many years have helped in this work. Their number is too large for me to mention all, but I should like to thank in particular my first collaborator, Dr. W. S. M. Grieve, who was with me at the start, and also my most recent collaborator, Dr. D. R. Augood, to whose skill and ability the success of much of the more recent work is very largely due. Finally, I place on record my special indebtedness to my colleagues at King's College, first to Dr. Gareth Williams, whose constant help has been invaluable, and then to Dr. W. C. Price and Dr. T. S. Robinson, who have provided us with expert advice and guidance in infra-red spectroscopy as well as with experimental facilities.

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