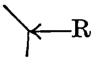
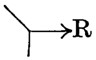
CCCLXXXVIII.—*The Nature of the Alternating Effect in Carbon Chains. Part XXII. An Attempt further to define the Probable Mechanism of Orientation in Aromatic Substitution.*

By Christopher Kelk Ingold and Florence Ruth Shaw.

Recent studies of reactivity transmission have led to the recognition in aromatic substitutions of orienting effects originating in the following combinations of inductively propagated electronic strain $(I, \longrightarrow)$ and tautomeric or electromeric transformations $(T, \curvearrowright)$ * (for summary see *Ann. Reports*, 1926, p. 129) :

Type				
Symbol	(1) $+I$	(2) $-I$	(3) $-I+T$	(4) $+I+T$
Examples	Toluene.	Phenylammonium ions. Phenylsulphones.	Halogenobenzenes. Phenylthionium ions.	Phenoxide ion.

On the other hand, previous results provide little positive information with regard to the paths whereby the effects thus arising traverse the nucleus. It is possible that the inductive and the

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* For reasons given elsewhere, the possible combinations represented by $+I-T$ and $-I-T$ will not here be separately discussed, and it is also unnecessary for our present purpose to consider superimposed polar orientation through space.

tautomeric disturbances travel by different routes and influence the reactivity in the various positions of the nucleus in different relative degrees. The one clearly established circumstance is that both types of disturbance affect primarily the ortho- and para-positions.

The paucity of information on this subject is partly due to the fact that a knowledge of the proportions in which isomerides are formed in substitutions furnishes only one of the two kinds of data which are necessary for an analysis of the influence of orienting groups on the reactivity in each nuclear position. The other, consisting of the relative velocities of the total substitutions ($o + m + p$) of different substances, is, in general, not available. In this paper, a preliminary analysis of certain cases is attempted with the aid of new experimental data.

Before proceeding to details, it is desirable to define the terms employed. By the phrase " the reactivity in a given nuclear position " is meant the velocity, relative to some standard, of the substitution which occurs in that position under the conditions of the comparison. The effect of an orienting group on the reactivity of each nuclear position may therefore be defined as the number of molecules substituted during a small element of time at the given nuclear carbon atom, divided by the number which would have been substituted during the same element of time at the same carbon atom had the orienting group been absent. This ratio may be termed the " coefficient of activation " (F) for the orienting group and the nuclear position considered.

The results recorded below refer to nitration. It is, of course, certain that the relative reactivities of different nuclear carbon atoms will be found to vary with the nature of the substitution studied (*e.g.*, nitration and mercuration). Nevertheless there are good grounds for the belief that the broad, qualitative conclusions (which alone it is desired to indicate in this preliminary communication) will be found to apply, without serious alteration, to the behaviour of the nucleus in a large class of substitution reactions.

Case 1. *Type* + I. *Example : Toluene.*—Toluene is nitrated to the extent of approximately 59% in its ortho-positions, 4% in its meta-positions, and 37% in its para-position. The disparity between the *op*-substitution on the one hand and *m*-substitution on the other is universally regarded as indicating the *op*-orienting tendency of the methyl group; but it may have arisen in various ways. For instance, the orienting group may have caused an increase in *op*-reactivity accompanied by a decrease of *m*-reactivity (alternation, in fact); or it may have given rise to an increase of *op*-reactivity, and left the *m*-position unaffected; or it may have produced a large increase in *op*-reactivity and a smaller increase in *m*-reactivity; and there are other possibilities. Actually each of the three alternatives mentioned has been assumed or implied in one or other of the theories of aromatic substitution which have been under discussion in recent years.

It is known from Wibaut's experiments (*Rec. trav. chim.*, 1915, **34**, 241) that toluene nitrates much more rapidly than benzene; but this does not decide the question at issue. Our study of the relative velocities of nitration of benzene and toluene has led to the conclusion that whilst the reactivity of each ortho- or para-carbon atom in toluene is increased roughly 30-fold, that of each meta-carbon atom is increased 2-fold by the directive action of the methyl group.

Benzene and toluene, both in excess, were nitrated together in a homogeneous solution; the reaction was allowed to proceed to completion and the product analysed. This method has an advantage over the alternative of carrying out parallel nitrations with benzene and toluene separately, inasmuch as uncertainties arising from imperfect, and consequently unequal, temperature control are avoided. The molecular ratio, *R*, in which the hydrocarbons are nitrated is not the ratio of the velocities, *ceteris paribus*, of the respective total substitutions, but may be used to determine it as follows.

It is assumed that the reactions are carried out in unit volume which does not change appreciably during the process. If x_0, y_0, and z_0 are the initial amounts of benzene, toluene, and nitric acid, respectively, and x and y are the quantities of benzene and toluene remaining after a time t, then at any moment

$$-dx/dt = k_x x\{x + y - (x_0 + y_0) + z_0\}$$

and

$$-dy/dt = k_y y\{x + y - (x_0 + y_0) + z_0\}.$$

These equations assume that the reactions are bimolecular and irreversible. This has been shown to be the case for the nitration of a considerable number of substances, including benzene, nitrobenzene, chlorobenzene, *op*-dinitrotoluene, and the three nitrobenzoic acids (Holleman and de Bruyn, *Rec. trav. chim.*, 1900, **19**, 79, 188, 364; 1901, **20**, 206, 352; Martinsen, *Z. physikal. Chem.*, 1905, **50**, 385; 1907, **59**, 605; Wibaut, *loc. cit.*). Phenol, however, is an exception, which is not surprising (Martinsen, *loc. cit.*; Klemenc, *Monatsh.*, 1914, **35**, 85; Arnall, J., 1923, **123**, 3111).

The above equations on simultaneous integration give

$$k_y/k_x = (\log y_\infty - \log y_0)/(\log x_\infty - \log x_0)$$

where x_∞ and y_∞ are the ultimate values of x and y, respectively. The two equations necessary to evaluate x_∞ and y_∞ are

$$x_\infty + y_\infty = x_0 + y_0 - z_0$$

and

$$R = (y_0 - y_\infty)/(x_0 - x_\infty),$$

and the final expression for the ratio of the velocities of the total substitutions is

$$\frac{k_y}{k_x} = \log\left\{1 - \frac{z_0}{y_0}\left(\frac{R}{1 + R}\right)\right\} \Big/ \log\left\{1 - \frac{z_0}{x_0}\left(\frac{1}{1 + R}\right)\right\}.$$

Naturally, the formula applies generally to the simultaneous nitration of pairs of aromatic substances, provided the assumptions made during its derivation are fulfilled. Even if they are not accurately fulfilled, the general conclusions still hold, for the replacement of k_y/k_x by R, which must in any case represent a too conservative estimate of the ratio of the speeds, leads to the same conclusions. If ω, μ, and π represent the proportions of the individual nitrotoluenes in the total nitrotoluenes produced, the respective coefficients of activation are

$$F_{\text{ortho}} = 3\omega k_y/k_x\,;\quad F_{\text{meta}} = 3\mu k_y/k_x\,;\quad F_{\text{para}} = 6\pi k_y/k_x,$$

and on substituting the numerical data, we find

$$F_{\text{ortho}} = 27{\cdot}6\,;\quad F_{\text{para}} = 34{\cdot}6;\quad F_{\text{meta}} = 2{\cdot}1.$$

Case 2. Type — I. Examples: Benzyltrimethylammonium Salts and Benzoic Acid.—The examples mentioned have been chosen to represent this type (which includes all benzene derivatives in which *m*-substitution is known to predominate) because the first corresponds, we consider, with the simple inductive effect, whilst the second theoretically admits of a superimposed electromeric change, and might by some be considered as belonging more properly to one of the categories mentioned in the footnote on p. 2918.

The notoriously slower velocity of many *m*-oriented, as compared with the majority of *op*-oriented, substitutions, taken together with the observations of Martinsen (*loc. cit.*), who has shown, *inter alia*, that the introduction of a carboxyl, sulphonic acid, or nitro-group into a benzene derivative already containing one or more orienting groups diminishes the velocity of further substitution, leaves little doubt that in *m*-substitutions generally the *op*-positions escape an equivalent amount of attack owing to the deactivating influence of the directing substituent. Strictly, the point is unproved, but it is rendered sufficiently probable by the existing evidence to warrant its adoption as a working hypothesis. The question remains as to whether, either generally throughout the category, or in individual cases, the *m*-position is activated, deactivated, or left unaffected. In certain examples in which a positive pole is attached to the nucleus the answer is clearly that the *m*-position, like the *op*-positions, is deactivated. For the substances mentioned in the head-line, we find that the coefficient of meta-activation is an extremely small fraction of unity, the *o*- and *p*-reactivity factors being smaller still, and we believe that this state of affairs is general amongst *m*-substituting benzene derivatives.

Case 3. *Type* — I + T. *Examples: The Halogenobenzenes, etc.*—This type includes the halogenobenzenes, the alkyl- and acyl-oxybenzenes, the acyl-, acyl-alkyl, and diacyl-aminobenzenes, nitrosobenzene, phenyl sulphoxides, phenylthionium salts, and all other compounds in which the atom attached to the ring attracts electrons more strongly than hydrogen (— *I*), but at the same time possesses unshared electrons which can be shared with the nucleus (+ *T*).

In all the investigated instances, predominating *op*-substitution is the rule; but a substantial amount of simultaneous *m*-substitution is not theoretically impossible, since examples can be conceived in which the inductive process might effectively compete with tautomeric action. In the series of orienting groups NRR′, OR, I, Br, Cl, F (R = alkyl) the tautomeric effect diminishes and the inductive effect increases towards fluorine, but even in fluorobenzene the substitution is almost exclusively ortho-para. On the other hand, the velocity of substitution diminishes throughout the series to such an extent that the right-hand members become qualitatively differentiated from the left-hand members, and from the *op*-orienting groups, belonging to Case 1, which act by simple induction (+ *I*). That is to say, the category under consideration provides examples of *op*-orienting groups which, unlike all other *op*-orienting groups, diminish the velocity of substitution: their coefficients of activation are fractional. In this respect they resemble the *m*-orienting groups of Case 2, but are distinguished from them by the fact that for the groups of Case 3 the meta-deactivation is even stronger than the *op*-deactivation, whereas the reverse holds for Case 2. From the left of the above series up to and including iodobenzene the values of k_y/k_x are greater than unity; for bromobenzene (0·2), chlorobenzene (0·01), and fluorobenzene (0·002) they are fractional, and the values given, although approximate, establish the order of the compounds.

The position assigned to the NHAc-group is based on nitration with a neutral reagent in a neutral or feebly acid medium (acetyl nitrate in acetic anhydride; Ingold and Ingold, J., 1926, 1310). The nitration of acetanilide with nitric acid in sulphuric acid as solvent is interesting inasmuch as the same salt-forming process which absorbs the unshared electrons also charges, and enhances the electron affinity of the nitrogen atom, so that on increasing the strength of sulphuric acid the circumstances of Case 3 continuously approach those of Case 2; this takes place with corresponding changes in the coefficients of activation, which become fractional, and, as Noelting and Collins's experiments indicate, in the proportions of the isomerides (*Ber.*, 1884, **17**, 262).

Case 4. *Type* + I + T. *Example : The Phenoxide Ion.*—The general conditions affecting the substitution of the phenoxide ion are attested by known results. In particular, the high *op*-reactivity of the ion in comparison with undissociated phenol is well illustrated by the recent experiments of Soper and Smith (J., 1926, 1582).

Discussion and Conclusions.—Consideration of the facts summarised above has led us to the following conclusions :

(i) That whereas inductive effects of either sign operate primarily on the ortho- and para-positions, an appreciable second-order effect, always of the same sign as the primary effect, is relayed on to the meta-position.

(ii) That whereas tautomeric effects also operate powerfully on the ortho- and para-positions, no similarly appreciable second-order effect reaches the meta-position.

(iii) That whilst inductive effects give rise to an essentially permanent (not necessarily constant) molecular condition, the tautomeric effect (apart, possibly, from a small permanent residuum) is essentially temporary in character, assuming much greater importance at the moment of attack by a reagent than in the quiescent period preceding it.

Conclusion (i) is reached directly from the consideration of Cases 1 and 2. It implies that *m*-substitution in Case 1 arises from second-order *m*-activation, and in Case 2 from second-order *m*-deactivation, which explains the velocity relations. A consistent deduction is that, as *op*-deactivation increases, the proportion of the effect relayed to the *m*-position decreases, so that the *m*-directive power of a group (Case 2) runs *inversely* as the velocity of *m*-substitution. This is certainly true for a series such as CO_2H(80%), NO_2(93%), $\overset{+}{N}Me_3$(100% meta), in which the velocities rapidly diminish towards $\overset{+}{N}Me_3$ and the figures in brackets represent the proportion of meta-nitration.

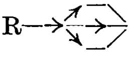
Conclusion (ii) follows from Case 3. Considering the series (p. 2922) NRR′, OR, . . ., Cl, F, the term $-I$ may for many purposes be neglected in the left-hand members in comparison with $+T$, which produces strong *op*-activation but no *m*-activation which is detectable in comparison. Again, if one imagines an extension of the series from NRR′ (*T* strong), through F (*T* weak), towards an extreme representative, such as $\overset{+}{\text{N}}$RR′R″, of Case 2,

$$\begin{array}{c}\xrightarrow{\text{decreasing } T} \\ \text{NRR}' \ldots (a) \ldots \text{F} \ldots (b) \ldots \overset{+}{\text{N}}\text{RR}'\text{R}'' \\ \xrightarrow{\text{increasing } -I}\end{array}$$

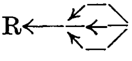
the change over (*a*) from *op*-activation to *op*-deactivation occurs higher in the series than the change (*b*) from *op*- to *m*-substitution. For groups lying near the first of these critical positions (*a*) in the filled-in series, it is obvious that whilst the tautomeric effect can annul or reverse the strong *op*-deactivation arising from inductive action, it cannot reverse the relatively feeble *m*-deactivation. Indeed it seems to us that the condition of the whole group lying between the critical points (*a*) and (*b*) can be interpreted only along the lines indicated. The application to Case 4 is that appreciable *m*-substitution might arise if the inductive effect (+ *I*) were sufficiently powerful. Arnall's claim (J., 1924, **125**, 811) to have established 2—3% of *m*-substitution in the nitration of phenol might, if confirmed, be an indication in this direction. For systems of groups falling wholly within any one of Cases 1, 3 and 4, *op*-directive power must run parallel with the velocity of *op*-substitution, but no such simple rule can be laid down for the comparison of groups belonging to the different cases.

Conclusion (iii) is tentative, and is introduced because it appears necessary for the reconciliation of conclusions (i) and (ii). That inductive effects give rise to a permanent condition of electronic strain agrees with the known data relating to the molecular dipole moments of benzene derivatives, and it is consistent with our knowledge of reactivity transmission that a fractional part of charges arising on the ortho- and para-carbon atoms should be transmitted to the meta-carbon atom. On the other hand, it is difficult to see how *op*-charges which would be produced by the tautomeric effect can avoid similar transmission to the *m*-position, unless it be that they are " externally neutralised," that is, unless the electron displacements become large only at those moments when the reagent molecule which excites them is already committed to ortho- or para-attack.

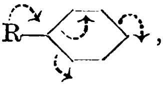
The above interpretation, which is consistent with the following graphical representations,



+ *I* (*op*-)



—*I* (*m*-)



+ *T* (*op*-)

is regarded as partly modifying, and partly giving definition to, the views originally expressed by Ingold and Ingold (*loc. cit.*), and as formulating in a more general way than has hitherto been possible the main principles which underlie the more recent communications from this laboratory on the subject of aromatic substitution. Only benzene substitutions are here dealt with, but the more important applications to naphthalene, quinoline, and certain other simple aromatic systems are sufficiently obvious. It will also be understood that the types discussed grade into one another, and in developing the work we shall investigate ω-halogenated and ω-carboxylated toluenes in order to emphasise this point.

EXPERIMENTAL.

Benzene was purified in the usual way. Toluene was purified by distillation, partial solidification (Ramsay), drying, and re-distillation (b. p. 110·4—110·8°). The other substances mentioned below were purified by distillation or crystallisation.

Toluene (1 mol.) and benzene (1 mol.) were nitrated together in a solution prepared from nitric acid (0·4 mol.) and acetic anhydride, the experiment being otherwise carried out as described by Holleman (*Rec. trav. chim.*, 1914, **33**, 1). Preliminary experiments had shown that for our purpose density determinations made with a moderately large pyknometer provided a more satisfactory method of analysis than measurements of refractive index. Accordingly, pure toluene was nitrated, without benzene, under the conditions indicated, and the mixed mononitro-derivatives were freed from unchanged toluene by distillation until the density remained constant. Mixtures of this product with similarly purified nitrobenzene had the following densities (*d*) at 25°; *p* denotes the percentage of nitrobenzene :

p	0·00	1·89	3·66	5·57	9·64	12·05	21·3	100·0
d	1·1526	1·1529	1·1537	1·1551	1·1566	1·1572	1·1616	1·1985

These points all lie on or close to the straight line represented by the equation $d = 1{\cdot}1526 + 0{\cdot}000459p$. The products of the mixed nitrations were likewise distilled to constant density to remove benzene and toluene, and the densities determined. They were d_{25}. 1·1555(i) and 1·1558(ii), which correspond with 6·3%(i) and 6·9%(ii) of nitrobenzene, that is, with 7·0(i) and 7·6(ii) molecules % of nitrobenzene. The agreement being apparently as good as could be expected from the method, the mean value, 7·3 molecules %, which gives $R_{\text{Me}} = 12{\cdot}7$, was used to calculate from the formula on p. 2921 that $k_y/k_x = 15{\cdot}7$. From this figure, by means of Holleman's data for the proportions of the isomerides (*loc. cit.*), the coefficients given in the introduction are obtained.

The investigation of the halogenobenzenes was carried out similarly with the following differences : (*a*) 1·0 mol. of nitric acid was used for the preparation of the acetyl nitrate solution, (*b*) the temperature of nitration was 45°, (*c*) the method of analysis was suited to the individual case. The product obtained from the experiments with fluorobenzene was distilled to remove unchanged benzene and fluorobenzene, and the remaining binary mixture hydrolysed with boiling sodium hydroxide solution to remove the fluorine as fluoride ion from the nitrofluorobenzenes—a process which is quantitative. The products obtained from chlorobenzene and bromobenzene were distilled to remove benzene, and the remaining ternary mixtures were hydrolysed under conditions known to be appropriate in each case. The liberated halide ions were estimated, and the residual binary mixtures insoluble in alkali submitted to ultimate analysis. By means of these methods, concordant determinations gave the following values : $R_F = 0{\cdot}0107$, $R_{Cl} = 0{\cdot}027$, $R_{Br} = 0{\cdot}36$, whence the figures given in the introduction were calculated. Competitive nitration of benzene and iodobenzene gave iodonitrobenzenes exclusively (R_I large), and anisole behaved similarly.

Since the medium used in the above experiments does not dissolve benzyltrimethylammonium picrate or benzoic acid sufficiently, a mixture of pure acetic acid and sulphuric acid in equimolecular proportion (15 mols. of each) was used as solvent for the nitration of these substances. The temperature was 0°. In each case, the benzene alone was nitrated and the other substance was recovered pure and unaccompanied by any trace of its nitro-derivatives; this was proved by m. p. and mixed m. p., and, for benzoic acid, confirmed by sublimation. In the course of the nitration of benzyltrimethylammonium picrate, picric acid separated from solution, but we do not regard this as invalidating the experiment, since the benzyltrimethylammonium ion remained dissolved.

The nitration of acetanilide was similarly investigated with identical results.

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