

## SOME FACTORS INFLUENCING SUBSTITUTION IN THE BENZENE RING<sup>1</sup>

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The problem of substitution in the benzene ring can be divided into two parts of a very different character, viz., the substitution of H-atoms and the substitution of other atoms or groups. In the first case the prominent question is, which H-atom will be replaced; in the second there exists the same question for the higher substituted benzene derivatives; but the principal thing to determine here is, which atoms or groups can be replaced at all. Up to the present the great bulk of the work has been done in the first part and the name, "substitution in the benzene ring" is usually applied to this part only. So I will restrict myself here to replacement of H-atoms; to treat both cases would take too much space.

A few historical data may be recalled by way of introduction. In 1865 Kékulé suggested his benzene formula; it was already known that a number of di-derivatives of benzene existed in three isomerides; but to determine whether a given di-derivative belonged to the series 1.2; 1.3 or 1.4 seemed to be very difficult. Kékulé himself said about it; "Es ist bei dem jetzigen Stand unserer Kenntniss kaum möglich die Orte an welchen sich die, den Wasserstoff des Benzols ersetzendes Elemente oder Radicale befinden, auch nur mit einiger Sicherheit zu bestimmen" (1). The solution of this problem was found mainly by Körner, Kékulé's pupil and assistant. In 1867 he remarked (2), that a compound  $C_6H_3X_3$  must have the asymmetric structure, when it can be obtained from the three isomerides  $C_6H_4X_2$  by introduction of X. As early as 1869 he published in a little known

<sup>1</sup>An essay prepared in connection with the dedication of the Sterling Chemistry Laboratory.

journal (3) an experimental proof, though somewhat extended, that the six H-atoms of benzene are of equal value, and introduced the names ortho, meta, para. At last, in 1874, there followed his renowned paper in the *Gazzetta Chimica Italiana* (4), in which he published his well known principle for the absolute determination of the substituents for compounds  $C_6H_4X_2$  and applied it to 126 substances which he had discovered and on a great number of others already known, but also synthesized by himself. By this admirable work, a solid basis was laid down for the absolute determination of positions in the benzene ring.

In 1869 Graebe (5) gave an absolute determination of position for the ortho-series, clearing up at the same time the constitution of naphthalene. Ladenburg (6) followed in the same year with an absolute determination for the meta-series by proving the structure of mesitylene; and in the same year he published a paper on the structure of the hydroxybenzoic acid melting at  $210^\circ$ , thus giving a basis for the absolute determination of the para-series. In the following years these studies were completed by Hübner, Griess and many other chemists; and thus within ten years the problem of the absolute determination of positions in the benzene ring, which seemed very difficult to solve in 1866, was made clear in its main features.

From the earlier investigations in this field, and in a still higher degree by the researches of Körner, it had become quite evident, that by the entrance of a new substituent in the benzene nucleus, the possible isomerides were not formed all together and that those really obtained differed considerably in quantity in almost all cases. Many rules were published to bring these facts under a general point of view; among the oldest were those of Hübner (7), Nölting (8) and Körner (4) himself. All three were put forward about the year 1875 and still give a fairly accurate expression of the facts.

Hübner wrote as follows:

In the preparation of the higher substituted benzene derivatives, the entering (negative) substituents take the p-position and with equal

ease the o-position with regard to the substituent already present which has the weakest negative or acid nature.

From this assumption it follows that, an acid (negative) substituent being already present and a second substituent, also of acid nature entering, this latter will avoid the p-position and o-position as much as possible and will occupy principally the meta-position.

Examples: the nitration of toluene yields o-p-compounds, that of benzoic acid the meta-compound.

Nölting gave a somewhat more precise expression of this same idea:

If in the position 1 is present a neutral, basic or weakly acid group, such as  $\text{CH}_3$ , Cl, Br, I,  $\text{NH}_2$  or OH, the action of Cl, Br, I,  $\text{HNO}_3$  and  $\text{H}_2\text{SO}_4$  yields the 1-4-compounds as principal products, as well as varying, but always small quantities of the ortho-compound. But when the position 1 is occupied by an acid group, such as  $\text{NO}_2$ ,  $\text{CO}_2\text{H}$ , or  $\text{SO}_3\text{H}$ , the same reagents cause the formation of 1-3-derivatives, together with small quantities of substances, belonging to the 1, 2 or the 1, 4 series.

Körner expresses himself in about the same terms:

When Cl, Br, I or  $\text{HNO}_3$  act on Cl-, Br- or I-benzene, on aniline, phenol or toluene, there is always formed as principal product a compound of the p-series; at the same time there is formed a compound of the o-series in 14–15 per cent of the cases. If the group already present has an acid nature, being  $\text{CO}_2\text{H}$ ,  $\text{NO}_2$  or  $\text{SO}_3\text{H}$  the action of the same reagents yields a compound of the 1-3 series as principal product, compounds of the 1, 2 series and often also of the 1, 4 series being obtained also.

Though it must be admitted that the authors published these rules independently of each other, there is a remarkable agreement between them. The acid groups direct a new substituent to the m-position, the halogens and the feebly acid (OH) or basic ( $\text{NH}_2$ ) groups to the p-o-positions. This has remained, generally speaking, the opinion of scientists about this question until now.

My attention was drawn to this problem by a research on the nitration of phenylnitromethane (9)  $\text{C}_6\text{H}_5 \cdot \text{CH}_2\text{NO}_2$ . As nitration of the compounds  $\text{C}_6\text{H}_5 \cdot \text{CH}_2\text{X}$ , where X = Cl, CN or

$\text{CO}_2\text{H}$  yields the p-o-derivatives, I expected the same influence for the group  $\text{CH}_2\text{NO}_2$ . The investigation showed on the contrary, that the nitrophenylnitromethane obtained belonged to the m-series; for oxidation produced m-nitrobenzoic acid. It became at once evident that the more or less acid nature of the group already present is very difficult to express in clear terms, and in consequence that the prediction of how a group which is present will direct a new entering group becomes very uncertain.

This state of matters was not improved by the testing of other rules given about orienting power, neither those that were already known, when I carried out this investigation (in 1895), nor those suggested later. Armstrong (10) stated that p-o-substitution takes place when the element already present is univalent, or when the atom of a group linked directly with the nucleus bears only univalent atoms. On the contrary m-substitution takes place when the atom bears polyvalent atoms. Example: Cl or  $\text{CH}_3$  direct a new group to p-o-positions,  $\text{NO}_2$  to the m-position.

Crum-Brown and Gibson (11) gave the following rule: The substituent already present is considered to be linked to hydrogen. If this hydrogen compound can be directly oxidized, the second entering substituent takes up the meta position; in the contrary case, it takes up the p-o-position. Example: HCl cannot be oxidized directly to  $\text{HClO}$ ; hence Cl directs a group to p-o;  $\text{H}-\text{CO}-\text{CH}_3$  can be directly oxidized to  $\text{HO}\cdot\text{CO}\cdot\text{CH}_3$  hence the group  $\text{CH}_3\cdot\text{CO}$ —directs to m.

There is still Vorländer's rule (12) stating that the groups causing m-substitution are unsaturated ( $\text{NO}_2$ , CN, CHO, COOH,  $\text{SO}_3\text{H}$ ) while those causing p-o-substitution are saturated (Cl, Br, OH,  $\text{CH}_3$ ,  $\text{CH}_2\text{OH}$ ,  $\text{CH}_2\cdot\text{CO}_2\text{H}$ ).

That these rules are all more or less inadequate and often in contradiction with each other, may be demonstrated by a few examples.

1. The nitration of phenylacetic acid gives p-o-compounds. According to Hübner-Nölting-Körner, it should yield the m-compound, the group  $\text{CH}_2\cdot\text{CO}_2\text{H}$  being decidedly acid: Armstrong's

rule also predicts *m*-substitution; since  $\text{CH}_3 \cdot \text{CO}_2\text{H}$  is not directly oxidisable to  $\text{HOCH}_2 \cdot \text{CO}_2\text{H}$  Crum-Brown and Gibson's rule predicts *p*-*o*-substitution, as does also Vorländer's rule.

2. The nitration of phenylnitromethane gives principally the *m*-compound. The group  $\text{CH}_2\text{NO}_2$  must be considered, without doubt, as being acid, though not so strong as  $\text{CH}_2 \cdot \text{CO}_2\text{H}$ . Hübner-Nölting and Körner's rules predict therefore *p*-*o*-substitution, Armstrong's rule *m*-; Crum-Brown and Gibson's rule *p*-*o* as also does Vorländer's rule.

3. Bézonnitrile gives on nitration the *m*-compound. The group CN being only weakly acid, Hübner-Nölting-Körner's rules predict substitution in the *p*-*o*-positions; Armstrong's rule in the *m*-position, Crum-Brown and Gibson's rule in *p*-*o*, and Vorländer's rule in the meta-position.

I leave without further mention the theoretical explanations of the substitution phenomena suggested by Flürscheim, Obermiller and Fry, because in my opinion none of them can give a full account of the facts observed; there is too much that is arbitrary in them. It can only be stated, that up to the present time no sufficient explanation can be given.

I tried therefore to penetrate into this field in another way, viz., by the quantitative study of the substitutions. At the beginning of my researches, this way was completely neglected; no methods were known to determine exactly the relative quantities in which the isomerides were formed simultaneously, when a new substituent was introduced, however useful the knowledge of these figures seemed, both from a theoretical and from an industrial standpoint. As will be shown now, this way has indeed led to some progress in this field of investigation.

In order to obtain a systematic review of the factors influencing substitution in the benzene ring, we shall have to consider successively (*a*) the influence of the (one or more) substituents already present; (*b*) the influence of the substituent newly introduced; (*c*) the influence of other factors.

## INFLUENCE OF ONE SUBSTITUENT ALREADY PRESENT

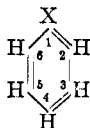
In a great many cases, especially for nitrations, the relative quantity in which the isomers are simultaneously formed are now determined by the methods worked out in my laboratory. This has shown that considerable differences exist, when the same atom or group is introduced into a series of compounds  $C_6H_5X$ . Table 1 will illustrate this point.

Böeseken and I have tried to explain these differences, and also the fact that there is either principally p-o-substitution or m-substitution, by studying the velocity of reaction of the substitution (13). Our starting point was Kekulé's benzene formula. In each compound  $C_6H_5X$ , the substituent X is situated at the

TABLE 1  
*Introduction of a nitrogroup into compounds  $C_6H_5X$*

SUBSTITUENT ALREADY PRESENT, DIRECTING TO p-o	PERCENTAGE OF			SUBSTITUENT ALREADY PRESENT, DIRECTING TO m	PERCENTAGE OF		
	ortho	meta	para		ortho	meta	para
F.....	12.4		87.6	NO <sub>2</sub> .....	6.4	93.2	0.25
Cl.....	30.1		69.9	CO <sub>2</sub> H.....	18.5	80.2	1.3
Br.....	37.6		62.4	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> .....	28.3	68.4	3.3
I.....	41.1		58.7				
CH <sub>3</sub> .....	58.8	4.4	36.8				
CH <sub>2</sub> Cl.....	40.9	4.2	54.9				

end of a conjugated system of double bonds. When a new substituent is introduced, there is first formed an addition product and the

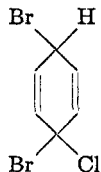


addition can take place, 1st at the double bond 1, 2; 2nd at the ends of the conjugated system 1, 4; 3rd at the double bond 5, 6. We assume X to exert either an accelerating or a retarding influence on the additions at 1, 2 and 1, 4, these bonds being under its direct influence; whereas its influence on the double bond 5, 6, which is not in direct connection with X, is nearly imperceptible.

If there is an accelerating influence, ortho and para-derivatives are mainly formed; if there is a retarding influence the velocity of addition at 5, 6 is greater and meta-derivatives are obtained. Thiele has stated in his researches on the addition at conjugated systems, that besides addition at the ends of the system  $C=C-C=C$ , there is also addition at 1, 2 in varying ratios. Again it will depend on the velocities of reaction at the atoms 1, 4 on the one hand and at 1, 2 on the other hand, as to what will be the principal product of the reaction; and the same can be said about the ratios in which ortho and para compounds will be formed. When the meta-isomer is the principal product, we have to admit concerning the formation of ortho-para products that the retarding influence or X is not great enough to hinder their formation.

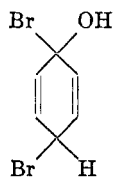
This hypothesis seems to have a considerable advantage over those suggested hitherto, because it avoids all vague suppositions about the nature of the substituents, more or less negative or positive, or about the force with which the atoms are linked to the benzene nucleus (as in the hypothesis of Flürscheim). Instead of these, it operates with the perfectly clear notion of the velocities of the reactions.

Nevertheless, exception has been taken to it on several grounds. van der Linden (14) objected as follows, first citing the action of bromine on chlorobenzene. According to our conception the first stage must be the formation of an addition product of the formula

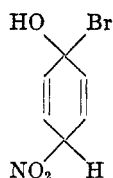


from which in the second stage HBr is eliminated. The elimination of HCl, however, with formation of p-dibromobenzene instead of the p-chlorobromobenzene actually obtained, appears equally probable. Similarly, the bromination of phenol could give

p-dibrombenzene instead of p-bromphenol, should the addition product



assumed to be formed, lose water, instead of HBr; and the nitration of brombenzene could give p-bromnitrobenzene, along with p-nitrophenol



None of these reactions has been observed.

In the second place van der Linden states, that the bromine attacks chlorbenzene much more slowly than benzene itself, though chlorine, as causing ortho-para-substitution, should be an accelerator. Regarding the first objection, there is no doubt as to the theoretical possibility of obtaining the reaction products suggested by van der Linden. This is a type of phenomenon often observed in organic reactions, and no adequate explanation of it is available. Why, for instance, is chlorine in the  $\alpha$ -chlor acids readily replaced by OH under the influence of caustic alkalis, and why does similar treatment eliminate HCl from  $\beta$ -chlor acids? Why is a halogen atom readily replaceable when linked to a singly linked Cl-atom, and not mobile when linked to a C-atom with a double bond? In the existing state of organic chemistry we are not in a position to answer these questions, so that for the present it appears to be idle to combat a theory on the ground of the possibility for reactions to take a course other than that actually followed by them. The only question is whether our representation of the reaction is possible, and as to that, there seems to be no doubt.



As for van der Linden's second objection, it is quite true that bromine attacks monochlorbenzene more slowly than benzene; but this fact has no bearing on the question as to whether chlorine accelerates addition at the conjugated system more than at the double bond 5, 6. So long as under the influence of chlorine addition at the positions 1, 2 and 1, 4 is more rapid than at position 5, 6 the substitution will take place at the ortho-position and the para-position and it is immaterial whether monochlorbenzene is attacked more slowly or more rapidly than benzene. It is only the ratio of the reaction velocities at 1, 2 and 1, 4 on the one hand, and at 5, 6 on the other hand which determines the type of substitution.

I am not at all blind to the weak points of our hypothesis. In the first place it affords no explanation as to why the halogens, hydroxyl, etc., should accelerate addition at the conjugated system and the groups nitro, carboxyl, etc., retard it. A confirmation of it could only be obtained by the actual measurement of the velocities in question; which has so far been impossible, the formation of intermediate addition products being even now hypothetical. Also the transition of these addition products into substitution products must be assumed as being performed with infinite velocity. When therefore Henrich in his well known book entitled "Theorien der organischen Chemie" writes (page 120 of the 2nd edition): "Diese Ansicht ist zurzeit wohl die plausibelste Interpretation der ortho-para und der meta-Substitution" I think, though appreciating his friendly criticism, he would have been nearer the truth if he had characterized our interpretation as less open to objection than any other.

In connection with the introduction of a second substituent into the compounds  $C_6H_5X$  the phenomenon which I have designated the *conservation of the substitution type* must now be considered. The expression signifies that when a given substituent causes substitution principally in the p-o-positions or in the meta-position, the effect of its influence is independent of the nature of the entering group; although for a given substituent there are considerable variations in the proportions in which the isomerides are formed (as we shall have to discuss more fully) the type remains unchanged.

I deduced this rule in my book "Die directe Einführung von Substituenten in den Benzolkern" from the facts known up to 1910. The investigations carried out since that time, in other laboratories as well as in mine, permit a somewhat modified view of this problem. First it may be stated that in very few instances only one of the three possible isomerides is obtained by the introduction of a second group in  $C_6H_5X$ ; it is observed in the sulfonation of the halogenbenzenes, where only the para-compound is formed. No instance is known in which only an ortho-derivative is obtained.

Whether there are cases of pure m-substitution seems doubtful. It is said that the nitration of benzonitrile should produce only the m-compound; the investigations of Beilstein and Kuhlberg (15) and of Schöpff (16) on this question should be repeated,<sup>2</sup> because they were not carried out quantitatively. In all carefully studied cases of m-substitution the formation of ortho- and p-isomerides or both of them has also been proved.

The case of pure p-o-substitution, i.e., without the formation of the m-isomeride even in small quantities, is not so often observed, and it seems certain that further investigations will still diminish their number. Take for example the introduction of a substituent in toluene. The nitration and sulfonation of this compound have been studied quantitatively; para- and ortho-compounds are the principal products, but it has been proved quite certainly that more or less of the m-compounds are obtained also. On the other hand the nitration of the halogenbenzenes seems to be a case of pure p-o-substitution: the eutectic point of mixtures of para-chlornitrobenzene and ortho-chlornitrobenzene, such as is obtained by the nitration of chlorbenzene coincides with that of a mixture of the pure components. But this method of determination is not so sharp as to allow the detection of 0.5 per cent of m-compound with certainty; and by other methods even this figure cannot be reached.

We have therefore to consider pure p-o-substitution, as well as pure m-substitution as limits, and all substitutions so far observed as more or less of a mixed type. These two types are in reality not so sharply differentiated as is generally believed.

<sup>2</sup> This is actually going on in my laboratory.

It is steadily becoming clearer that there is no such marked distinction but that there are transitions between the types. A very good example of this was observed in my laboratory in connection with the nitration of toluene, benzylchloride, benzylidene chloride and benzotrichloride (17). The percentage proportion of the three isomeric nitro derivatives is given, in table 2.

The nitration of toluene and benzyl chloride is of the p-o-type; on the other hand, in the nitration of benzylidene chloride we have a transition, whilst in that of benzotrichloride the type is wholly one of m-substitution.

The possibility of causing such a large variation in the relative quantities of the isomerides as is indicated by this example renders it very evident that gradual changes of the substitution

TABLE 2

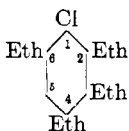
NITRATION OF	PERCENTAGE OF			TEMPERATURE
	ortho	meta	para	
$C_6H_5CH_3$ .....	58.8	4.4	36.8	20-30°
$C_6H_5CH_2Cl$ .....	40.9	4.2	54.9	
$C_6H_5 \cdot CHCl_2$ .....	23.3	33.8	42.9	
$C_6H_5 \cdot CCl_3$ .....	6.8	64.5	28.7	

type will not infrequently be observed in connection with further investigations in this field.

There remains the further problem as to whether the rule of the conservation of the substitution type will hold also for these cases of transition; for instance whether the substitution type as given by the nitration of benzotrichloride also applies to its chlorination and so on. First then it must be stated, when we must consider that the substitution type has changed. Suppose that the group X in  $C_6H_5X$  exercised no directing power. Owing to the fact that there are two ortho places, two meta places, but only one para place, the quantities of the para-o-isomerides and of the m-isomeride formed, should be in the ratio (2+1):2; or there should be obtained 60 per cent o + p-compound and 40 per cent m-compound. It seems therefore logical to admit that

the substitution type is unchanged, as long as there is formed more than 60 per cent of p + o-compounds for the p-o-type and more than 40 per cent of the m-compound for the m-type. According to this, the nitration of benzylidene chloride would still belong to the p-o-type. Defined in this way, the rule of the conservation of the substitution type finds confirmation in nearly all cases so far observed. There are, however, some exceptions stated, that must be discussed here.

In the first place Böeseken has noticed that all the substituents capable of entering directly into the benzene nucleus are of a similar nature, all being electronegative, such as NO<sub>2</sub>, SO<sub>3</sub>H and the halogens. For example, substitution in chlorobenzene always produces p-o-compounds only, a phenomenon due to the electronegative nature of each group or atom entering the molecule. He anticipated therefore that for the entrance of neutral or electropositive groups the rule of the conservation of the substitution type would be inapplicable; in order to prove this, Sieger (18) studied in his laboratory the introduction of ethyl into chlorobenzene by the Friedel-Crafts reaction. He actually found 65 per cent of m-chlor-ethylbenzene, 25 per cent of o-chlor-ethylbenzene and 10 per cent of the corresponding p-compound to be formed. The only question is whether this m-compound is a primary reaction-product or not; and this point has not been decided. The introduction of alkyl into benzene by means of the Friedel-Crafts reaction is a very complicated process, and involves not only synthesis but also a rupture of the molecule. It is therefore quite possible that primarily there is formed a higher substitution product such as



which on the removal of the alkyl groups situated on 2, 4 and 6 under the influence of AlCl<sub>3</sub> gives m-chlor-ethylbenzene. This explanation is quite rational, as an inference from the production of m-xylene from both hexamethylbenzene and pseudocumene

by the action of aluminium chloride. The alkyl groups removed by the action of this agent are consequently situated in the p-position and the o-position. In the example under consideration, the removal of alkyl would appear to be very probable, since the action of aluminium chloride on the mixture of benzene and ethylchloride was continued for three days. The only possible conclusion is, that Sieger's research does not prove the rule of the conservation of the substitution type to be inapplicable to the ethyl group.

Secondly, Böeseken's observation appears to hold for another remarkable type of substitution, viz., the mercuration reactions studied by Dimroth and his pupils. Dimroth discovered the extreme readiness of mercury to replace hydrogen of the benzene nucleus when aromatic compounds are heated with mercuric acetate, and he applied this reaction to nitrobenzene, toluene, benzoic acid, phenol and other compounds. He has stated that from nitrobenzene and from benzoic acid ortho-derivatives are obtained, in contradistinction to the m-compounds produced by nitration, chlorination, and so on. A study of Dimroth's papers gave me the impression, that these reactions must be more complex than he seems to have realised. There was the possibility of his observation of the formation of the o-derivatives being correct, but the action being accompanied by the production of the m-derivatives and the p-derivatives in considerable proportions. A renewed research on the mercuration of nitrobenzene<sup>3</sup> proved this view to be correct. Wibaut and Jürgens heated nitrobenzene with mercuric acetate, and brought the reaction mixture into contact with brine, as prescribed by Dimroth, obtaining by this method compounds of the formula  $C_6H_4 \begin{matrix} NO_2 \\ HgCl \end{matrix}$ . Their separation proved to be very difficult, and his directions quite inadequate. Without separating them Wibaut and Jürgens treated the compounds with bromine. Mercury was replaced by bromine, forming a mixture of monobrom-nitrobenzenes, and the ratio of the three isomerides was determined by thermal analyses. They found 49 per cent of the o-compound present, 42 per cent of the

<sup>3</sup> Carried out in my laboratory by Wibaut and Jürgens; not yet published.

m-compound and 9 per cent of p-bromnitrobenzene. The nitro-group exercises its m-directive influence in considerable degree, even in this reaction; according to what has been said on a preceding page the substitution type is still meta.

The last exception from the above mentioned rule that I shall cite is an absolutely forgotten fact, observed by Barth and von Schreder (19). It is the formation of resorcinol, phloroglucinol and pyrocatechol by fusion of phenol with six times its quantity of sodium hydroxide. The hydroxyl group, orienting in all other known cases to p-o-positions, directs a second and third hydroxyl group to the m-place under the circumstances of this experiment. It seems possible that at the high temperature of this reaction the substitution takes place in another direction than at ordinary temperature; very little is known about this point. Another possibility seems to be that pyrocatechol is the primary product this being rearranged to resorcinol by the action of the molten sodium hydroxide, a reaction that has many analogues.

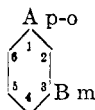
#### INFLUENCE OF TWO OR MORE SUBSTITUENTS ALREADY PRESENT

Beilstein (20) had focussed the almost general opinion about this subject as follows: "If a substituent C enters into a compound  $C_6H_4AB$ , both A and B exert an influence, but the group (A or B) whose influence predominates directs C to the place it will occupy."

Accepting the results of the research on the positions occupied by second substituents introduced into  $C_6H_5X$ , and on the quantitative determinations of the isomers simultaneously formed, I tried to predict the position occupied by a third substituent C after entry into  $C_6H_4AB$  in a clearer manner along the following lines: Given the position taken up by C when introduced into  $C_6H_5A$  and  $C_6H_5B$ , given also the ratio, in which the isomers  $C_6H_4AC$  and  $C_6H_4BC$  are formed; is it possible to deduce from these data the position taken up by C introduced into  $C_6H_4AB$ , and the ratio in which the isomerides are eventually formed? A positive answer on this question could be obtained, if the influence of both groups already present could be defined more

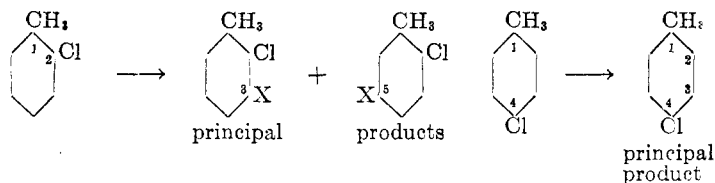
definitely than in Beilstein's rule. The velocity of the substitution caused by the influence of A and B must be the decisive factor. For suppose we have A causing a substitution  $n$ -times ( $n > 1$ ) faster than B, then the H atoms being under the influence of A will be replaced  $n$ -times faster than those under the influence of B and the compounds  $C_6H_3ABC$ , in which C is directed by A, will be the principal products of the introduction of C into  $C_6H_4AB$ . These velocities, however, cannot be measured directly; but it is possible to deduce the series of diminishing velocities.

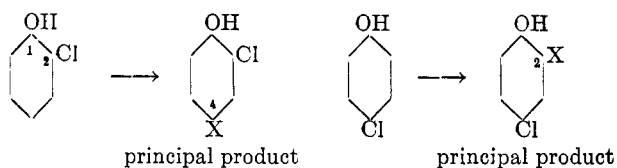
In the first place it can be shown that substitution at  $m$ -positions must be much slower than at  $p$ - $o$ -positions by considering the compounds of the type



in which A directs a new substituent to the positions 2, 4 and 6 and B to the position 5, an example being  $m$ -chlorbenzoic acid ( $A = Cl$ ,  $B = CO_2H$ ). With such a compound substitution at both  $p$ - $o$ -positions and at  $m$ -position 5 (3 being occupied) would be anticipated, but in all compounds of this type, new substituents avoid the  $m$ -position; and only compounds with the new substituent at the positions 2, 4 or 6 are obtained. The best explanation of this phenomenon is, that substitution at  $p$ - $o$ -positions is very much more rapid than at  $m$ -positions.

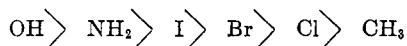
The series of substitution-velocities for the substituents directing to  $p$ - $o$ -positions on the one hand, and to  $m$ -positions on the other, can be deduced from the facts in the following way: Take for instance  $o$ -chlortoluene and  $p$ -chlortoluene, or ortho-chlorophenol and  $p$ -chlorophenol:



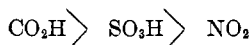


Cl, CH<sub>3</sub> and OH direct a new substituent to p-o-positions. Now we observe that in both chlortoluenes a new substituent enters principally in p-o-positions relative to chlorine, and that the compounds in which X is p-o- with respect to CH<sub>3</sub> are obtained in smaller proportion. We conclude, therefore, that Cl has a greater directive force than CH<sub>3</sub>, or in other words that Cl causes a greater velocity of substitution than CH<sub>3</sub>, though the difference cannot be very great.

In contrast with this effect, when a third substituent is introduced into the chlorphenols, we find that compounds with the new substituent in the positions p- or o- relative to OH are exclusively obtained. The conclusion is that OH induces a much greater velocity of substitution than Cl. A systematic search of the literature of all the known cases of introduction of a third substituent into compounds of the type C<sub>6</sub>H<sub>4</sub>XY reveals the series of diminishing velocities

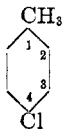


for the p-o directing substituents and



for the m-directing substituents.

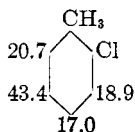
For the prediction of the position entered by a third substituent, the knowledge of the quantitative ratio in which the isomerides are formed, when X is introduced into C<sub>6</sub>H<sub>5</sub>A and into C<sub>6</sub>H<sub>5</sub>R is still wanted, besides a knowledge of these series, as can be illustrated by an example. Suppose it is desired to predict the position in which the substituent will enter on sulphonation of p-chlortoluene



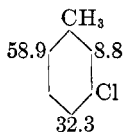


Since Cl induces a greater velocity than  $\text{CH}_3$ , the main portion of the yield would be expected at first sight to be the 3-sulphonic acid, the 2-isomer being a by-product. But the sulfonation of chlorbenzene gives exclusively the p-compound, whereas that of toluene yields a large proportion of the o-compound. It is, therefore, to be anticipated that the acid with the sulfo-group at position 2 will be the principal product, a view in accordance with the observations of Wynne and Bruce.

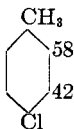
The desire for a clearer insight into the laws of substitution made imperative a quantitative knowledge of the velocities of substitution, caused by the groups already present, one of them being put arbitrarily = 1, because their absolute values cannot be determined as yet. Wibaut (21) accordingly undertook an investigation of the nitration products of the chlortoluenes. By determining the relative proportions of the isomeric nitrochlortoluenes formed, it would be possible to calculate the ratio of the velocity of substitution induced by  $\text{CH}_3$  and that induced by Cl in the chlortoluenes. He found that in the nitration of o-chlortoluene all four possible isomerides are formed in the ratio given by the scheme



that in the nitration of m-chlortoluene three of the four possible isomerides are formed in the ratio



and that the nitration of para-chlortoluene corresponds with the scheme



From these figures he calculated that the velocity of substitution caused by  $\text{CH}_3$  and by  $\text{Cl}$  is in the ratio 1:1.475.

At this point it became of interest to ascertain the ratio of the velocities when chlorine only and  $\text{CH}_3$  only, were present. In other words the relative velocity of the nitration of chlorbenzene and of toluene. With this end in view, Wibaut (22) prepared a mixture of equivalent quantities of chlorbenzene and toluene and introduced into this mixture a small quantity of concentrated nitric acid. Under these conditions the quantity of nitrotoluenes and of chlornitrobenzenes formed must be in the same proportion as the velocities of nitration of these two compounds.

Though the different determinations showed not unimportant discrepancies, it was evident that toluene nitrated much more rapidly than chlorbenzene, just the reverse of what had been expected. This result was corroborated further by the nitration of chlorbenzene and of toluene separately in acetic anhydride solution. It follows that the velocity ratios induced by the simultaneous presence of two substituents in the benzene nucleus are wholly different from those induced by the substituents separately. Despite this fact the proportion in which the isomerides are formed must remain about the same; since otherwise it would be impossible to predict from the proportion of the isomerides  $\text{C}_6\text{H}_4\text{AC}$  and  $\text{C}_6\text{H}_4\text{BC}$  formed by introduction of  $\text{C}$  into  $\text{C}_6\text{H}_5\text{A}$  and into  $\text{C}_6\text{H}_5\text{B}$ , the ratio of the isomerides produced by the introduction of  $\text{C}$  into  $\text{C}_6\text{H}_4\text{AB}$ .

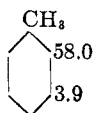
The nitration of p-bromtoluene affords another example of this possibility of prediction. To ascertain, approximately, the proportion in which the two isomeric nitro-p-bromtoluenes are formed, it is necessary to know:

1. The proportion of the nitrotoluenes obtained by the nitration of toluene (23).
2. Similar data for the bromnitrobenzenes (24).
3. The ratio of the velocities of substitution induced by bromine and methyl.

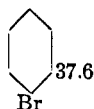
This last value was not determined directly but was derived from the ratios  $\text{CH}_3:\text{Cl}=1:1.475$  (25) and  $\text{Cl}:\text{Br}=1:0.88$  (26).

We have therefore:  $\frac{\text{Cl}}{\text{CH}_3} \times \frac{\text{Br}}{\text{Cl}} = 1.475 \times 0.88$  or  $\text{Br}:\text{CH}_3=1.3:1$ .

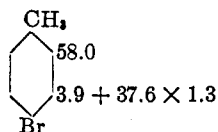
In the nitration of toluene the following percentages



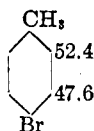
of o- and m-nitrotoluene are obtained; and in that of brombenzene the percentage



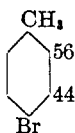
of the ortho-compound, so that, according to calculation the nitration of p-bromtoluene should yield



or in per cent



Actually



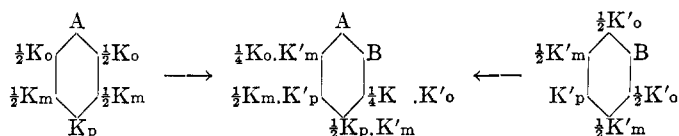
was obtained. I should fail to give a correct view of this matter if I omitted to mention that the agreement between calculation and experiment is sometimes less satisfactory. This defect may be partly due to the difficulty inseparable from these quantitative determinations, but in my opinion there are two principal causes:

1. Obviously the presence of two substituents in the same nucleus may sometimes exert a disturbing influence.

2. The reliability of the method of calculation has not been fully demonstrated.

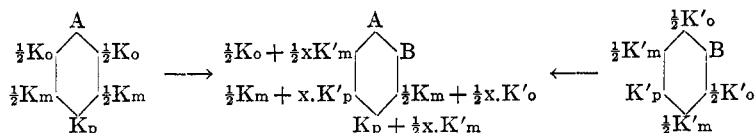
As to this point it may be observed that two methods of calculation have been proposed:

*a.* The influence of the two substituents already present on the H-atoms of the benzene nucleus is proportional to the product of the influence of the two groups separately. When the ratio in which the isomerides are formed by the introduction of X into  $C_6H_5A$  is indicated by  $K_o:K_m:K_p$  and by the introduction of X into  $C_6H_5B$  by  $K'_o:K'_m:K'_p$  this method of calculation (called the "product rule") is expressed by the scheme:



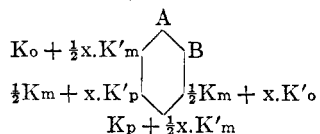
This is in accordance with the influence of substituents on the dissociation constants of aromatic acids. This constant of benzoic acid is, e.g., magnified  $a$  times by the introduction of a chlorine atom; and  $b$  times by that of a nitro group; now the dissociation constant of chloronitrobenzoic acid is about  $a \times b$  times as great as that of benzoic acid.

*b.* The product is not taken, but the sum, according to the conception of "directing forces;" and the coöperation of two forces in the same direction is expressed by their sum. As the directing forces of two substituents will be in general unequal, one being,  $x$  times greater than the other, the figures for the ratio in which the substituents are formed, must still be multiplied by this factor. One obtains therefore the scheme



In this method of calculation, it is still questionable whether the figures must be halved when one of the places ortho or para is already occupied, since it seems possible that the directing force

is then concentrated on the free place. The scheme would be in the latter case as follows:



No decision between these two methods of calculation has been possible as yet. The only thing that can be said so far as the figures are now available, is that in the cases in which the two substituents already present direct a new group to the same place the "product rule" agrees nearer with the experiment than the "sum rule;" and that the contrary occurs when the substituents already present endeavour to bring a new group to different places.

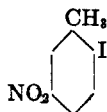
Summing up, it may be said that the quantitative aspect of substitution is a problem far from solution, but that much greater progress has been obtained from the qualitative standpoint. In my book "Die directe Einführung von Substituenten in den Benzolkern" I have shown that in 342 examples of the introduction of a third group into  $C_6H_4AB$  there are only a few instances of discrepancy between the position actually entered by the third group and that predicted theoretically, either by the product rule or the sum rule, since both give the same result as to predicting which isomeride will be the principal product and which others the by-products.

I stated also that a critical study of these exceptions had revealed the probability that most of them would disappear as a result of further research. I shall indicate how this probability has developed into certainty for some examples submitted to closer investigation.

1. In the literature it is stated that bromination of o-iodtoluene gives

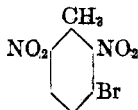


and that nitration yields



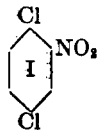
The position occupied by the nitrogroup in this compound has been shown by an investigation of Reverdin (27); that entered by the bromine is only assumed from analogy (28). According to Reverdin's result  $I > CH_3$ ; but then bromine also should enter the p-position with respect to I. The position of the bromine atom could be determined by reduction of the nitro-o-iodtoluene, and diazotization of the iodtoluidine thus obtained. If the reaction is not exceptional, the brom-iodtoluene produced must be identical with the compound obtained by direct bromination of iodtoluene.

The investigation (29) was not so simple as we expected, because neither the nitration nor the bromination of iodtoluene proceeded smoothly. In addition, the iodtoluidine proved to be a substance of low stability, resinifying in contact with air; and its diazotization also involved difficulties. On the other hand, the direct bromination of o-iodtoluene yielded a complex mixture, the principal product of which had to be isolated by fractional distillation. The fact that the two samples of brom-o-iodtoluene were liquid introduced an additional difficulty in connection with their identification, although it could be overcome by the aid of nitration, both specimens undergoing elimination of I and yielding

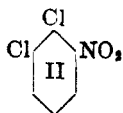


identical with the nitration product of m-bromtoluene.

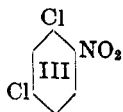
2. A second exception mentioned in the literature is the chlorination of o-chlornitrobenzene (30). It is stated that not only the isomerides



and



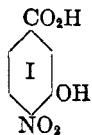
are formed, but that



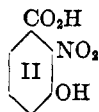
is also produced, even in a greater proportion than the other two.

The formation of I and II accords with anticipations, Cl directing a new substituent to p-o-positions and NO<sub>2</sub> to the m-position, but the formation of III would be quite contrary to expectation. On repeating this investigation (31), we did actually obtain a dichloronitrobenzene melting at 31°, this temperature being the melting point of III. The substance however proved to be the eutectic mixture of I and II, which by a coincidence melts at this same temperature.

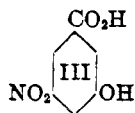
3. The last example I shall mention is the nitration of m-hydroxybenzoic acid. Long ago Griess studied this reaction and gave as the products:



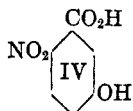
and



but also



The formation of III does not accord with the substitution rules because the directing power of OH to p-o is very much greater than that of CO<sub>2</sub>H to m. On repeating this research in my laboratory (32), we also obtained acids I and II, and in addition two others, the acid



and some dinitrobenzoic acid. Griess had also obtained dinitrobenzoic acid but had mistaken it for acid I. The acid deemed by him to have structure III was in reality acid IV. In the account given by Griess there is much confusion, but on disentangling the threads of his work the apparent exception disappears.

TABLE 3  
*Nitration in sulfuric acid solution (33)*

SUBSTANCE	PERCENTAGES OF		
	ortho	meta	para
Aniline.....	2.1	46.6	51.3
Formanilide.....	3.0	0.8	96.2
Acetanilide.....	4.5		95.5
Benzanilide.....		2.9	97.1

I anticipate that further investigation will lead to a similar elimination of the small number of other exceptions still indicated in the literature. We may therefore conclude, that by the aid of the above mentioned series of diminishing velocity of substitution, and by that of the percentage ratios found for the isomerides simultaneously formed by the introduction of a second substituent into C<sub>6</sub>H<sub>5</sub>X, it is possible to predict with sufficient accuracy the particular isomerides which will be produced by the introduction of a third group into C<sub>6</sub>H<sub>4</sub>AB.

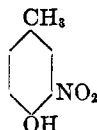
In table 1 (see page 192) we have shown, that every substituent already present brings with it its own figures for the percentages of di-derivatives formed by the introduction of a second group or atom. Some investigations are available to demonstrate that even *slight variations of the group present* may often



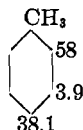
cause a very marked difference in these figures. We have always seen in that table a marked difference of influence between the groups  $-\text{CO}_2\text{H}-$  and  $-\text{CO}_2\text{C}_2\text{H}_5$ . But it is much more pronounced for derivatives of aniline.

The character of the nitration product is wholly changed by the acylation of the  $\text{NH}_2$  group, the m-isomeride being almost completely lacking in it.

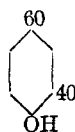
A very interesting case presents itself in the nitration of p-cresol (34) on the one hand and of its carbonate on the other. According to the investigations of Staedel (35), Frische (36) and others the nitration of p-cresol yields exclusively



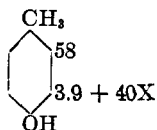
besides some dinitroproduct. As the yields of mononitroproducts from toluene and from phenol<sup>4</sup> are given by the figures



and



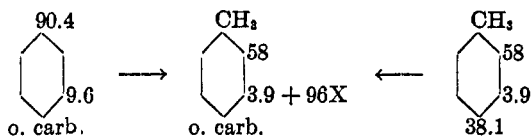
the calculation gives



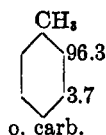
it is evident that only a large figure for X explains the result of the nitration of p-cresol.

<sup>4</sup> According to *Gattermann*, *Die Praxis des org. Chemikers* 10th ed., p. 277, 50 gr. phenol yield 30 gr. o-nitrophenol = 40 per cent of the theoretical value. I suppose that the other 60 per cent is p-nitrophenol. These figures are only a rough estimation.

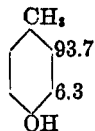
On the other hand the nitration of phenolcarbonate yielded only 9.6 per cent of the 2-nitrocompound ( $\text{OH} = 1$ ). We have therefore the following calculation for the amount of nitrocompounds obtained in the nitration of p-cresyl carbonate:



the investigation giving



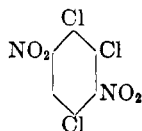
Calculation coincides in this case approximately with the facts, only when  $X = \text{O}$ , for then we have  $\left(\frac{58}{3.9}\right)$  being equal to  $\frac{93.7}{6.3}$



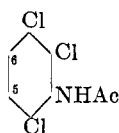
The transformation of p-cresol into its carbonate therefore causes  $X$  to pass from very large to zero, i.e., the directive force of  $\text{OH}$ , which is very large in comparison with that of  $\text{CH}_3$ , is completely annihilated by its esterification with carbonic acid.

With respect to *types of higher substitution*, such as the introduction of a fourth substituent into  $\text{C}_6\text{H}_3\text{ABC}$  or a fifth into  $\text{C}_6\text{H}_2\text{ABCD}$ , little systematic work has been accomplished hitherto. In perusing the literature, I gained the impression that usually the isomerides formed are in accordance with the rules previously cited; but in my laboratory three very striking facts have been observed, indicative of the large amount of work still to be done in this wide field of research. They are the following:

1. In a research on the trichlorodinitrobenzenes, Hüffer (37) required the isomeride

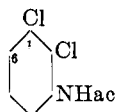


and tried to obtain it in the following way. He expected that in the nitration of

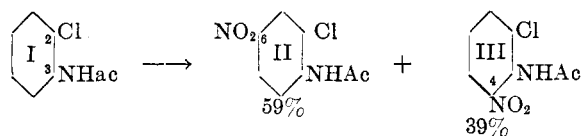


the nitrogroup would enter position 6, because the directing power of NHAc is generally much greater than that of chlorine. This anticipation was not fulfilled, for the nitration product had the nitrogroup at 5, as could be proved by the elimination of NHAc. The chlorine atoms at 2 and 4 exert an influence on position 5 and therefore their resulting directing power must be regarded as being stronger than the directing power of the group NHAc, although the type of the substitution is modified.

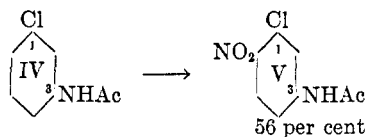
2. A more striking example is afforded by the nitration (38) of



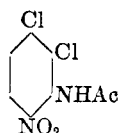
In this reaction there seemed to be every reason to expect



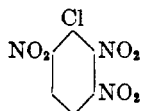
the nitrogroup to enter position 6, for the nitration of I yields 59 per cent of II and only 39 per cent of III. On the other hand the nitration of IV



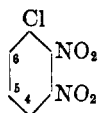
yields 56 per cent of V (39). It was found, however, that the nitration of the dichloracetanilide previously mentioned gave almost exclusively



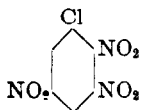
3. The third example is even more perplexing.<sup>5</sup> I required the chlortrinitrobenzene of the formula



and tried to obtain it by the nitration of

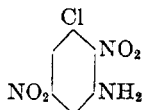


I expected the formation of two isomerides, the third nitro group entering one molecule at 4, and the other at 6 under the influence of the Cl atom. The 4-isomeride was actually obtained; but instead of producing the 6-isomeride, the nitrogroup entered the position 5 quite unexpectedly, for this position is meta to chlorine and para to NO<sub>2</sub>. The structure

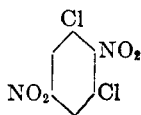


<sup>5</sup> Not yet published.

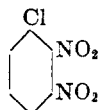
was proved by treating the compound with alcoholic ammonia. The product was a known substance



melting at 57°. On replacement of  $\text{NH}_2$  by chlorine it also yielded a known compound namely the dichlorodinitrobenzene with the formula



It must however be observed, that in the nitration of



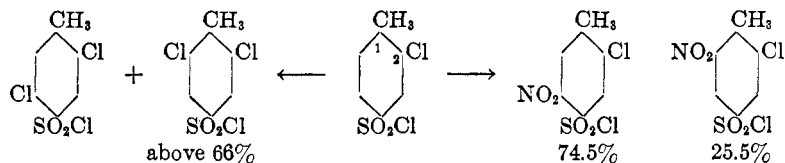
besides the two isomerides just mentioned, a considerable quantity of an oily substance is formed, having the composition of a trinitrochlorbenzene. It is very probable that this oil contains the isomeride sought for, though I have not yet succeeded in isolating it.

We have still to consider the *rule of the conservation* of the *substitution type* in the case where *two or more substituents are already present*.

Its validity can then only be judged if the ratio in which the isomerides are formed by the introduction of a second group into  $\text{C}_6\text{H}_5\text{X}$  and into  $\text{C}_6\text{H}_5\text{Y}$  are known for the case of two substituents already present.

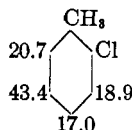
In the case of the presence of more than two substituents, the application of the rule becomes more and more difficult, though it seems that a solution may be effected in manner similar to that given for di-substituted benzene derivatives. In the light of what has been observed above, the exceptions stated, may perhaps disappear. For instance, Davies (40) found that

in the nitration and in the chlorination of 2-chloro-*p*-toluene sulfonylchloride the nitro group and the chlorine atom do not enter the same place in the principal products:



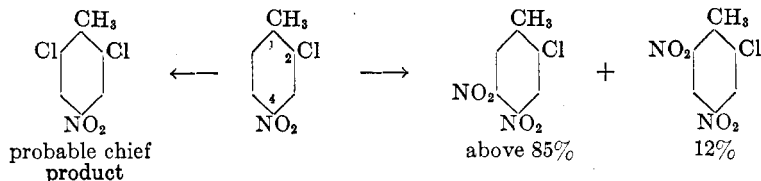
The *m*-directing groups causing generally a slower substitution than the *p*-*o* directing substituents, it is to be expected that the substitution in this compound should be the same as in *o*-chlorotoluene; for the nitration of benzene sulfonic acid also yields much *o*-compound.

Wibaut (41) showed, that in the nitration of *o*-chlorotoluene, the isomerides are formed in the ratio



The nitration of 2-chloro-*p*-toluene sulfonylchloride corresponds therefore to the expectation; but not so the chlorination. It must however be borne in mind that nothing is known either concerning the directive power of the  $\text{SO}_2\text{Cl}$  group or the chlorination of benzene sulfonylchloride. If this should yield almost exclusively the *m*-derivative, the result of the chlorination of the chlorotoluene sulfonylchloride would be more comprehensible.

A second exception, also mentioned by Davies (42), occurs in the chlorination and the nitration of 2-chloro-4-nitrotoluene:



For the same reason as above, it would be expected that chlorine would also occupy place 5.

It seems to me however, that Davies did not succeed completely in proving that the dichloronitrotoluene mentioned is really the principal product of the chlorination. For the chlorination with the calculated quantity of chlorine yielded a complex mixture containing some unchanged 2-chlor-4-nitrotoluene and therefore of course also higher chlorinated products. From this mixture 2-chlor-4-nitrotoluene crystallised in an amount of 30 per cent of the theory. Now it is quite possible that the remaining oil, being the principal product of the reaction, consists principally of 2, 5-dichlor-4-nitrotoluene. This could be easily proved by reduction of the nitrogroup and elimination of  $\text{NH}_2$ , all the dichlor-toluenes being known.

#### INFLUENCE OF THE ENTERING GROUP

The substituents already present determine the type of the substitution; but the positions, occupied by the new entering substituent within the type can vary between large limits. Tables 4 to 8 give a review of some quantitative determinations, made so far on the introduction of a second substituent in  $\text{C}_6\text{H}_5\text{X}$ . The figures in these tables were not always obtained (and could not be so) under strictly comparable conditions, the sulfonations, e.g., requiring usually a high temperature, the nitrations on the contrary a low one. Nevertheless the differences are so marked that it can hardly be supposed, that they are caused only by differences in the mode of investigation. It may be observed, that it is very difficult in this kind of investigation to decide what must be understood by "comparable circumstances". Take for example the temperature; must the reactions be compared at the same temperature or at temperatures of the boiling points, or at temperatures representing the same fraction of the absolute critical temperature? Let us suppose that we decide to work at the same temperature; now the halogens often require a catalyst for their introduction in the benzene nucleus, whereas for the introduction of the nitro group no catalyst is necessary. Are the results obtained in both cases comparable, and which catalyst must be considered? It is evident that these questions and many others of the same kind are by no means solved.

TABLE 4

*Introduction of a second substituent into chlorbenzene*

SUBSTITUENT INTRODUCED	PERCENTAGE OF			
	ortho	meta	para	
Cl.....	39.0	6.0	55.0	} Fe catalyst
Br.....	11.2	1.6	87.2	
NO <sub>2</sub> .....	30.1		69.9	
SO <sub>3</sub> H.....			100.0	

TABLE 5

*Introduction of a second substituent into brombenzene*

SUBSTITUENT INTRODUCED	PERCENTAGE OF			
	ortho	meta	para	
Cl.....	41.5	6.0	52.5	} Fe catalyst
Br.....	13.1	1.8	85.1	
NO <sub>2</sub> .....	37.6		62.4	
SO <sub>3</sub> H.....			100.0	

TABLE 6

*Introduction of a second substituent into toluene*

SUBSTITUENT INTRODUCED	PERCENTAGE OF		
	ortho	meta	para
Br.....	39.7		60.3
NO <sub>2</sub> .....	56.0	3.1	40.9
SO <sub>3</sub> H.....	31.9	6.1	62.0

TABLE 7

*Introduction of a second substituent into phenol*

SUBSTITUENT INTRODUCED	PERCENTAGE OF		
	ortho	meta	para
Cl.....	49.8		50.2
Br.....	9.8		90.2
NO <sub>2</sub> .....	40.0 <sup>4</sup>		60.0 <sup>4</sup>



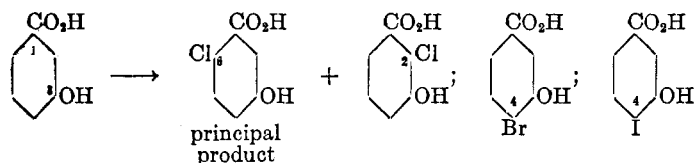
But to return to the tables, no adequate explanation can be given as yet of the large difference in the figures. These are very striking for the halogens Cl and Br, so nearly related to one another, the entrance of Br causing in all cases the formation of much less ortho compound and much more para compound than that of chlorine. One would be inclined to assume here a stereochemical influence, the larger bromine atom being unable to substitute a H atom so easily in the ortho position, in the neighbourhood of the substituent already present. This suggestion finds some support when the figures for the introduction of the nitro group (mass 46) and the sulfo group (mass 81) are considered. Here also the lighter groups gives the higher figures for the ortho compounds, and even the same is true by comparing the halogens with the nitro group and the sulfo group.

TABLE 8  
*Introduction of a second substituent into benzoic acid*

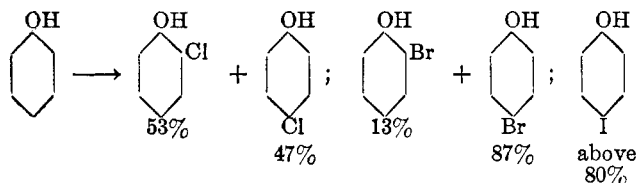
SUBSTITUENT INTRODUCED	PERCENTAGE OF		
	ortho	meta	para
NO <sub>2</sub> .....	18.5	80.2	1.3
SO <sub>3</sub> H.....		93.0	7.0

The latter always produces the lower percentage of ortho compound.

Of course, the great influence of the entering group on the positions it will occupy is present also in the introduction of a new substituent into the higher substituted benzene derivatives. No quantitative data are available but a perusal of the literature shows at once that the principal products, obtained by the introduction of halogens, the nitro group, the sulfo group, etc. do not have these substituents in the same position. I will give only one example, recently investigated by my pupil Beyer (43). He studied the introduction of the three halogens Cl, Br, and I into *m*-hydroxybenzoic acid. The directing force of CO<sub>2</sub>H being much smaller than that of OH, it is to be expected that the isomerides with the halogens on 2, 4 or 6 will be formed exclusively.



This was indeed the case; but the chlorination yielded the two acids  $\text{CO}_2\text{H}$ ,  $\text{OH}$ ,  $\text{Cl} = 1, 3, 6$  and  $1, 3, 2$  while the bromination and the iodination gave only the acids with halogen at 4. This result is surprising when it is compared with the ratio in which the chlorphenols and the bromphenols are formed by the introduction of chlorine and bromine in phenol (44) (the introduction of chlorine cannot yet be executed in such a way that only mono-iodine compounds are formed).



Regarding these figures, the formation of the two chlor-*m*-hydroxybenzoic acids is comprehensible. But in the bromination and iodination of *m*-hydroxybenzoic acid, the almost exclusive formation of the acids with the halogen on 6 would be expected, because the introduction of these halogens into phenol yields practically only the *p*-compounds. Again the idea suggest itself, that the mass of the halogens plays a rôle here, the large bromine and iodine atom not being able to occupy a place next the carboxyl group, notwithstanding the directive power of  $\text{OH}$ , but finding a place near the much lighter hydroxyl group.

#### OTHER INFLUENCES

Besides the influence of the groups already present and of those entering the molecule, which are the dominating factors in the orientation of new substituents, there are still some others. They are not able in most cases to change the type of the substitution, but they can often modify in a considerable degree the ratio in which the isomerides are formed.

### 1. Temperature

The influence of temperature is shown in tables 9 to 11. In most cases hitherto studied, an elevation of the temperature of reaction in introducing a second substituent into  $C_6H_5X$  causes an increase of the ortho- (and meta-) compounds in the substitution type p-o, and of the isomerides ortho and para, when the type is meta. For the nitrations the change in the ratio of the isomerides is in most cases only small. In the nitration of toluene (45) the temperature could be varied even between  $-30^\circ$  and  $+60^\circ$ , being a difference of  $90^\circ$ ; yet the ratio of the isomerides was only little changed.

Also the bromination of toluene gives only a slight change in the ratio p:o (apart from the benzylbromide formed), when the temperature varies  $50^\circ$ . At  $25^\circ$  39.7 per cent of ortho-bromtoluene is obtained; at  $75^\circ$  the percentage is 45.3. In the bromination of phenol a very considerable change of temperature can be applied (see table 12) and here the variation of the ratio p:o is much greater. It is interesting to see that on the contrary this ratio is nearly insensible to change of temperature in the chlorination of phenol, as table 13 shows.

The variation in the ratio of the isomerides can be very large in sulfonations; the classic example of this is the sulfonation of naphthalene, yielding at  $80^\circ$  the  $\alpha$ -acid in a quantity of 96.4 per cent and at  $160^\circ$  the  $\beta$ -acid up to 81.7 per cent (46). This same phenomenon is also observed with benzene derivatives. In the sulfonation of benzene-monosulfonic acid with sulfuric acid of 98 per cent, Polak obtained at  $183^\circ$  14.6 per cent benzene-p-disulfonic acid and 85.4 per cent of the m-isomeride, while at  $233^\circ$  the figures were 25 per cent and 75 per cent. The temperature causes a considerable change in the ratio, especially in the sulfonation of toluene, as may be seen in table 14 (47).

The increase of the by-product m-toluene sulfonic acid to four times the quantity is of particular interest in this case.

These large variations could possibly be due to the transformation of the isomers into each other, as is well known in the case of isomeric sulfonic acids, e.g., in the case of the p- and

TABLE 9

PERCENTAGE FORMED OF	NITRATION OF					TEMPERATURE*
	$C_6H_5Cl$	$C_6H_5Br$	$C_6H_6$	$C_6H_5\cdot CO_2H$	$C_6H_5\cdot CO_2C_2H_5$	
ortho.....	30.1	37.9	41.1	18.5	28.3	} °C
meta.....				80.2	68.4	
para.....	69.9	62.1	58.9	1.3	3.3	} 0°
ortho.....	26.9	34.4	39.1	14.4	25.5	
meta.....				85.0	73.2	} -30°
para.....	73.1	65.6	60.9	0.6	1.3	

\*For  $C_6H_5\cdot CO_2\cdot C_2H_5$  temperature =  $-40^\circ$ .

TABLE 10  
*Sulfonation of toluene*

PERCENTAGE FORMED OF	TEMPERATURE OF SULFONATION			
	0°	35°	75°	100°
ortho.....	42.7	31.9	20.0	13.3
meta.....	3.8	6.1	7.9	8.0
para.....	53.5	62.0	72.1	78.7

TABLE 11  
*Bromination of phenol*

	TEMPERATURE					
	-30°	60°	90°	131°	153°	180°
Percentage of p-bromphenol.....	97.0	90.2	90.7	81.6	79.4	77.0

TABLE 12  
*Nitration of toluene*

PERCENTAGE FORMED OF	TEMPERATURE OF REACTION			
	-30°	0°	+30°	60°
ortho.....	57.2	58.0	58.8	59.6
meta.....	3.5	3.9	4.4	5.1
para.....	39.3	38.1	36.8	35.3

o-phenolsulfonic acids. We therefore carried out an investigation on this point (48). The question was to determine if there is formed primarily only one toluene sulfonic acid, which is transformed afterwards into its isomerides. The research showed undoubtedly that this is not the case. First the m-acid under-

TABLE 13  
*Chlorination of phenol*

PERCENTAGE FORMED OF	TEMPERATURE		
	40°	90°	155°
para.....	47.3	50.2	48.8
ortho.....	52.7	49.8	51.2

TABLE 14  
*Sulfonation of toluene*

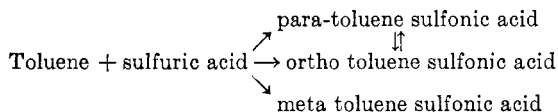
TEMPERATURE	CONCENTRATION OF THE ACID	C <sub>7</sub> H <sub>8</sub> :ACID	PERCENTAGE OF ISOMERIDES		
			ortho	meta	para
°C	per cent	grams			
0	96	1:6	45.2	2.5	52.3
35	96	1:6	33.3	5.3	61.4
75	96	1:6.4	20.2	7.0	72.8
100	96	1:6	17.4	10.1	72.5

TABLE 15  
*Transition of the p- and o- toluene sulfonic acid into each other*

TEMPERATURE	RATIO IN MOLES			RATIO OF THE ISOMERIDES		HOURS	STARTING ACID
	Sulfonic acid	H <sub>2</sub> SO <sub>4</sub>	H <sub>2</sub> O	para	ortho		
°C							
100	1	36.6	8.1	61.8	39.2	1½	p-toluene sulfonic acid
100	1	36.6	8.1	63.2	36.8	4	o-toluene sulfonic acid

went no change when heated with sulfuric acid at 100°. But the p- and o-acids might be transformed into each other by this same method. However, even at 75° this process was very slow. Only at 100° and with a large excess of sulfuric acid were both transformations considerable giving about the same state of equilibrium.

No meta-acid was formed in these transformations. As considerable quantities of both ortho- and para-acid are already formed at 0° and at 35° and the transformation of these acids into each other at these temperatures is extremely slow, if any takes place at all, it is evident that they must be formed directly from toluene, along with m-toluene-sulfonic acid. The sulfonation of toluene must therefore be represented by the following scheme:



the vertical arrows concerning only temperatures of 75° and higher.

The question might still be: is toluene the intermediate product in the transformation of the p- and o-acids into each other, so that the reaction must be represented by the scheme p-acid  $\rightleftharpoons$  toluene  $\rightleftharpoons$  o-acid? This is excluded by the fact that in the transformation of both acids into each other no meta-acid is formed.

### *2. Influence of the medium*

The investigations of Menshutkin have proved that the reaction velocity depends in a high degree on the solvent in which the process goes on. The introduction of a second substituent into  $C_6H_5X$  can give rise to three simultaneous reactions, viz., the formation of the compounds ortho, meta, and para. These reactions often have very different velocities resulting in the formation of these isomerides in very different quantities. It seemed probable that the velocity of the three reactions would not be modified in the same degree by the solvent and that therefore the ratio in which the isomerides are formed would change with the solvent. An investigation on this point was made in the bromination of phenol (44), which could be effected in carbon disulfide, glacial acetic acid and in carbon tetrachloride solution in such a way that only mono-substituted products were obtained. The same result could be reached by a bromination without a solvent. Table 16 gives a review of the results, showing

that in this case the influence of the solvent is very small, if any exists at all. The figures are the percentages of para compound formed. In aqueous solution it was impossible to carry out the reaction in such a way, that only mono-substituted products were formed. Here the influence of the medium was therefore very considerable. The influence of water on the proportion in which the isomerides are formed is also very pronounced in the nitration of the acylanilides (49). This influence does not exist, however,

TABLE 16  
*Bromination of phenol in different solvents*

30°	60°	SOLVENT
86.2	87.4	CS <sub>2</sub>
87.5		Acetic acid
88.6		CCl <sub>4</sub>
	90.2	No solvent

TABLE 17  
*Influence of the concentration of nitric acid*

TEMPERATURE	CONCENTRATION OF HNO <sub>3</sub>	PERCENTAGE OF		ANILIDE
		ortho	para	
°C	<i>per cent</i>			
-20	80	35.7	64.3	} Formanilide
	90	18.5	81.5	
-20	80	40.7	59.3	} Acetanilide
	90	23.5	76.5	
-20	80	41.1	58.9	} Benzanilide
	90	20.0	80.0	

in the nitration of nitro benzene nor of the halogen benzenes. In the case of the acylanilides it is not only the concentration of the acid, but also of the substance mixed with it, that determines the ratio of the isomerides. We carried out some investigations on the nitration of acetanilide in which the concentration of the acid was always the same, but in which the water was wholly or partially replaced by acetic acid. The results are shown in Table 18.

A very considerable factor in the nitration of aniline and its derivatives is, whether the nitration is carried out with nitric acid alone or in sulfuric acid solution. The nitration of aniline

TABLE 18  
*Nitration of acetanilide*

TEMPERATURE °C	ACID, MIXTURE	PERCENTAGE OF			
		ortho	meta	para	dinitro
-20	80 per cent HNO <sub>3</sub> + 20 per cent CH <sub>3</sub> ·CO <sub>2</sub> H				50.2
	81 per cent HNO <sub>3</sub> + 10 per cent C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> + 9 per cent H <sub>2</sub> O	30.0	1.2	68.8	
	80 per cent HNO <sub>3</sub> + 20 per cent H <sub>2</sub> O	40.7		59.3	

TABLE 19  
*Nitration of aniline and acylanilides*

TEMPERATURE °C	NITRATION IN	PERCENTAGE OF			COMPOUND
		ortho	meta	para	
-20	Nitric acid				Aniline; only tarry matter formed
	Nitric acid 96 per cent	1.4	47.9	51.3	Aniline
-20	Nitric acid 90 per cent	18.5		81.5	} Formanilide
	Sulfonic acid 96 per cent	3.0	0.8	96.2	
-20	Nitric acid 90 per cent	24.5		75.5	} Acetanilide
	Sulfonic acid 90 per cent	4.5		95.5	
-20	Nitric acid 90 per cent	19		81.0	} Benzanilide
	Sulfonic acid 96 per cent		2.6	97.4	

itself or of its nitrate in nitric acid alone has as yet not succeeded; only tarry substances are obtained. Table 19 shows the large differences obtained by the two modes of nitration.



## 3. Influence of catalysts

In the chlorination and bromination of aromatic compounds it is often necessary to make use of catalysts in order to obtain a regular and rapid substitution. Their influence has been studied quantitatively in the bromination of toluene (50). Van der Laan dissolved 3 cc. bromine in 50 cc. toluene in darkness and used as catalysts antimony bromide, ferric bromide and aluminium bromide. The latter two were powerful agents; when used in quantities of 0.2 or 0.4 per cent of the bromine they completely prevented the substitution in the side chain, even in sunlight; antimony bromide is a much weaker catalyst; for, when added in a quantity of 9 per cent of the bromine, 19 per cent of benzylbromide is still formed. Table 20 gives a review

TABLE 20  
*Bromination of toluene*

CATALYST	CONCENTRATION OF CATALYST (MOL ON 1 MOL Br)	PERCENTAGE OF		PER CENT BENZYLBROMIDE (BROMTOLUENES + BENZYLBR. = 100)
		ortho	para	
None.....	0	41.8	58.2	45.4
SbBr <sub>3</sub> .....	0.034	38.9	61.1	44.2
FeBr <sub>3</sub> .....	0.01	37.0	63.0	0
AlBr <sub>3</sub> .....	0.017	49.2	50.1	0

of van der Laan's experiments at 50°. There is only a marked difference in the ratio o-p when AlBr<sub>3</sub> is used.

Another investigation on the influence of catalysts was carried out by van der Linden (51), who studied the introduction of chlorine and bromine into chlorbenzene and brombenzene. The results are shown in tables 21 to 24.

The most obvious result is the high percentage of the m-compound, which is formed by the bromination of chlorbenzene and of brombenzene, using Al as a catalyst. This is due to the fact that the action of Al is powerful enough to destroy the products formed under its influence, and to transpose the halogen to another position in the nucleus.

There are still other factors influencing the substitution in the benzene ring; the subject is not at all exhausted by what

has been said in these pages, though the most important points are treated. I have confined myself almost wholly to the investigations that have been executed in my laboratory.

TABLE 21  
*Chlorination of chlorbenzene at 60 to 65°*

CATALYST	PERCENTAGE OF		
	ortho	meta	para
AlCl <sub>3</sub> .....	29.7	4.6	65.7
FeCl <sub>3</sub> .....	39.2	5.3	55.5

TABLE 22  
*Bromination of chlorbenzene*

TEMPERATURE °C	CATALYST	PERCENTAGE OF		
		ortho	meta	para
130	None	17.5	1.2	81.3
55	AlBr <sub>3</sub>	15.0	9.0	76.0
55	FeBr <sub>3</sub>	11.0	1.5	87.5

TABLE 23  
*Chlorination of brombenzene at 75°*

CATALYST	PERCENTAGE OF		
	ortho	meta	para
AlCl <sub>3</sub> .....	30.0	5.4	64.6
FeCl <sub>3</sub> .....	42.0	7.1	50.9

TABLE 24  
*Bromination of brombenzene at 55°*

CATALYST	PERCENTAGE OF		
	ortho	meta	para
AlCl <sub>3</sub> .....	8.3	30.1	61.6
FeCl <sub>3</sub> .....	13.1	1.8	85.1

The problem of the substitution in the benzene ring is very complicated, and many of the researches on it, described in the chemical literature, are now worthless, because the condi-

tions of the experiments are not described in detail. This may induce students in this field to give as accurate a description as possible of all their investigations, in order to prevent their having to be repeated later thus causing waste of time which could be better employed.

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