ORIENTING INFLUENCES IN THE BENZENE RING

A REVIEW OF EXPERIMENTAL EVIDENCE

JOHN SMITH REESE, IV[1]

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland

Received March 5, 1932
Revised to November 28, 1932

The entry of a second group or radical into the nucleus of a monosubstituted benzene is well characterized by the lack of random in respect to the position attacked. Indeed, such apparently is also the case for any aromatic substitution reaction in which there are one or more substituents present and two or more positions open to substitution. Thus it is a very general phenomenon and one of no slight complexity. In its simplest form, where a single substituent enters the ring of a monosubstituted benzene, it is the fact that all three possible isomers are not formed in equal amounts which gives rise to this problem. (It is to be noted that possibly twice as much of the ortho and meta isomers as of the para isomer would be the normal circumstance in the absence of directive influences.) Furthermore, the ratio of isomers formed varies enormously with the character of the original substituent. These facts summarize briefly the well-known problem of orienting influences in the benzene ring.

That each aromatic substituent possesses a characteristic directive influence has been known for many years, and not a few hypotheses have been offered to explain the observation that a group was either ortho-para or meta directing. But it is not easy to classify the many substituents in this way, for an almost infinite variation in the ratios of the isomers is apparently possible. Though such a situation is caused in large measure by the great number of possible substituents, there are other factors as well. The influence of temperature, reaction medium, and catalysts should not be heedlessly neglected. The rôle of these factors and the consequent difficulty of attaining comparable reaction conditions for the estimation of the relative directive strengths of various substituents has

---

[1] The major part of this paper was accomplished while the author was at The Johns Hopkins University. Revision and additions were made during the course of his work at The Victoria University of Manchester, Manchester, England, as a Senior Fellow of The Textile Foundation of Washington, D. C. Present address, Massachusetts Institute of Technology, Cambridge, Massachusetts.

been emphasized by Holleman (97). In view of such difficulties and the fact that every case of aromatic substitution bears evidence upon the question, it is not surprising that in the many years no final or generally accepted solution to the problem has been attained.

In recent years both the theoretical and experimental aspects have been developed and much has been accomplished. Of particular value is the full appreciation of the fact that the problem is fundamentally one of reaction rates. But it is not the purpose of this paper to discuss either the theory or the relative merits of the various hypotheses. Excellent reviews of this nature have been done by Holleman (97), by Francis (67), and by Stewart (191). On the other hand, it is believed that a presentation of the collected experimental evidence may be of some interest and value.

The extent of such an undertaking was fully appreciated. At the same time it is possible to gain a real understanding of the problem from a fairly limited field. Thus by considering only the entry of a second substituent into the ring of monosubstituted benzenes, we take certainly the most fundamental if not the simplest aspect of the problem. Yet even then the possible number of substituents is almost numberless and consequently only the simplest and most significant ones can be considered here. Obviously, a choice must be made from among those of which definite information concerning orienting influences is available. The following nine substituents have been selected: $-COOH$, $-NO_2$, $-SO_3H$, $-CH_3$, $-OH$, $-NH_2$, $-Cl$, $-Br$, and $-I$. Except for the first three, they represent the simplest types of substituents. The three exceptions are chosen primarily because they are perhaps the most striking of meta orienting substituents, and in the case of $-SO_3H$, because no satisfactory or direct evidence concerning the orienting influence of its parent group, $-SH$, is available. On the whole, these nine substituents are surely a representative series, since all of the other possible groups may be considered as their derivatives.

Substituents such as $-HgCl$, in which a group is attached through a metallic element, and other similar possible groups are not considered here since their orienting influences have not been satisfactorily studied. Actually, the carboxyl, nitro, and sulfonic acid radicals might be omitted, for they are obviously derivatives of simpler groups. As for their meta orienting nature, it will appear later that under certain conditions even their parent groups may become meta orienting, or they themselves para or ortho orienting. To continue, however, there is similarly almost no limit to the type of group which may be introduced into the benzene ring, as a second substituent. Therefore, only three types of secondary substitution, namely, halogenation (exclusive of fluorination), nitration, and sulfonation have been chosen. Once again the problem so limited is by no means satisfactory, yet it is concerning these types of substitution reactions only that sufficient evidence is available. It is true, of course, that much study has been devoted to the introduction of alkyl, amino, hydroxy, and carboxyl groups, and even to mercurization, yet the information is relatively meagre and the methods vary so as to offer no satisfactory standard for comparison. Thus, within the three carefully chosen limitations, the immediate problem is clearly set forth, principally to seek what information in each case is offered in the literature concerning the relative proportion in which the isomers of disubstituted benzenes are formed. Now, although such is actually the heart of the problem, it must be recognized that other factors play an important rôle. Hence it will be with especial regard to reaction conditions that the present examination of the experimental facts is undertaken.

Although it is hoped by such an attempt to arrive at some general conclusions, the main object nevertheless must be the presentation of a comprehensive review of the relevant facts. Yet in doing so there are many investigations which add nothing new or significant or which have been greatly enlarged or improved upon by later studies. Consequently, much has been omitted from the text, but in order to accomplish the intended purpose these studies are given in the supplementary references at the end of this article. In this way it is hoped that this paper will prove to be a ready source of information for all interested in this problem, as well as a contribution to the theoretical aspect of the question. The material is arranged according to the nine substituents and in the order as given above. Finally some attention will be devoted to derived substituents and to the rôle of molecular rearrangements.

THE CARBOXYL SUBSTITUENT: BENZOIC ACID

Benzoic acid, the benzene derivative containing the carboxyl group as a single substituent, has been chlorinated to give chlorobenzoic acid by a number of workers. The first satisfactory investigation was that of Beilstein and Schlumm (25). Chlorinating with potassium chlorate and hydrochloric acid they obtained principally the *m*-chlorobenzoic acid. Their work was later supplemented by Claus and Buecher (35) who, using the same method, showed that some of the ortho isomer also resulted. Similarly, the use of either antimony pentachloride or calcium chloride, according to Holleman (98), will give the same isomers. On the other hand, Lossen found that a hypochlorite in a dilute aqueous solution of benzoic acid at a temperature under 50°C. will give the *o*-chlorobenzoic acid with some of the para and a smaller quantity of the meta isomer. But with calcium chloride, the same worker obtained principally the para isomer together with some of both the meta and ortho isomers (98). Again, the use of sodium hypochlorite gave Lossen nearly equal amounts of the ortho and para derivatives (98).

Furthermore it is of some interest that Pisoni in 1847 chlorinated benzoic acid in a solution of excess caustic potash with chlorine gas and obtained the *o*-chlorobenzoic acid (98). In striking contrast, liquid chlorine and ferric chloride was found by Bornwater and Holleman (28) to cause meta substitution exclusively. A 95 per cent yield of the meta isomer and a little of the ortho derivative were obtained by Gluud and Kempf (80) by treatment with concentrated hydrochloric and nitric acids. Passing on to the bromination of benzoic acid, one finds that Holleman again provides information of some interest. He refers to a number of workers, showing that bromination with bromine water in a sealed tube leads principally to the meta acid and probably one or both of the other isomers (reference 98, p. 116). The probable formation of all three isomers is indicated by Claus and Reh (36) who actually obtained them on bromination with potassium bromate and hydrobromic acid in a dilute water solution at 70–80°C. Yet a quantitative yield of the metaderivative is reported by Wheeler and McFarland (208) who brominated in the presence of iron wire or gauze.

With respect to iodination, there are only four sources of information. Although the methods are quite different, the meta isomer occurred in each case. Peltzer used potassium iodate and Birnbaum and Reinherz heated silver benzoate with iodine (see reference 98, p. 118). Datta and Chatterjee (47) iodinated with iodine and nitric acid in glacial acetic acid. Finally, a good yield of the *m*-bromo- and *m*-iodo-benzoic acids was obtained by halogenation in the presence of a mixture of fuming nitric acid and nitrosulfonic acid formed by passing sulfur dioxide through fuming nitric acid until 50 per cent nitrosulfonic acid is present (203).

It is apparent that, although the carboxyl radical is considered to be a strong meta directing group as opposed to an ortho-para directing substituent, no evidence is forthcoming to prove that the meta isomer is formed exclusively as a general case. Furthermore, where the meta isomer occurs in large amounts, it is frequently accompanied by some of the ortho isomer even though para substitution is totally absent. Yet ortho substitution is generally supposed to be accompanied by para substitution. This particular case suggests that ortho substitution can possibly occur equally well with meta substitution.

But the above is not the only inference to be drawn from the evidence, for although the influence of temperature has been completely neglected, that of the reaction medium has already been pointed out by Holleman (98). He calls attention to the fact that in the case of chlorination, the meta isomer seems to be formed in acid solution, whereas the ortho and para isomers occur in neutral or basic solutions. His interpretation of these effects, however, is not necessarily correct, for it seems more probable that an alkaline medium acts to prevent meta in favor of para substitution.

In any case this particular aspect in which a complete reversal of the orienting influence is effected may be of considerable significance. In addition it must be recalled that the carboxyl group has been considered in the introduction as a derivative of the methyl radical and hence should possess on that basis a para orienting influence. As previously indicated, here is a case where a typical meta orienting substituent actually may under certain conditions cause substitution in the para position. But before taking up the nitration of benzoic acid it must be pointed out that the effect of certain catalysts is quite marked. Unfortunately no conclusions can be drawn unless one assumes that they affect the acidity of the reaction medium.

TABLE 1

Nitration of benzoic acid

NITRATION AT	ORTHO ISOMER	META ISOMER	PARA ISOMER
degrees C.	*per cent*	*per cent*	*per cent*
−30	14.4	85.0	0.6
0	18.8	80.2	1.3
30	22.3	76.5	1.2

TABLE 2

Nitration of benzoic acid at 30°C.

	ORTHO ISOMER	META ISOMER	PARA ISOMER
	per cent	*per cent*	*per cent*
Without H_2SO_4	22.3	76.5	1.2
With H_2SO_4	19.6	75.5	4.9

The influence of the carboxyl group on the introduction of the nitro group has been rather successfully studied. Although the results of the many early workers are rather conflicting, a very complete investigation by Holleman (100) has made the case relatively clear. Using absolute nitric acid he obtained the results as presented in table 1. To determine the influence of sulfuric acid, Holleman (96) carried out an additional investigation, using a great excess of concentrated sulfuric acid (see table 2). In addition, however, there is another study which appears to involve a molecular rearrangement. Francis (65) found that benzoyl nitrate, $C_6H_5 \cdot CO \cdot ONO_2$, when dissolved in nitrobenzene was converted after six months into *m*-nitrobenzoic acid to an extent of about 60 per cent. Holleman (reference 98, p. 128) doubts that a true molecular rearrangement has occurred in this case, since benzoyl nitrate on storage is known to decompose into benzoic anhydride and nitric acid anhydride. In any case he states that the *m*-nitrobenzoic acid was completely free of its isomers. The exclusive formation of a single isomer suggests, however, that the change is virtually a rearrangement.

In regard to the above evidence it is hardly necessary to mention that the meta substitution which generally prevails on nitration of benzoic acid is accompanied principally by ortho substitution and to only a slight extent by para substitution. This is virtually a case of ortho-meta substitution, although, according to current theories, a substituent directs an incoming group either to the ortho and para positions or to the meta position. These experiments illustrate not only this point, but also the influence of temperature and the presence of sulfuric acid. It is readily seen that rise in temperature favors an increase in the amount of the ortho, a decrease in the amount of the meta, and a slight increase in the para isomer. Particular attention is called to this temperature effect, for, as will be seen later, it is the same in all cases except where molecular rearrangements are known to take place. With respect to the influence of sulfuric acid, it is clearly shown that more of the para isomer is formed, principally at the expense of the ortho isomer, whereas meta substitution is but slightly, almost negligibly, hindered. Although sulfuric acid exerts a similar influence in several other cases, the effect is by no means so marked as that of temperature.

Turning now to the introduction of the sulfonic acid group, one finds that though it has been variously studied, a brief examination of the bulk of the evidence proves it to be only partially understood. Recently, however, the author (169) has undertaken this problem and has been able to throw some light on the question.

Generally speaking, previous work had shown that benzoic acid might be readily sulfonated with strong sulfuric acid at high temperatures (ca. 200°C.) and by long duration of heating (two to twenty-four hours). In this way about 90 per cent of the product is the *m*-sulfobenzoic acid and the balance is the para isomer. Furthermore, Maarse (139), to whom credit for the above evidence is also due, incidental to his lengthy investigation, had demonstrated that the meta isomer may be converted under the ordinary reaction conditions into the para isomer to the extent of about 15 per cent, although the reverse reaction was found to occur to about a threefold greater degree. Besides the work of Maarse, however, there are two investigations which deserve attention. In the first of these, Holdermann (95) studied the effect of the presence of metallic sulfates, such as those of mercury, copper, cadmium, etc,. and found that the sulfonation reaction was in no way influenced. In the other, Auger and Vary (8) found that sulfonation in the presence of iodine always gave a mixture of all three isomeric sulfobenzoic acids, of which the ortho acid amounted to only 1 per cent. On the other hand, the author (169) has shown that ortho substitution normally occurs even in the absence of a catalyst. Indeed this investigation indicates that the ortho isomer was formed as an intermediate product which, under the reaction conditions, was isomerized to the meta derivative to such an extent that its presence among the products could scarcely be detected. Furthermore, the reaction was definitely proved to be an indirect one, the probable scheme being the formation of an addition compound between the sulfuric acid and the benzoic acid, a condensation to form a benzoylsulfuric acid, followed by an isomerization to the *o*-sulfobenzoic acid and thence to the meta isomer. Other evidence, especially that provided by Maarse (see above), indicates that the para acid is formed by a rearrangement of the meta acid. Briefly, therefore, the sulfonation of benzoic acid has been shown to lead principally to the meta isomer by an indirect reaction. Furthermore, a close association between the ortho and meta isomers has been shown to exist, a situation complementary to that between ortho and para isomers when aniline, toluene, and phenol are sulfonated (see later sections of this paper). This case certainly suggests again that ortho substitution may be associated not only with para but also with meta substitution. Altogether the evidence concerning the sulfonation of benzoic acid agrees well with that obtained from halogenation and nitration, except that the former appears as an indirect, and the two latter as direct, substitution reactions.

THE NITRO SUBSTITUENT: NITROBENZENE

Nitrobenzene, in which the nitro group is the substituent, has been variously halogenated but the evidence is somewhat unsatisfactory. The earliest work is that of Kekulé (126), who chlorinated with antimony trichloride in the presence of iodine and obtained mostly the *m*-chloronitrobenzene with a little of the para isomer. A few years later Laubenheimer (133), chlorinating with chlorine gas in the presence of 10 per cent of iodine at temperatures slightly over 0°C., reported the formation of only the *m*-chloronitrobenzene. Beilstein and Kurbatow (24) chlorinated with antimony trichloride and chlorine, but their results add nothing to the evidence already given. The relative catalytic effect of ferric chloride, aluminum chloride, and stannic chloride was studied by Goldschmidt and Larsen (81) and the strength of these salts was found to decrease in the order given. The meta isomer was found in each case. The investigation of Scheufelen (177) is the only one available concerning the bromination of nitrobenzene. Using ferric bromide and ferric chloride to aid bromination with bromine and at temperatures from 60° to 110°C., he obtained only the meta isomer.

Only a few remarks can be offered concerning these facts. A catalyst in the nature of a so-called halogen carrier is apparently necessary. This fact perhaps explains why the meta isomer occurs exclusive of the ortho, for such catalysts are generally known to favor strongly either the para or the meta position. Under such conditions it is not unusual that no ortho substitution has been reported. Obviously, however, the work here has not been thorough or exhaustive, and more study is certainly to be desired.

The nitration of nitrobenzene apparently offers a less difficult task than the halogenation. It has been quite successfully investigated by Holleman and de Bruyn (105). They have shown not only that meta substitution prevails nearly completely, but also that the ortho and para isomers are simultaneously formed. That considerably more of the ortho isomer occurs is of the same significance as pointed out in the case of benzoic acid. In table 3 the influence of acid strength as well as that of temperature is clearly shown. The relative proportion of isomers is seen to be but slightly affected by the acid strength in the experiments at 30°C. The time required for nitration is however strongly influenced, for with 94.5 per cent and 95.9 per cent acid, it is still incomplete, whereas with 97.6 per cent acid this is not so. In another place Holleman (reference 98, p. 71) gives more data. The nitration with 94.5 per cent acid required 11½ hours to give a 67.1 per cent yield of the dinitro product, whereas nitration with the 95.9 per cent acid requires but 2 hours to yield up to 73.2 per cent of the theoretical quantity. He ascribes the fact that the smaller degree of nitration requires more time to the difference in water content between the two acids used, amounting to only 1.4 per cent. Holleman also concludes that, since the time required for nitration does not appreciably change the relative proportion of the isomers, they are formed at equal reaction rates. In addition to the effect of acid strength or presence of water, a rise in temperature is seen to cause the usual increase in the ortho isomer, the considerably smaller increase in the para, and the decrease in the meta isomer. When

TABLE 3

The nitration of nitrobenzene

TEMPERATURE	CONCENTRATION OF NITRIC ACID	RESULTING ISOMERS			EXTENT OF NITRATION
		Ortho	Meta	Para	
degrees C.	*per cent*	*per cent*	*per cent*	*per cent*	
0	98.58	6.4	93.2	0.25	Complete
30	94.50	8.1	91.2	0.7	Incomplete
30	95.90	8.5	91.0	0.5	Incomplete
30	97.6	8.1	90.9	1.0	Complete
0	98.58 (H_2SO_4)	4.8	93.5	1.7	Complete
40	97.6 (H_2SO_4)	6.8	91.8	1.4	Complete

sulfuric acid is present, the temperature effect is not so great, but the amount of para isomer formed is nevertheless greater than when nitric acid alone is used. The sulfuric acid, like the rise in temperature, is thus seen to exert its usual effect.

Although the above study is quite satisfactory, there are several more investigations which deserve attention. In one, the effect of mercuric nitrate has been studied by Holdermann (95); its only effect was found to be to increase the yield of the dinitro product from 23.5 per cent to 28 per cent of the theoretical, only the meta derivative being obtained. In a second, the use of $(SO_2OSO_2ONO_2)_2$ as a nitrating agent was studied. The authors, Pictet and Karl (163), state that an intermediate addition compound was observed which led only to the *m*-dinitrobenzene. This second investigation suggests a possible reaction scheme involving a molecular rearrangement. The last study to be mentioned concerning nitration is that made by Adkins (1), who found that the action of nitrogen pentoxide on nitrobenzene leads exclusively to the *m*-dinitrobenzene. Further study should be devoted to this case, since information concerning the exclusive formation of a single isomer should be of great importance in solving this problem.

The sulfonation of nitrobenzene has been well nigh completely neglected except for a few workers. Of these, Limpricht (135) has shown that all three isomeric nitrobenzenesulfonic acids are formed when nitrobenzene is treated with fuming sulfuric acid. Though he determined their relative amounts, they were left unidentified except as nitrobenzenesulfonic acids. Nevertheless, Ekbon (56), in a paper on this subject, states that Limpricht obtained about 95 per cent of the meta acid, around 5 per cent of the ortho acid, and the para acid evidently to a very slight degree. This question, however, has been very satisfactorily investigated by Obermiller (155). Sulfonating with sulfuric acid (100 per cent) together with oleum (20 per cent sulfur trioxide) for 2 hours at temperatures up to 60–70°C., he obtained a total yield of 98.3 per cent, of which 98.4 per cent was the meta acid and only 1.6 per cent the para acid. Even by a careful search Obermiller was unable to detect any of the ortho acid among the products. Recalling however the case of benzoic acid, in which the absence of the ortho acid was caused by a molecular rearrangement, and looking forward to other similar cases of sulfonation, it is quite probable that the same is true here also. Generally, therefore, though the case of nitrobenzene apparently contradicts the conception that substitution occurs normally at all three positions, it is quite possible that the absence of ortho substitution on halogenation and sulfonation is the result rather of unusual and specific reaction conditions.

THE SULFO SUBSTITUENT: BENZENESULFONIC ACID

The introduction of a second substituent into the nucleus of benzenesulfonic acid appears to be fairly unsettled. Even in the simple case of halogenation, a hint of the difficulties is provided. Thus, Fittig (61), following up the earlier work of Garrick (72), who heated the sulfonic acid with bromine in a sealed tube but failed to identify an isomer other than the meta, states that the yield consists largely of the *o*- and somewhat of the *p*-monobromosulfonic acids. But Limpricht (136) obtained a satisfactory yield of the meta acid together with some by-products. He treated, however, the silver salt of the sulfonic acid. Though these results are conflicting, the earlier ones may possibly be discarded as unreliable.

The evidence for the nitration of benzenesulfonic acid is chiefly the result of Obermiller's work (155), though Limpricht (135) does report a yield consisting of 90 per cent of one isomer and 10 per cent of a second and third together. The results obtained by Obermiller are presented in table 4. It is readily observed that all three isomers are simultaneously formed and that though meta substitution predominates, it is accompanied principally by ortho and to a smaller degree by para substitution. Also the effect of rising temperature substantiates well what has been indicated previously as the usual phenomenon. Furthermore, it must be noted that considerable amounts of the para isomer may be formed under certain conditions. Another most interesting point, recalling Obermiller's work on the sulfonation of nitrobenzene, is that whereas the nitration of benzenesulfonic acid and the sulfonation of nitrobenzene may hypothetically lead

TABLE 4

The nitration of benzenesulfonic acid

EXPERIMENT NO.	ACTUAL PER CENT OF ISOMERS			PER CENT OF THEORY	RELATIVE PER CENT OF ISOMERS			TOTAL
	Meta	Ortho	Para		Meta	Ortho	Para	
I	68.3	19.9	6.2	94.4	72.4	21.1	6.5	100.0
II	56.4	24.3	9.2	89.9	62.8	27.0	10.2	100.0
III	55.7	23.8	8.7	88.2	63.2	27.0	9.8	100.0
IV	53.6	26.9	11.5	92.0	58.2	29.3	12.5	100.0
V	40.0	27.4	12.2	79.6	50.3	34.3	15.3	100.0

I. Nitration with 80 per cent nitric acid, but with previous addition of concentrated sulfuric acid, at 20–30°C.
II. Nitration with 80 per cent nitric acid, without addition of sulfuric acid, at 20–30°C., finally at 50–60°C.
III. Nitration with 80 per cent nitric acid at 30–40°C., finally at 40–50°C.
IV. Nitration with 80 per cent nitric acid at 90–100°C.
V. Nitration with 80 per cent nitric acid at 150–60°C.

to the same results, the actual yields differ not merely in the relative proportions of the isomers but in the total absence of the ortho isomer in the latter of the two reactions. But inasmuch as in the former reaction there is a normal temperature influence, and since in the latter there is a distinct possibility of a molecular rearrangement and an abnormal temperature effect, two distinct mechanisms of benzene substitution are presumably involved. This question will receive further attention below.

TABLE 5

Sulfonation of benzenesulfonic acid

DURATION OF HEATING	AT 183°C.	AT 209°C.	AT 233°C.
I. Sulfonations in medium containing free sulfur trioxide			
hours 4	(mono)	2.0 per cent para	4.7 per cent para
6	—	(2.3 per cent) para	(trisulfo)
12	—	3.0 per cent para	(trisulfo)
18	—	3.0 per cent para	(trisulfo)
24	6.1 per cent para	7.0 per cent para	(trisulfo)
30	—	6.1 per cent para	(trisulfo)
II. Sulfonations with concentrated sulfuric acid (98 per cent)			
3	—	—	11.2 per cent para
4	—	11.1 per cent para	—
6	(mono)	(10.0 per cent) (10.2 per cent) para	12.9 per cent para
12	(mono)	—	19.9 per cent para
18	(mono)	13.7 per cent para	—
24	(mono)	16.1 per cent para	22.0 per cent para
30	—	15.1 per cent para	—
48	14.6 per cent para	22.7 per cent para	28 per cent para
96	—	(trisulfo)	(trisulfo)
168	31.6 per cent para	(trisulfo)	(trisulfo)

III. Transformation of meta acid → para acid at 209°C.

12 hours heating	5.8 per cent para
24 hours heating	9.5 per cent para

IV. Transformation of para acid → meta acid at 209°C.

12 hours heating	6.9 per cent meta
24 hours heating	11.0 per cent meta
168 hours heating	67.0 per cent meta (trisulfo)

The orienting influence of the sulfo group in the formation of benzenedisulfonic acid was a decidedly unanswered question until Holleman and Polak undertook its investigation. Indeed Holleman (reference 98, p. 76) has shown how contradictory was the evidence previous to this time. Although the earlier workers indicate in each case that no ortho isomer is formed, no conclusion can be reached from their results as to whether the para or the meta isomer predominates. The evidence given by Holleman and Polak (110), however, offers a most interesting insight into the question. They studied the effect of temperature, strength of acid, and duration of heating on the one hand and, on the other, the transformation of the para into the meta acid and vice versa. Their results are presented in table 5.

By their work Holleman and Polak have sustained the report that no ortho acid occurs and that the meta isomer predominates. In sections I and II of table 5 they show how the proportion of the para isomer is affected by duration of heating, rise in temperature, and water content of acid reagent. The use of sulfuric acid containing considerable free sulfur trioxide made possible the sulfonation in total absence of water, whereas the use of sulfuric acid (98 per cent) involved the presence of water from the start. A considerably larger proportion of the para acid is formed in the latter case. Furthermore, both higher temperatures and longer heating seem to favor formation of the para acid. To show that this increase of the para acid was caused by a transformation of the meta acid, they treated pure *m*-benzenedisulfonic acid with sulfuric acid (98 per cent) at 209°C. Their results are given in section III of table 5. By comparison with figures in section II, the per cent conversion is seen to be insufficient to account for the formation of the para acid under similar conditions. On the other hand, their results, as in section IV of table 5, show that the transformation of the para acid into the meta acid proceeds to a greater degree, and it is thus seen that for a heating period of 168 hours, the 67 per cent conversion could practically account for the amount of meta acid formed by sulfonation of the monosulfonic acid under like conditions. On the other hand, an examination of section I of table 5 shows that the para acid formed by treatment with oleum could easily be accounted for by conversion of the meta acid into the para acid. Inasmuch as the effect of higher temperatures is to favor para at the expense of meta substitution, and since this is also the case in the sulfonation of benzoic acid, it seems possible that these reactions may follow a similar course. If so, it is important to determine whether or not ortho substitution occurs first, followed by a complete rearrangement to the meta acid. In common with the sulfonation of nitrobenzene and benzoic acid, the sulfonation of benzenesulfonic acid does not lead ultimately to the ortho isomer. Also these reactions, it is to be noted, may be contrasted with halogenation and nitration not only by the occurrence of rearrangements but also by the fact that higher temperatures do not favor ortho but rather meta or para substitution.

THE METHYL SUBSTITUENT: TOLUENE

The orienting influence of the methyl group is studied by the introduction of substituents into the ring of toluene. Thus the halogenation of toluene has been very extensively investigated. Indeed the amount of information available is so great and varied that it is difficult at first to draw any conclusions. To make possible, therefore, a better understanding of the experimental data, a few points may first be emphasized. It is immediately recognized that substitution in the methyl group or side chain occurs simultaneously with that in the ring, though special conditions may partially or completely suppress one or the other reaction. In this respect attention should be given to the effect of light, heat, catalysts, and in some measure to the concentrations of the reactants. Consideration of these factors will help to bring order out of apparent chaos. The experimental evidence follows, given in a very brief manner, owing to the unfortunate lack of space.

Glinzer and Fittig (79), by bromination of an excess of toluene in the dark and at ordinary temperatures, obtained a mixture of the *o*- and *p*-bromotoluenes. Similar results were obtained by Huebner and Majert (118), although they chlorinated boiling toluene with gaseous chlorine in the presence of iodine. The use of gaseous chlorine once again, although at water bath temperature and with molybdenum pentachloride as a catalyst, leads principally to *p*-chlorotoluene, some *m*- and probably some *o*-chlorotoluene, according to Aronheim and Dietrich (7). With a method similar to that of Heubner and Majert, Michael and Norton (145) showed that the action of iodine chloride led to *p*-iodotoluene. The effect of temperatures from 97–113°C. and of the presence of iodine was well investigated by Jackson and Field (122), who concluded that high and low temperatures favor side chain and ring substitution, respectively, benzyl bromide becoming the principal product at the boiling point of toluene (111°C.), and that 10 per cent or more iodine is necessary to prevent formation of benzyl bromide at this temperature.

The effect of light was early studied by Schramm (179), who showed that in both chlorination and bromination with iodine present, the ortho and para isomers occurred in both the presence and absence of light. Exposure to light, however, when iodine is not used, effects substitution in the side chain exclusively. According to Schramm, 2 per cent of iodine is sufficient to nullify the influence of light. Somewhat later Seelig (182) confirmed the finding that chlorination at the boiling point led largely to side chain substitution, and in addition showed that the presence of iodine, molybdenum pentachloride, and ferric chloride induces nevertheless a predominant yield of the para and in any case some of the ortho isomer. Chlorination of an ice-cold mixture was found by Seelig to provide as much as 65 per cent of *o*-chlorotoluene and as little as 25 per cent of *p*-chlorotoluene. The work of this investigator indicates that when in the absence of a catalyst side chain substitution is at a minimum, ortho substitution prevails over para substitution. Pointing out the fact that Beilstein and Geitner (22) had obtained on chlorination the ortho isomer as the main product, this evidence strongly suggested the possible ortho orienting nature of the methyl substituent.

Using sulfuryl chloride as a reagent, Toehl and Eberhard (199) obtained at 160°C. one-third of their product as benzyl chloride and two-thirds as a mixture of *p*-chlorotoluene and the 3,4-dichlorotoluene. Edinger and Goldberg (55) used sulfuryl bromide together with nitric acid (1.4) and benzene as a solvent. A mixture of *p*- and *o*-bromotoluene amounting to 85 to 95 per cent was obtained. Iodinating in the same fashion (54) they obtained the corresponding iodo derivatives amounting to 60 to 70 per cent of the theoretical quantity. O. Silberrad (187) and his coworkers have also used sulfuryl chloride, but in conjunction with a variety of catalysts. Chlorinating at 70°C. with aluminum chloride and 1 per cent sulfur chloride in the reagent, Silberrad obtained 88 per cent of a mixture of *o*- and *p*- chlorotoluenes in the approximate proportion of 1:1.3, respectively. In another report (186) they state that the use of phosphorus pentachloride, manganous chloride, or arsenic acted to prevent ring substitution and to favor formation of benzyl chloride. The reactions were carried out with boiling toluene. The use of sulfuryl chloride in place of chlorine apparently permits ring substitution even at a high temperature. Catalysts generally favor ring substitution, but it is of significance that some actually aid the formation of benzyl chloride.

Though Seelig found that ferric chloride as a catalyst favored para substitution, Thomas (195) used it as a reagent with boiling toluene to give a mixture of chlorotoluenes and no benzyl chloride. Cohen and Dakin (38), using an aluminum–mercury couple and chlorinating with chlorine, presumably at room temperature, obtained 65 per cent of the ortho and 35 per cent of the para isomer from a total yield of 80 per cent of the theoretical. Chlorinating with ammonium plumbic chloride, Seyewitz and Biot (184) obtained *o*-chlorotoluene. Whereas ferric chloride seems to favor para substitution, ammonium plumbic chloride effects ortho substitution.

The question of side chain versus ring substitution was reopened by the study of Cohen, Dawson, and Crossland (39) on the action of electrolytic chlorine. By comparative studies between chlorine from pyrolusite and hydrochloric acid and electrolytic chlorine from carbon electrodes and hydrochloric acid and the presence of carbon, they determined that even with boiling toluene, electrolytic chlorine attacked only the ring. Extending these studies, Schleuderberg (178), using platinum electrodes in diffused light, showed that at the temperature of melting ice and at current densities above 1.3 ampere hours side chain substitution occurred appreciably. His findings were as follows: (1) Lower current density favors ring substitution and total efficiency. (2) Electrolytic chlorine will substitute in the side chain of boiling toluene. (3) Chlorine obtained from unstable compounds such as plumbic chloride and ferric chloride substitutes in the ring. Further work by Cohen, Dawson, and associates (40) has confirmed the fact that benzyl chloride is formed even at low current densities and in the dark. For an average they obtained 10 per cent benzyl chloride and 90 per cent *o*- and *p*-chlorotoluenes. Similar experiments, though in the presence of light, gave 64 per cent side chain and 36 per cent ring substitution. Investigation of the effect of moisture indicated an 8 to 9 per cent shift in favor of ring substitution. Another electrolytic study was made by Fichter and Glanzstein (60) who, using a glacial acetic acid medium and darkness, obtained the para and ortho isomers in the ratio 2.5:1. But they report Muehlhofer as having found more of the ortho isomer. Generally the work on electrolytic chlorination indicates that ring and specifically para substitution are thereby favored. At the same time high temperatures and light appear as stronger factors in aid of side chain substitution. The findings of Cohen and coworkers to the contrary do not appear to be completely confirmed by later work. Electrolytic chlorine nevertheless fills a rôle very similar to catalysts.

The effect of catalysts as well as temperature and light has been the subject of an excellent study by Van der Laan (200). Results of bromination with bromine show that both with and without catalysts, temperature is a dominant factor in the formation of benzyl bromide. Without a catalyst, a temperature of 50°C. causes about equal amounts of side chain and ring substitution, while at 100°C. no ring substitution occurs at all. The presence of antimony bromide at 50°C. and above has practically no effect. The effect of light is well defined, however, for without a catalyst at 30°C. there is 99 per cent side chain substitution, whereas with catalysts such as antimony bromide, aluminum bromide, or ferric bromide, there results a mixture of polybromotoluenes and no benzyl bromide. Here it seems that catalysts exert a stronger influence than light. Van der Laan's experiments in darkness with so-called bromine carriers showed that even with increasing amounts of antimony bromide there always remain appreciable amounts of benzyl bromide. On the other hand, comparatively small quantities of aluminum bromide or ferric bromide will prevent side chain substitution completely. Adding aluminum in an aluminum–mercury couple instead of the free metal apparently has no effect. The figures for phosphorus, however, indicate a catalyst favoring side chain substitution, without effect on the ortho-para ratio. But it should be pointed out that this ratio is affected by the other catalysts studied. Presence of antimony bromide or ferric bromide decreases the proportion of ortho to para, whereas aluminum bromide acts in the opposite way. Change of the ortho-para ratio with temperature is quite well defined. Both ortho and side chain substitution are favored by rise in temperature. Generally it may be said that Van der Laan's work demonstrates well the specific effect of such factors as temperature, light, and catalysts with regard to bromination.

Using the same reaction Holleman and Polak (109) have studied the influence of concentrations of reactants and found that as the proportion of toluene to bromine increases, side chain substitution occurs to a greater degree, an effect which is greatly augmented by higher temperatures. Their work also indicates that only at 50°C. is there any appreciable effect on the ortho-para ratio, more ortho substitution occurring at lower concentrations of bromine. It appears, therefore, that an increase in temperature and a decrease in concentration of bromine augments both ortho and side chain substitution.

An interesting review of this problem has been made by Bancroft (19). Drawing on the work of others as well as on his own he summarized the situation concerning bromination and chlorination as follows:

Toluene and bromine:

Ring and chain substitution in the dark; concentration and temperature effect.

Ring and chain substitution with bromine and water.

Chain substitution in sunlight.

Chiefly chain substitution in sunlight in presence of nitrobenzene.

Chiefly ring substitution in the dark in presence of nitrobenzene.

Ring substitution with ferric bromide, ferric chloride, etc.; concentration effect.

Ring (and chain) substitution with iodine bromide; concentration and temperature effect.

Toluene and chlorine:

Ring and chain substitution in the dark; temperature effect.

Chain and some ring substitution in the dark with water or dilute sodium hydroxide.

Chain substitution in the daylight.

Ring substitution with ferric chloride, iodine chloride, antimony pentachloride, etc.

Ring substitution by electrolysis.
Chain substitution with sulfur as a carrier.
Chain substitution with phosphorus pentachloride.

One can see here how closely alike are bromination and chlorination, enough so in any case to consider them together. Of special interest is the fact that the presence of sulfur and phosphorus pentachloride favors chain substitution. It has already been mentioned that Silberrad found phosphorus pentachloride to act in this way and in addition Andrich and Le Blanc (3) have found oxygen to exert a similar influence in the bromination reaction. Indeed it might be well at this point to recall the close relationship of oxygen, sulfur, and even phosphorus.

Although chain substitution may be hindered by darkness and low temperatures, certain types of solvents or reaction mediums have the same effect. Bruner and Vorbrodt (30a) found bromination of toluene in the side chain to be less than 0.86 per cent whether in darkness or light when the reaction was carried out in the following solvents: carbon bisulfide, carbon tetrachloride, benzene, chloroform, acetic acid, phenylcyanide, nitrobenzene. Not only this point but the variation in effectiveness of the solvents suggests the importance of the reaction medium. The work of Elbs and Jaroslawzew (57) is also of interest in this respect. They treated toluene and iodine dissolved in glacial acetic acid with sodium persulfate. Their yield amounted to 86 per cent and consisted mainly of *o*- with some *p*-iodotoluene. It would appear here, however, that perhaps the salt rather than the solvent exerted the greater influence.

An acid medium was employed by Datta and Fernandes (48), who chlorinated toluene in aqua regia. Using nitric and hydrochloric acids in the ratio 1:1, they obtained principally benzyl chloride and considerable *o*-chlorotoluene. But with a ratio of 2 HCl:1 HNO_3 the formation of benzyl chloride scarcely occurred at all, while ortho substitution prevailed together with some para substitution. The reactions were carried out at water bath temperature. It should be noticed that chain and ortho substitution occur together under the first conditions and that when the former is suppressed, para substitution begins to occur at the same time that ortho substitution predominates. A similarity between chain and ortho substitution is surely suggested, as well as the ortho orienting nature of the methyl substituent.

Ortho substitution apparently occurs to a greater extent in the case of bromination also, as shown by Datta and Chatterjee (45). Using nitric acid (1.35) and bromine they obtained a 40 per cent yield of *o*-bromotoluene and some 3,4-dibromotoluene. Iodination in the same way gave merely a mixture of the para and ortho isomers (46). No benzyl bromide apparently was obtained by Stark (190), who also used an acid medium. Bromination with hypobromous acid gave him a 73 per cent yield consisting of a mixture of the ortho and para isomers.

Another investigation to be mentioned here is that of Wahl, Normand, and Vermeylen (205). Chlorinating in the presence of iron and at 30–60°C., they obtained 57.8 per cent of *o*-chlorotoluene. With ammonium plumbic chloride, as reported by Seyewitz and Biot (184), they could obtain no reaction. The use, however, of plumbous chloride at 700°C. gave them 62 per cent of the ortho and 38 per cent of the para isomer. Comparing the result of the iron catalyst reaction with the studies of Aronheim and Dietrich (7), Thomas (195) and Seelig (182), all of whom used ferric chloride, it appears that they obtained an unusual yield of the ortho isomer. The contradictory nature of Van der Laan's work (200) should also be recalled. Chlorination with plumbous chloride appears unusual in the same way with a predominance of ortho substitution. However at 700°C. it would be difficult to predict results. Higher temperatures generally favor ortho substitution, yet it is also known that under such conditions substituents are likely to change positions in the ring.

Before concluding the discussion of halogenation of toluene a few general remarks should be made. Temperature plays such a rôle that heat favors ortho as well as chain substitution, whereas cold aids in ring and specifically in para substitution. Light definitely aids chain and hinders ring substitution. Its effect on the ortho–para ratio would be of interest could it be successfully determined. With respect to concentration of reactants, it may be said that an excess of toluene is in favor of chain and possibly ortho substitution. The situation with regard to catalysts and reagents other than the pure halogens is scarcely so well defined. Superficially the most effective ones are those leading to para substitution, such as antimony trichloride, molybdenum pentachloride, iodine, ferric chloride, etc. Inasmuch as they simultaneously further ring substitution, the most abundant and exact data concerns them and consequently shows the methyl group as a para orienting substituent.

Turning now to the other type of catalyst, that favoring ortho substitution, there appear to be several. Recalling Seelig's work, that of Datta and Fernandes, Cohen and Dakin, and similarly the investigation of Wahl, Normand, and Vermeylen, it appears not infrequently that ortho substitution predominates. As will be evident throughout this paper, high temperatures favor ortho substitution generally just as in this case, but with chain substitution possible and favored by the same circumstance, it is probable that much chain substitution occurs in place of ortho substitution. For this reason, and because of the fact that ortho substitution does frequently constitute the major reaction, it is well to consider the possibility of the methyl group as an ortho orienting substituent. Furthermore, as has been indicated here and there, certain conditions and catalysts favor either chain and ortho substitution or ring and para substitution. Indecisive as the evidence may be as to whether toluene effects largely ortho or para substitution, considerable support is given to this view from studies on nitration.

Concerning the nitration of toluene a discussion of evidence will be reserved until the experimental work has been presented. Thus Rosenstiehl (172) has nitrated toluene with nitric acid (1.475) and indicates that the main product is *o*-nitrotoluene with half as much of the para isomer. Monnet, Reverdin, and Noelting (146) have shown that the meta isomer occurs simultaneously, though in almost negligible amounts, together with the ortho and para isomers. Leeds (134) nitrated toluene with nitrogen peroxide and obtained, besides polynitrated products, principally if not exclusively *o*-nitrotoluene. Noelting and Forel (153) state that nitration of toluene with nitric acid alone gives a preponderant yield of the para isomer (ca. 66 per cent), whereas nitration with a nitric and sulfuric acid mixture gives the same yield of the ortho isomer. They found the reaction temperature and concentration of acids to exert an influence on the ratio of isomers. Welter (206) has demonstrated the effect of temperature, obtaining, at 30–35°C., 60 per cent of the ortho and 40 per cent of the para isomer; at 50–55°C., 85 per cent of the ortho and 15 per cent of the para iromer. Holdermann (95) investigated the effect of catalysts on the nitration reaction when nitric acid was used both alone and together with sulfuric acid. Experimenting with copper, copper nitrate, mercury, mercurous nitrate, mercuric sulfate, nickel, cobalt nitrate, and ammonium vanadate at 5–10°C., he found the yield of ortho isomer to vary but negligibly from that obtained without a catalyst, namely 59 to 60 per cent. The use of nitric acid (1.52) alone gave 52.6 to 52.7 per cent of the ortho isomer and similar results in the presence of catalysts. Orton (159) nitrated toluene using nitric acid (94 to 95 per cent) of 1.3 to 1.4 per cent nitrous acid content. A mixture of the ortho and para isomers amounting to 17 to 18 per cent of the theory resulted. A quantitative yield, however, was obtained by employing a glacial acetic acid medium. Pictet and Khotinsky (164) treated toluene with acetyl nitrate, securing 88 per cent of the *o*-nitro and 12 per cent of the *p*-nitro derivative. Boedtker (27) nitrated toluene at water bath temperature with ethyl nitrate, adding aluminum chloride to the reaction mixture little by little. The yield consisted of 20 g. of the ortho and 4 g. of the para isomer. According to Friswell (69) nitration of toluene always gives 60 to 65 per cent of the ortho and 35 to 40 per cent of the para isomer.

Concerning the influence of temperature, Holleman and van den Arend

(112) made an excellent study, nitrating with nitric acid (1.475). Repetition of this work several years later by Holleman and coworkers (114) gave presumably more accurate results. Their results are given in table 6. Kidokoro (130) investigated this problem but his results add little except to show that the presence of sulfuric acid favors the para isomer, raising it from 45 per cent to 60 per cent, the balance being apparently the ortho isomer.

Davis, Worral, Drake, Helmkamp, and Young (49) investigated the effect of mercuric oxide. Using 10 g. of mercuric oxide to 200 g. of toluene, they obtained results which indicate substitution to take place about equally in the ortho and para positions. Gibson, Duckham, and Fairbairn (77) nitrated with strong nitric acid and with mixed sulfuric and nitric acids in various proportions. The effect of temperature and their determination of the meta isomer are the most satisfactory parts of their work. Though rise in temperature increases ortho substitution but slightly, the persistence of this effect throughout three series of experiments makes it convincing. On account of the variable quantities of reactants and the slight change in the ratio of isomers, no other conclusions can be drawn, although it is obvious that substitution does occur in all three positions.

TABLE 6

Nitration of toluene with nitric acid (1.475)

TEMPERATURE	NITROTOLUENES		
	Ortho	Meta	Para
degrees C.	*per cent*	*per cent*	*per cent*
−30	57.2	3.5	39.3
0	58.0	3.9	38.1
30	58.8	4.4	36.8
60	59.6	5.1	35.3

Of peculiar interest is the work of Menke (142). The exclusive preparation of *o*-nitrotoluene by nitration with ferric nitrate in acetic anhydride solution is certainly unique, for no case of this kind has yet been mentioned. It will be recalled how para is generally supposed to accompany ortho substitution. However from another point of view concerning the relation of the isomeric positions this is not an unusual circumstance, for meta substitution likewise frequently occurs practically alone. Haines and Adkins (88) have nitrated with nitrogen pentoxide in a carbon tetrachloride medium, but the boiling point (228°C.) of their product gives no information as to its composition.

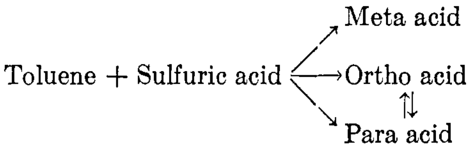
Reviewing the experimental evidence now, it is apparent that either ortho or para substitution may prevail. The latter type, however, appears as a more special case, particularly in view of the excellent studies of Holleman and coworkers and of Gibson, Duckham, and Fairbairn. Their work definitely marks the preponderance of ortho substitution. In addition, one will readily realize that the ratio of isomers depends not merely on the nature of the methyl substituent but also on the reagent, concentration of reactants, reaction medium, temperature, and catalysts. But it is only concerning the temperature that any inferences can be made. Thus, rising temperature increases the yield of the ortho isomer and decreases that of the para isomer. Higher temperatures also favor meta substitution, which fact should not be neglected. Indeed the occurrence of the meta isomer and the above temperature effect marks this reaction as taking place in the manner previously described as the normal one. Finally it should be emphasized that the ortho orienting nature of the methyl substituent receives considerable support from the above evidence.

Concerning the case of sulfonation, it will be seen that on account of the occurrence of molecular rearrangements the facts are rather confusing. Nevertheless, the very thorough work of Holleman and Caland (104) is quite satisfactory. Considerable study had previously been devoted to this problem, but no decisive results had been obtained. Inasmuch as this earlier work offers nothing of special interest, attention will be given directly to that of Holleman and his coworker. Their study included the effect of temperature, the concentration of the sulfuric acid, the ratio of toluene to acid, and the presence of salts. In addition, they compared sulfuric acid with chlorosulfonic acid as sulfonating agent and investigated the transformation of the isomeric toluenesulfonic acids into one another. It was also of importance that they proved the simultaneous formation of the meta together with the para and the ortho isomers. This had previously been a much disputed question.

Of least interest perhaps is their study of sulfonation in the presence of salts. They used potassium sulfate, mercurous sulfate, and silver sulfate, and determined that they did not appreciably affect the proportion of isomers. From their other studies, however, it may be readily observed that meta substitution always occurs, varying from 2.5 per cent under certain conditions up to 14.4 per cent under other conditions. In the latter case the amount of meta substitution exceeds that of ortho by 10.7 per cent, para substitution occurring to the extent of 81.7 per cent. By comparison with the other results, this particular case was apparently due principally to the high temperature of 100°C. and partially to the small ratio of toluene to acid, namely 1:41.5. This is somewhat contrary to the conception that para and ortho substitution are always associated together, for in that case meta substitution should not occur at all.

Now although no conclusions regarding the effect of acid strength and proportion of toluene to acid can be definitely made, the influence of rising temperature should be especially noted. In favoring para at the expense of ortho substitution, it is quite inconsistent with cases of halogenation and nitration. Nevertheless, recalling the sulfonation of benzoic acid and benzenesulfonic acid it is not surprising that Holleman actually found the ortho and para isomers to be interconvertible. He showed that the transformation takes place to a greater extent in the direction ortho to para than vice versa. This is especially true at temperatures above 35°C. The possibility that rising temperature favors para substitution by aiding the transformation of the ortho isomer is fairly obvious.

Indeed a closer examination of his results throws considerable light on the sulfonation of toluene. Having shown that neither the para nor the ortho acid gives the meta acid when subjected to the reaction conditions, Holleman suggests the following reaction scheme:



But this scheme is only partially satisfactory, for it does not indicate whether para or ortho substitution occurs to a greater extent. Provided no change in the position of a substituent group were possible, the isomer ratios would be a measure of the orienting influence. In this case, however, one must determine the exact extent of the intramolecular rearrangement in order to estimate to what degree substitution originally occurred in either the para or the ortho position. From information here available, it can only be supposed that ortho substitution occurs at least to the same extent if not further than para substitution, as indicated by nitration experiments. Since the studies on the transformations show that they are greatly increased by higher temperatures, the usual temperature effect, which produces more para isomer at higher temperatures, is readily explained on the assumption of greater initial ortho than para substitution. Finally, Holleman showed that the use of chlorosulfonic acid gave rise to approximately the same proportion of isomers as did the use of sulfuric acid.

Harding (90) also used chlorosulfonic acid, but his work confirms that of Holleman and Caland and supplements it to the extent of showing that a local excess of toluene favors para substitution, while a constant excess of acid favors ortho substitution.

The two remaining investigations to be discussed merely indicate a strong para orienting influence. Ray and Day (167) sulfonated with sulfuric acid (1.84) and a trace of iodine. After one hour at 100°C. they obtained the para acid exclusively in a 90 to 95 per cent yield. Gebler (76) similarly obtained an 87 per cent yield of the para acid by heating one part of toluene with 2.5 parts of trihydrogen sodium sulfate, $NaH_3(SO_4)_2$, under a reflux condenser for fifteen to sixteen hours. Nevertheless, these are both special methods of sulfonation and do not invalidate the idea that the sulfo group is mainly introduced in the ortho position and that the final product is caused by a molecular rearrangement of a large part of the ortho acid. Concerning the work of Ray and Day it is not surprising that sulfonation at 100°C. and in the presence of iodine led only to the para acid, for high temperatures favor the rearrangement and iodine is generally a catalyst favoring para substitution.

Generally the sulfonation of toluene is seen to be a case where the true orienting influence is hidden by a molecular rearrangement. At the same time one can readily infer the ortho orienting nature of the methyl substituent, which would confirm the findings with regard to halogenation and nitration. Though this point of view can hardly be insisted upon at present, the methyl substituent does appear to be more nearly ortho orienting than any other.

THE HYDROXYL SUBSTITUENT: PHENOL

The methods used in the halogenation of phenol may be divided conveniently into two groups according to whether or not a solvent is used, although apparently the reaction is quite satisfactory either way. Thus Dubois (51) chlorinated with sulfuryl chloride and obtained a monochlorophenol which was identified as the para isomer. Using chlorine gas with cooling, the same worker (52) obtained a mixture of monochlorophenols of which it could only be inferred that the major part was the para isomer. On the other hand a preponderant yield of the ortho isomer was identified as such by Faust and Mueller (59). They treated liquid phenol with chlorine, a method later used by Hasse (91), whose results do not confirm those of Faust and Mueller. That the higher temperature (41°C.) necessary for liquid phenol may have caused a main yield of the ortho isomer is substantiated by a patent belonging to Merck in Darmstadt (143). This patent claims an almost exclusive yield of the ortho isomer by treatment of phenol at 150–180°C. with either chlorine or bromine. This claim is confirmed by a similar investigation of Bramley (30), although he did obtain also the para isomer, together with a little dichlorophenol. Concerning chlorination, supposedly at room temperature, the Jahresbericht (124) describes *o*-chlorophenol as the by-product and *p*-chlorophenol as the main product. The same case is stated for bromination and iodination with iodine and iodic acid. With regard to this, Varnholt (204) has reported that chlorination of phenol under cooling leads to a mixture of *o*- and *p*-chlorophenols, of which 30 per cent is the ortho isomer. From the above work it appears that on chlorination at ca. 180°C., the ortho isomer forms the major product, while at ca. 0°C. the para isomer predominates. It is of interest then that at 90°C. Holleman (99) obtained equal yields of *o*- and *p*-chlorophenols (49.8 per cent ortho, 50.2 per cent para). Bromination at the same temperature, however, according to Holleman gives 9.3 per cent of *o*- and 90.7 per cent of *p*-bromophenol. Though rising temperature favors ortho substitution in both chlorination and bromination, according to Holleman and Rinkes (111) at 180°C. the *p*-bromophenol still amounted to 77 per cent of the yield. With regard to chlorination, they state that temperature similarly has but slight effect and that the per cent of ortho isomer is little higher than in bromination. In no case could they detect the meta isomer.

In the same investigation, Holleman and Rinkes studied the effect of carbon disulfide, glacial acetic acid, and carbon tetrachloride when used as solvents. Bromination at temperatures from −30°C. to 30°C. gave preponderant yields of para with the balance as the ortho and none of the meta isomer. Use had been made previously of carbon tetrachloride at low temperatures by Lossen (138), who in this way obtained only the *o*-chlorophenol. Gomberg and Stone (83) used the same method to prepare the *o*-chlorophenol, but their work merely indicates that more ortho isomer is thus obtained than by direct chlorination. Baines (11) also used carbon tetrachloride as a reaction medium for bromination, but he did not determine whether the ortho or the para isomer was in excess. Nevertheless, for chlorination carbon tetrachloride seems to favor ortho substitution. With regard to bromination, Hantzch and Mai (89) report that a dilute carbon disulfide solution yields the pure para isomer up to 85 per cent of the theoretical. This result is in good agreement with that of Holleman and Rinkes. Similarly, work by Huebner and Brenken (117) and by Meldola and Streatfield (141) with respect to the use of glacial acetic acid offers quite analogous results.

Halogenation in alkaline mediums, on the other hand, gives unusual results. Both Chandelon (33) and Skraup and Beifuss (188) obtained in this way more of the ortho than of the para isomer. Indeed, by chlorination with sodium hypochlorite in a caustic potash solution, Chandelon obtained in addition to dichlorophenol, only the *o*-chlorophenol. Skraup and Beifuss found that bromination in pyridine or in an aqueous alkaline solution, such as sodium hypobromite, at room temperatures gave up to 54 to 64 per cent of *o*-bromophenol together with small amounts of di- and tri-bromophenols. On the other hand, Tishchenko (198) treated an aqueous solution of phenol with a concentrated solution of sodium carbonate containing one equivalent of bromine and reported a yield of over 70 per cent *p*-bromophenol. In analogous experiments, using chlorine in place of bromine, equal quantities of both *o*- and *p*-chlorophenol were obtained. On the whole, it appears that an alkaline solution actually favors ortho substitution. In this respect it is interesting to recall a similar situation in the case of halogenation of benzoic acid.

In summarizing the evidence on halogenation it can be said that bromination occurs too strongly at the para position to be much affected by temperature or the reaction medium. Chlorination, however, varies considerably, ortho substitution being favored by higher temperatures, by the use of carbon tetrachloride, and by an alkaline reaction medium. Otherwise para substitution occurs to a greater degree than ortho substitution. Although the temperature effect corresponds to what has been considered normal, the absence of the meta isomer appears as unusual. With respect to nitration, however, it is seen that substitution readily occurs in all three positions.

From all the evidence available the nitration of phenol leads generally to more *o*- than *p*-nitrophenol. This is indicated by the very early work of Fritzche (70) and is definitely stated by Gatterman (74). Nitration with a mixture of sodium nitrate and sulfuric acid in aqueous solution at 20–25°C. will give 30 g. of the ortho and 5 to 10 g. of the para isomer. It might also be mentioned here that, according to Holleman (98, p. 164), gradual addition of dilute nitric acid to phenol will favor nitration in the ortho position. But the most recent study shows practically equal yields of the two isomers. Thus Beaumont and Haemmerle (20), nitrating in water, alcohol, or glacial acetic acid with nitric acid (1.35) at 7–12°C., obtained 77 to 82 per cent yields of nitro compounds. These products consisted of 40 per cent of *o*-nitrophenol, 35 to 40 per cent of *p*-nitrophenol, and 2.5 per cent of 2,4-dinitrophenol. They also found that higher temperatures favored ortho substitution, while lower temperatures favored para substitution, an observation which had been made much earlier by Goldstein (82). The influence of temperature is also very accurately shown in an investigation by Arnall (5). His results are given in table 7. The temperature effect, though not great, is the same as observed by Goldstein. Of greater interest, however, is the fact that Arnall always obtained a definite yield of the meta isomer. That this is not caused by the use of glacial acetic acid is shown by his experiments with a variety of other solvents, including acetone, ether, and alcohol. With all of them approximately the same yield of nitrophenols was obtained. He did find, however, that the total yield of nitrophenols varied from 98.7 per cent in glacial acetic acid to only 55 per cent in absolute alcohol. In addition to showing that nitration occurs in all three positions, Arnall's work confirms the ortho orienting influence of the hydroxyl group toward an incoming nitro group.

Other methods besides the use of nitric acid generally indicate the preponderance of ortho substitution. Unfortunately Weselsky (207), nitrating in an ether solution with nitrogen trioxide, failed to determine the relative amounts of the ortho and para isomers. But Auwers (9), by treating 1 g. of phenol in a benzene solution with nitrogen peroxide in the cold, secured 0.5 g. of the *o*- and 0.4 g. of the *p*-nitrophenol. On the other hand, Wieland (209) obtained nearly twice as much para as ortho, using the same method except that the solvent was a mixture of benzene and benzine. Natanson (150) nitrated with ethyl nitrate and sulfuric acid at 55°C. and reported 22 per cent of *o*-nitrophenol and 0.5 per cent of *p*-nitrophenol. Francis (65) also reported the ortho isomer to be in excess when he nitrated a carbon tetrachloride solution of phenol with benzoyl nitrate. Pictet (162) used acetyl nitrate in the same way to obtain 52 per cent of the ortho and 48 per cent of the para isomer. Nitration with bismuth nitrate and acetic anhydride, according to Spiegel and Hayman (189), gives the ortho and para isomers in the ratio 2:1.1. Despite, therefore, one or two cases to the contrary, the evidence indicates generally the prevalence of ortho over para substitution. In addition, Arnall's work indicates meta substitution even though its occurrence in halogenation is very doubtful. Finally, nitration appears to occur in the normal fashion, involving all three positions and the usual temperature effect.

TABLE 7

Nitration of phenol in glacial acetic acid

PER CENT OF HNO_3 IN CH_3COOH	AT 10°C.			AT 25°C.			AT 45°C.		
	Ortho	Meta	Para	Ortho	Meta	Para	Ortho	Meta	Para
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
5	57.6	3.3	40.0	58.1	2.9	39.0	59.4	2.4	38.2
10	57.8	3.1	39.1	59.2	2.7	38.1	60.6	2.2	37.2
20	58.9	2.8	38.3	60.3	2.4	37.3	61.5	2.1	36.4

The sulfonation of phenol presents a problem very similar to that of toluene. In both cases and also in that of aniline, as will be seen later, a transformation of the ortho into the para isomer hides the true orienting influence of the substituent group. As first shown by Kekulé (129), sulfonation leads to both *o*- and *p*-phenolsulfonic acid. The transformation of the ortho into the para isomer was investigated by Post (166), who showed that long heating, high temperatures, and stronger sulfuric acid were favorable to this conversion. Schultz and Ichenhauser (180) have confirmed the work of Post by showing that long heating leads largely to the para isomer. Obermiller (154), sulfonating at 20°C. with 100 per cent sulfuric acid, obtained about two parts of the ortho to three parts of the para acid. He found lower temperatures and weaker acids to favor ortho substitution. More recently Margueyrol and Loriette (140) have prepared the para acid by treating phenol with sulfuric acid (94.5 per cent) for five to six hours at 125–130°C.

Now although none of the above workers reports the formation of any *m*-phenolsulfonic acid, there is reason to believe that some meta substitution does occur. Salomonoff (174) sulfonated phenol for a period of several days at room temperature and reported the formation of a very small quantity of a third isomer. Though recognizing the possibility that this may be phenylsulfuric acid, Holleman (98, p. 166) states that the meta acid may be among the reaction products, inasmuch as fusion with caustic potash gives a little resorcinol. Furthermore it has been shown, according to the same authority, that neither the para nor the ortho isomer, but only the meta acid will in this way give resorcinol.

The phenylsulfuric acid is believed by Holleman (98, p. 170) to be an intermediate product, since this compound is found with the reaction products after sulfonation for 3 hours at 0–5°C. Furthermore, heating the potassium salt of phenylsulfuric acid in a sealed tube at 150–160°C. converts it into the potassium salt of *p*-phenolsulfonic acid. He ascribes the absence of the ortho isomer to high temperature. These experiments certainly suggest a very probable reaction scheme, viz.,

$$\mathrm{Ph\cdot OSO_3H} \rightarrow o\text{-}\mathrm{HO\cdot C_6H_4\cdot SO_3H} \rightarrow p\text{-}\mathrm{HO\cdot C_6H_4\cdot SO_3H}$$

Reference should be made here to a very excellent review of this problem by Olsen and Goldstein (157). They show that the ortho acid increases from less than 5 per cent at 70°C. to over 50 per cent at 20°C. The ortho acid is also shown to vary from 10 per cent when fuming sulfuric acid is used, to nearly 60 per cent for acid between 80 to 85 per cent at a sulfonation temperature of 35–40°C. But of special interest is their statement that the transformation of the ortho into the para acid is true molecular rearrangement.

If now the para acid is formed largely by transformation of the ortho acid, the hydroxyl group appears as an ortho orienting substituent. Both sulfonation and nitration lead therefore to this conclusion. In any case it is important to notice that sulfonation of both phenol and toluene appears to proceed in similar fashion.

THE AMINO SUBSTITUENT: ANILINE

Unfortunately there is not an abundance of evidence concerning the halogenation of aniline. In one of the earliest investigations Kekulé

(128) allowed bromine to react on aniline in a benzene solution and obtained, in addition to dibromo- and tribromo-aniline, *p*-bromoaniline with admixture of almost negligible amounts of either the meta or the ortho isomer or both. Using gaseous bromine mixed with air, exactly similar results were obtained. With regard to chlorination, Holleman (98, p. 138) states that Hafner treated aniline in an excess of either concentrated sulfuric or hydrochloric acid with chlorine and obtained *p*-chloroaniline. Similarly, bromination leads to *p*-bromoaniline. Bromination was also studied by Hoffman (94), who treated aniline with 1.5 times the amount of powdered iodine and obtained, besides hydriodic acid and aniline hydroiodide, *p*-iodoaniline. The para isomer was also obtained by Fuchs (71), who brominated aniline in a glacial acetic acid medium. Elbs and Volk (58) iodinated in concentrated hydrochloric acid with iodine and sodium persulfate. In addition to a main yield of 2,4-diiodoaniline, there resulted a very small amount of *p*-iodoaniline.

All of the above evidence points to a strong para orienting influence. Indeed, the ortho and the meta isomers do not appear to occur at all. Nevertheless, Holleman (98, p. 134) mentions two cases in which considerable ortho substitution occurs. Thus Chattaway and Orton (34) showed that aniline could be chlorinated with acetylchloramidodichlorobenzene. Using chloroform as a reaction medium, they found that *o*- and *p*-chloroaniline were formed in about equal amounts. Of considerable interest also is the fact that Fries (68) was able to obtain crystallized addition products by treating aromatic amines in glacial acetic acid with bromine and hydrogen bromide. The addition of water caused a quick conversion in which the ortho and para derivatives always resulted. This study shows how the formation of an intermediate addition compound may well be the first step in these substitution reactions.

Besides indicating the para orienting nature of the amino group, the above investigations offer very little. It seems highly improbable that para substitution occurs alone and therefore more exact information with regard to the possible extent of ortho and meta substitution is needed. Furthermore no one has investigated the effect of temperature, and, as will appear throughout this paper, the temperature effect becomes an index of the type of substitution reaction involved.

Though the same criticism may be made of the evidence regarding nitration, the situation is nevertheless more satisfactory The earliest study is that of Huebner (116), who nitrated aniline sulfate with a mixture of fuming sulfuric and nitric acids. His product consisted of more *m*- than *p*-nitroaniline and of a very slight amount of the ortho isomer This result is confirmed by Bruns (31), whose yield of nitroanilines was 10 to 15 per cent of the ortho isomer, and 45 to 50 per cent of the para and meta isomers together. Bamberger (14), however, obtained only the ortho and para isomers. His procedure was to treat aniline with nitrogen pentoxide in an ether solution, which easily accounts for his results. For both Huebner and Bruns, by using sulfuric acid, were virtually nitrating aniline sulfate and not aniline. The amino salt substituent is well known as a meta orienting one and inasmuch as Bamberger avoided its presence he did not obtain the meta isomer. Nitrating with nitrogen peroxide, just as with the pentoxide, Bamberger (15) again obtained small amounts of the ortho and para isomers, though principally diazoaminobenzene Meta substitution again failed to occur when Hoff (93) treated aniline nitrate with acetic anhydride. The *o*- and *p*-nitroanilines were obtained in the ratio of eight to one, in addition to diazo compounds. Here then it seems unusual that no meta isomer resulted, but one must remember that this is probably a case of molecular rearrangement, not of direct nitration of aniline salt. Holleman, Hartogs, and van der Linden (107) have made a somewhat more thorough investigation along the same line, treating aniline nitrate with glacial acetic acid. Their results are as follows:

ANILINE NITRATE	GLACIAL ACETIC ACID	TEMPERATURE	YIELD	NITROANILINES		
				Ortho	Para	Meta
		degrees C.	*per cent*	*per cent*	*per cent*	*per cent*
4 g.	40 cc.	0	29.7	82.1	2.9	15.0

Here there is the same preponderant yield of the ortho isomer, but the para and the meta isomers also occur in appreciable amounts, the former to a greater degree than the latter. Proof that this reaction is not the usual type, but in fact a molecular rearrangement, is provided by Holleman and his collaborators. They treated phenylnitroamine with sulfuric acid and secured the results given below:

PHENYL-NITROAMINE	SULFURIC ACID (74 PER CENT)	TEMPERATURE	YIELD	NITROANILINES		
				Ortho	Para	Meta
		degrees C.	*per cent*	*per cent*	*per cent*	*per cent*
5 g.	50 cc.	−20	66.1	95	3.5	1.5

Comparison of these results with those above suggests at once that the formation of phenylnitroamine is an intermediate step in the conversion of aniline nitrate to nitroaniline. The function of the glacial acetic acid would appear to be that of a dehydrator, and indeed it may be that acetic anhydride (as in Hoff's experiment) might act so strongly as to prevent meta substitution completely. The same workers have nitrated aniline with nitric acid in a sulfuric acid medium. They have also treated aniline nitrate with concentrated sulfuric acid, both with and without nitric acid. Their results are given in table 8.

It is strange that so little of the ortho isomer occurs and that the main yield is divided between the meta and para isomers. In comparing these figures with those for conversion of aniline nitrate and phenylnitroamine with acetic acid and sulfuric acid, respectively, it is fairly obvious that in this case a different reaction mechanism is involved. A determination of the temperature influence might also serve to distinguish these two cases. The principal value of this study, however, is in demonstrating the simultaneous formation of all three isomers and the fact that meta substitution does occur so prominently.

TABLE 8

Nitration of aniline at −20°C.

NO.	CC. OF SULFURIC ACID PER GRAM OF ANILINE	NITROANILINES			PER CENT YIELD AT −20°C.
		Ortho	Meta	Para	
		per cent	*per cent*	*per cent*	
1	5	1.4	47.9	50.7	75
2a	20	2.1	46.6	51.3	94.5
2b	20	1.0	47.5	51.5	97
3	50	1.3	49.1	49.6	80
4	3 g. of aniline nitrate in 40 cc. of H_2SO_4 (95 per cent)	4.0	39.0	56.0	91
5	3 g. of aniline nitrate in 40 cc. of H_2SO_4 (90 per cent)	4.5	39.5	56.0	92
6	2 g. of aniline nitrate in 40 cc. of H_2SO_4 (80 per cent) 20 cc. HNO_3	5.0	32.0	62.0	91

Other investigators, using a variety of nitrating agents, have generally obtained more of the ortho than of the para and none of the meta isomer. This was the case with Witt and Utermann (210), who used a mixture of nitric acid and either acetic anhydride or glacial acetic acid. Both Francis (65), using benzoyl nitrate in carbon tetrachloride, and Pictet (162), using acetyl nitrate in dilute carbon tetrachloride or acetic anhydride, obtained the ortho derivative exclusively. It must be mentioned however that all these investigations were made with acetanilide. Notwithstanding this, Menke (142) did obtain the pure ortho isomer from aniline by nitration with cupric nitrate trihydrate in an acetic anhydride medium and at a temperature below 30°C. Quite opposed to this finding is that of Bacharach (10). Using lithium nitrate instead of cupric nitrate, he obtained only the *p*-nitroacetanilide. Bacharach himself suggested that the difference is caused by the nature of the nitrate. Yet here again, when in the presence of acetic anhydride, it is probably acetanilide which results.

Thus, it is generally either an aniline salt or acetanilide which is nitrated and for this reason it is difficult to judge the orienting influence of the amino group. Only in the work of Bamberger are these complications absent. The use of nitrogen pentoxide or peroxide in an ether medium apparently gives the best results. Nitration of acetanilide also gives the ortho and para isomers and thus it would seem that the influence of the acetamino group is very close to that of the amino group. Meta substitution in excess of the other types occurs only in the presence of sulfuric or nitric acid or by conversion of aniline nitrate or phenyl nitroamine. Inasmuch as Holleman and his coworkers have shown that nitration of acetanilide in the presence of sulfuric acid with nitric or acetic acid or with acetyl nitrate all lead to some meta substitution, it seems fair to assume that meta substitution occurs normally together with ortho and para substitution. Attributing any extensive meta substitution to the presence of the amino salt group, and neglecting Bacharach's result with lithium nitrate, it then appears that the sulfuric and nitric acids reagent causes substitution in the para position, while nitrates such as acetyl nitrate, benzoyl nitrate, or cupric nitrate cause substitution mainly in the ortho position. Thus with this type of evidence it is well-nigh impossible to designate the orienting influence of the amino substituent.

The sulfonation of aniline has not received the attention it merits except in a few instances. In the first place Gattermann (73) states that sulfonation with concentrated sulfuric acid leads to a satisfactory yield of the para isomer, namely sulfanilic acid, and adds that small amounts of the ortho isomer are simultaneously formed. Though he mentions no meta substitution, Armstrong and Berry (4) report the partial conversion of aniline sulfate into *m*-anilinesulfonic acid when treated with fuming sulfuric acid. It may therefore be assumed that all three isomers are formed, at least in some cases. Of considerably greater significance, however, is the work of Bamberger and Hindermann (16) and of Bamberger and Kunz (17). They found that in the sulfonation of aniline, the sulfate was first formed, then dehydrated to give phenylsulfamic acid, which was then transformed into *o*- and *p*-anilinesulfonic acids. Furthermore, Holleman (98, p. 143) states that aniline may be converted into phenylsulfamic acid by treatment in the cold with either chlorosulfonic acid or fuming sulfuric acid. The potassium salt of this derivative treated with glacial acetic acid and a few drops of sulfuric acid and allowed to stand at 0°C. for 80 hours changes over to the extent of about 44 per cent into *o*-anilinesulfonic acid. The ortho isomer, however, when heated for 7 hours with concentrated sulfuric acid at 180–190°C., is transformed into the para acid. This change appears to be quite analogous to that of *o*-toluenesulfonic acid into its para isomer. It has already been suggested that toluene follows an analogous reaction scheme. In any case it is of peculiar interest, since both phenol and benzoic acid are also sulfonated in a strictly similar manner.

Although sulfonation indicates the amino substituent to be a para orienting group, the evidence shows that the ortho isomer is first formed. Nevertheless the combined evidence of halogenation, nitration, and sulfonation leads to no definite conclusion, although much is thereby learned concerning the mechanism of substitution reactions.

THE HALO SUBSTITUENTS: (CHLORO-, BROMO-, AND IODO-BENZENE)

Generally, the introduction of a second substituent into the nucleus of chloro-, bromo-, or iodo-benzene is very much the same problem. Furthermore, the orienting influence of each is so nearly the same that they may profitably be considered together. For the sake of brevity, however, the evidence in regard to halogenation will not be given according to each separate investigation but rather collectively. (See, however, the supplementary references.)

The evidence as a whole shows that the presence of a catalyst such as aluminum chloride, ferric chloride or bromide, thallous chloride, aluminum, or iron, as well as heating, greatly facilitates both chlorination and bromination. Also iodination is effected through the presence of iodic, sulfuric, or nitric acids and usually heating. Although para substitution prevails, there is no evidence to prove that substitution at the other positions does not occur. Indeed, several investigators report substitution in all three positions. In each of these cases, however, a catalyst was present. Also it is apparent that no distinction can be made between the orienting influences of the three halo substituents.

Holleman and van der Linden (113) chlorinated and brominated both bromo- and chloro-benzene. Their results are presented in table 9. Athough they halogenated in the presence of a catalyst in every experiment except one, this one case is sufficient to show that, even in the absence of a catalyst, substitution occurs at all three positions. In addition one can see that para substitution prevails in all cases, though a considerable amount of the ortho isomer is also formed. One should notice especially, however, the case of bromination of bromobenzene in presence of aluminum powder. The 19 to 30 per cent of the meta isomer does not substantiate the idea that ortho and para substitution are closely related and opposed to meta substitution.

But before going on to nitration, attention should be called to an investigation carried out by Copisarow (43). He showed that the action of aluminum chloride on bromobenzene caused the formation not only of dibromobenzene, of which all three isomers occurred though principally the para isomer, but also of benzene. In a similar way Neumann (151) obtained diiodobenzene by heating iodobenzene with concentrated sulfuric acid. Apparently a halogen atom is transferred from one nucleus to another.

Concerning the nitration of these derivatives, the studies of Holleman and de Bruyn (101, 102, 106) are the most thorough and satisfactory.

TABLE 9

Halogenation of chloro- and bromo-benzene

CATALYST	ORTHO	META	PARA
a. Chlorination of PhCl at 55–75°C.			
	per cent	*per cent*	*per cent*
$AlCl_3$	29.5 to 30	4 to 5	65.5 to 66
$FeCl_3$	38.5 to 39.5	4 to 5	54 to 56
b. Chlorination of PhBr			
$FeCl_3$	41.5 to 42	6 to 7	51 to 52.5
$AlCl_3$	30 to 34	4.5 to 8	57 to 65
c. Bromination of PhCl			
Al powder	11 to 15	6 to 13	75 to 78
Fe powder	11 to 11.5	1.2 to 1.7	87 to 88.5
None	17.5	1.2	81.3
d. Bromination of PhBr			
Al powder	8 to 10	19 to 30	61 to 71
Fe powder	13.1 to 13.7	1.8 to 1.9	84 to 85

TABLE 10

Nitration of chlorobenzene, bromobenzene, and iodobenzene with nitric acid (1.5)

	NITRATION AT −30°C.			NITRATION AT 0°C.		
	PhCl	PhBr	PhI	PhCl	PhBr	PhI
Percent ortho isomer	26.6	34.4	39.1	29.8	37.6	41.1
Per cent of para isomer	73.1	65.3	60.9	69.9	62.1	58.7

Their collected results (see table 10) permit a comparison of the orienting influences of the three halo substituents and show in addition the important influence of temperature. Three points may be mentioned with regard to these results: (1) No meta substitution apparently occurs. (2) Higher temperatures favor ortho substitution. (3) The chloro substituent exerts a stronger para orienting influence than the bromo substituent just as in the case of halogenation. Thus although this reaction is normal in respect to the temperature effect, it is abnormal with respect to the absence of meta substitution.

Although several workers studied this problem previous to Holleman, none of their work is of any significance excepting that of Coste and Parry (44). Their results are given in table 11. It is strange that the cold fuming acid gives a greater yield than the hot fuming acid. But more unusual is the fact that less *o*-nitrobromobenzene is obtained at the higher temperatures than at the lower. In all other cases of nitration higher temperatures increase the amount of ortho isomer.

As for the more recent studies, those of Schaarschmidt (175) should be mentioned. He used nitrogen peroxide in the presence of aluminum or ferric chloride to nitrate bromobenzene and obtained the ortho and para isomers in the ratio of six to ninety-four, respectively. Inasmuch as Wieland obtained the para isomer exclusively when nitrating phenol with nitrogen peroxide, these results do not seem to be caused by the catalyst This supposition has indeed been confirmed by Schaarschmidt and his coworkers (176) in a subsequent investigation. This time they nitrated with nitrogen peroxide, but in a carbon tetrachloride solution and without a catalyst. With chlorobenzene 22 per cent of the ortho and 78 per cent of the para isomer were obtained; with bromo- and iodo-benzene, 5 per cent of the ortho and 95 per cent of the para isomers were obtained. Thus with bromobenzene the proportion of the isomers was approximately the same. Schaarschmidt himself states that the presence of the aluminum chloride, though it increased the yield to 80 to 90 per cent, produced little change in the ratio of isomers. He adds that change of temperature similarly had slight effect. In the presence of aluminum chloride, however, he has found an intermediate addition compound, $2AlCl_3 \cdot 3N_2O_4 \cdot 3C_6H_5Br$. It may be through this compound that the aluminum chloride aids the reaction.

TABLE 11

Nitration of bromobenzene

NITRATING AGENT	PARA ISOMER	ORTHO ISOMER	YIELD	PARA/ORTHO RATIO
	per cent	*per cent*	*per cent*	
Fuming HNO_3 at 100°C	65.3	34.7	66.3	1:0.53
Cold fuming HNO_3	60.5	39.5	95.2	1:0.65
HNO_3 (1.42) + H_2SO_4	69.4	30.6	97.7	1:0.44
HNO_3 + H_2SO_4 in glacial acetic acid	ca. 66.0	ca. 34.0	81.4	1:0.51
HNO_3 + H_2SO_4 in glacial acetic acid	66.3	33.7	89.4	1:0.51

Quantitative yields of the para isomer from both bromo- and iodobenzene have been obtained by Varma and Kulkarni (202), who nitrated with a mixture of nitrosulfuric and nitric acids. By employing nitrogen pentoxide, Adkins (1) has also obtained a quantitative yield of *p*-nitrobromobenzene.

A final example of the nitration of halobenzenes is the work of Nagidson and Kalishevski (149). They state that nitration of chlorobenzene with nitric acid yields the para isomer principally, whereas nitration with sodium nitrate and sulfuric acid leads chiefly to the ortho isomer. But the formation of considerable 2,4-dinitrochlorobenzene in the latter case invalidates their conclusion.

The information concerning sulfonation is quite definite though not very extensive. In all cases the para isomer is obtained practically to exclusion of the other isomers. For instance, Otto (160) has sulfonated chlorobenzene with strong sulfuric acid. He obtained pure *p*-chlorobenzene sulfonic acid, which was proved to be the only isomer formed. More recently Ray and Day (167) have sulfonated chlorobenzene and bromobenzene at 110°C. and 100°C., respectively, using sulfuric acid (1.84) and a trace of iodine. They state that whereas other methods of sulfonation lead to a mixture of the ortho and para isomers, their method yields only the para derivative. That their results are actually caused by iodine is to be doubted. Bromobenzene has also been sulfonated by other workers, all of whom obtained only the para isomer (84, 144, 152). Chlorosulfonic acid likewise reacts with bromobenzene to yield the para isomer, as has been shown by Beckurts and Otto (21). Koerner and Paterno (131) obtained the para derivative by sulfonation of iodobenzene with concentrated sulfuric acid at water bath temperature. On the whole it appears that the same result is obtained whether chloro-, bromo-, or iodo-benzene is sulfonated. In fact, with strong acids and heating, para substitution prevails almost exclusively. No ortho substitution has been detected, yet it is possible that transformation to the para isomer has caused it to be overlooked. It is obvious that a more thorough study of this question is needed.

In view of all the experimental facts, the halobenzenes appear as the strongest of para orienting derivatives yet considered. But there is considerable evidence lacking. For instance, it is only with halogenation that substitution in all three positions is known to occur. For nitration, it is a question whether meta substitution takes place, while for sulfonation it is ortho as well as meta substitution which is doubtful. Inasmuch as all three isomers can be prepared by halogenation, it seems likely that the same should be the case for nitration and sulfonation. In general, further investigation is desirable before any more conclusions be drawn.

TABLE 12

The orienting influence of some derived substituents

SUBSTITUENT	DISUBSTITUTED BENZENES			TEMPERATURE	REFERENCE NUMBER
	Ortho	Meta	Para		
	per cent	*per cent*	*per cent*	*degrees C.*	
—COCl	?	90.2	2.1	−10	(42)
—COOH	18.5	80.2	1.3	0	(100)
—CHO	21.4*	78.6		10	(64)
—COOMe	21.0 (low)	73.2	5.8 (high)	0	(100)
—COOEt	28.3	68.4	3.3	0	(100)
—$COOC_8H_{17}$ (*n*)	39.8*	60.2		0	(211)
—$COCH_3$	45	55	—	0	(98)
—$COOC_{16}H_{33}$ (*n*)	48*	52		0	(211)
—$COOCH_2Br$	?	*m*	?		(119)
—$CH_2N(CH_3)_2$, picrate	?	88	?	−5	(85)
—CN	*o*	80.5	(*p*)	0	(12)
—$CH_2NH(CH_3)$	?	69	?	−5	(85)
—$CH(CN)_2$	32.1*	67.9		−10	(64)
—CCl_3	6.8	64.5	28.7	25	(103)
—CH_2NMe_2	?	58	?	0	(86)
—$C(COOEt)_3$	43.4*	56.6		−10	(63)
—CH_2NO_2	*o*	50	14	0	(13)
—CH_2NH_2	8	49	43	0	(86)
—CH(OH)CN	56.4*	43.6		−9	(64)
—CH(COOEt)CN	62.8*	37.2		−9	(64)
—$CHCl_2$	23.3	33.8	42.9	25	(103)
—$CH_2CH_2NMe_2$ picrate	13	21	66	0	(85)
—CH_2CH_2NHMe	*o*	15	61	−8	(85)
—$CH_2CH_2NMe_2$	20	14	66	−8	(85)
—CH_2CN	17	14	69	−13	(12)
—$CH_2CH_2NH_2$	23	13	64	−5	(85)
—$C{\vdots}C{\cdot}COOH$	27	7.7	65.0	−30	(12)
—CH_2Br	93*	7		17	(63)
—$C{\vdots}C{\cdot}COOEt$	36	6.1	57.9	−30	(12)
—CH_2Cl	40.9	4.2	54.9	25	(103)
—CH_3	58.0	3.9	38.1	0	(114)
—CH_2CH_2Cl	ca. 30	(*m*)	ca. 70	−13	(108)
—CH:CHCOOH	*o*	?	*p*	0	(201)
—NO_2	4.8	93.2	1.7	0	(105)
—NH_3HSO_4	2.1	46.6	51.3	−20	(107)
—NH_3NO_3	5	32	62	−20	(107)
—OCH_3	*o*	—	—		(162)
—OC_2H_5	*o*	—	—		(162)
—OH	57.6	3.3	40.0	10	(5)

TABLE 12—*Concluded*

SUBSTITUENT	DISUBSTITUTED BENZENES			TEMPERATURE	REFERENCE NUMBER
	Ortho	Meta	Para		
	per cent	*per cent*	*per cent*	*degrees C.*	
$-OCOOC_2H_5$	(*o*)	?	*p*		(75)
$-NH_2$ (in ether medium)	*o*	—	*p*	−20	(14)
$-N(CH_3)_2O$	ca. 50	?	ca. 50	0	(18)
$-NH(C_6H_5CO)$	41.1	1.5	57.4	−20	(107)
$-N(CH_3CO)_2$	40.4	1.6	58.0	−20	(107)
$-N(CH_2C_6H_5)NO$	24	—	76	0	(170)
$-NH(C_2H_5CO)$	21.1	1.2	77.7	20	(6)
$-NH(CH_3CO)$	19.4	2.1	78.5	20	(6)
$-NH(HCO)$	18.1	2.0	79.7	20	(6)
$-N{:}CHC_6H_5$	5.5	0.6	93.9	20	(6)
$-NO$	?	?	*p*		(120)
$-SH$	(No data)				
$-SCN$	20	0	80	0	(32)
$-SCH_3$ (sulfonation)	10	—	90		(115)
$-SCH_3$ (bromination)	6	—	94		(115)
$-SO_2CH_3$ (bromination)	—	—	*p*	100	(29)
$-S_2C_6H_5$ (bromination)	—	—	*p*		(29)

* After number, signifies per cent of ortho and para isomers together.
o, *m*, and *p* signify large amounts of ortho, meta, and para isomers, respectively.
( ) signify smaller amounts of respective isomers.
— signifies apparent absence of respective isomer.
? signifies the formation of this isomer to be a question.

DERIVED SUBSTITUENTS

Though in concluding the discussion of the halobenzenes the principal purpose of this paper has been accomplished, it may prove of value to consider briefly some other substituents. These may be looked upon for the most part as derivatives of simpler radicals and in the presentation of the following data are therefore termed derived substituents. With a few exceptions the evidence is taken from studies on nitration. The omission of halogenation and sulfonation, where side chain substitution and molecular rearrangements are common, has been deemed advisable for the sake of comparable figures. Thus the data on the proportion of isomers formed by the mononitration of about fifty derived substituents have been collected and presented in table 12. Though strictly comparable reaction conditions are probably not attainable, figures representing such conditions were chosen where possible. Again, the effect of temperature is not very pronounced, but it seemed advisable to indicate the approximate reaction temperature. Furthermore, the order of the substituents has been chosen primarily so as to place them in groups according to the simplest substituent to which each seems most closely related, and secondly in the order of decreasing meta substitution. When the formation of the meta isomer becomes virtually negligible, the order is that of increasing para substitution.

In several cases the relation of the type and derived substituents may not seem obvious. Thus the —COOH radical and its derivatives should belong to the toluene group. Yet the benzoic acid group is sufficiently characteristic to be placed apart. The $—NH_3X$ radicals may also seem to be misplaced, but their directive influence relates them rather to the $—NO_2$ than to the $—NH_2$ substituent. Incidentally, the covalency of the nitrogen in both the $—NH_3X$ and the $—NO_2$ radicals is four, as contrasted to three in the $—NH_2$ radical. It should also be explained that the data for aniline have been particularly chosen. The nitration was accomplished with nitrogen pentoxide in an ether medium, conditions which presumably would prevent the formation of the salt complex. Unfortunately the derivatives of thiophenol have not been investigated by nitration, and for this reason the evidence from bromination and sulfonation has been given.

Though this tabulation is presented for whatever value it may have, there are several observations which can be offered. The practically general occurrence of all three isomers, the exclusive or nearly exclusive formation of any one, and the occurrence in virtually like amounts of any two isomers to the exclusion of the third are all apparently possible results. This lack of any limitation to the proportions in which the isomers occur suggests a certain equality among them. Furthermore, it is also seen that when the percentage of either the meta or para isomer becomes overwhelming, the principal by-product is the ortho isomer. This generalization favors the view that a substituent is of either an ortho-para or ortho-meta directing type. But it must also be pointed out that if ortho substitution preponderates, the chief by-product is never the meta isomer. Under such circumstances there is an apparent relation between ortho and para substitution which is in support of the orthodox conception.

In once more considering the arrangement of table 12, it must be said that the conception according to which similar directive influences are to be expected among structurally related compounds is quite in accord with the usual point of view. Yet the —CN radical, for example, exhibits a directive influence which is scarcely similar to that of toluene. This contradiction is possibly only apparent, for there are several cases where the normally accepted directive influence of a substituent has been reversed. An excellent illustration is the nitration of benzaldehyde, as studied by Reddelien (168). Having isolated an addition compound between benzaldehyde and nitric acid of the type $C_6H_5CHO \cdot HNO_3$, he treated it on the one hand with sulfuric acid and on the other with acetic anhydride in addition to the acid. In the former case, the chief product was *m*-nitrobenzaldehyde and in the latter case, *p*-nitrobenzaldehyde. He further indicates that whereas traces of *o*-nitrobenzaldehyde were found in both cases, on neither occasion did the para and meta derivatives occur together. Furthermore it will be recalled that benzoic acid (or more properly, the alkali benzoate) may be halogenated principally in the ortho and para positions under suitable conditions. Other examples are the introduction of the carboxyl group into the ring of benzoic acid in the ortho and para positions and similarly the mercurization of the same compound at the ortho position (6). On the other hand, the work of Shoesmith and McGechen (185) has shown how meta substitution may occur in the ring of a typical para orienting compound. They found that toluene treated with *tertiary*-butyl chloride and aluminum or ferric chloride gave *tertiary*-butyltoluenes, both meta and para, in the ratio of about seventy of the former to about thirty of the latter. And finally, the nitration of phenylboric acid is of interest in this respect. Ainley and Challenger (2) found that nitration of this compound gave 71.9 per cent of *m*-nitrophenylboric acid and 28.1 per cent of its ortho and para isomers together. But Seaman and Johnson (181), using an excess of fuming nitric acid in the presence of acetic anhydride, obtained a total yield of 65 per cent, of which 95 per cent was *o*-nitrophenylboric acid and 5 per cent its para isomer. However one may interpret such results, they inevitably suggest that a given substituent need not possess an unalterable directive influence.

It is possible that reversed directive influence is caused by a difference in the mechanism of the substitution reaction. But whether or not an explanation can be found along such lines, reaction mechanism is a factor which cannot be overlooked. Though various hypotheses have been proposed, no complete theory has been accepted. At the same time it is apparently clear that substitution reactions belong to two general classes. Thus it is usual to distinguish between direct and indirect substitution as between direct replacement of hydrogen atoms and formation of an intermediate compound with side chain. A discussion of this matter is given by Blanksma (26) and also later by Holleman (98). A very similar distinction between two types of reaction mechanism can be based on the influence of temperature. In many cases, especially those of nitration, the effect of higher temperature is invariably to increase the proportion of the ortho isomer. However in the sulfonation of several aromatic compounds, notably toluene, aniline, and phenol, the effect of higher temperature is to increase the proportion of the para isomer. The fact that molecular rearrangements within the benzene ring are known to occur only in the second type, suggests that these are indirect reactions.

Believing therefore that such rearrangements as well as those involving the side chain are of importance, a number of interesting cases have been collected. Many of these are provided by Porter (165) incidental to his monograph on molecular rearrangements. In the first place he presents a case which throws additional light to the nitration of aniline, namely, the conversion of phenylnitroamines to nitroanilines. He says that phenylnitroamine, when warmed with sulfuric acid or dissolved in acetic acid saturated with hydrogen chloride, rearranges to form *o*- and *p*-nitroaniline. Inasmuch as phenylnitroamine is formed by nitrating aniline with nitrogen pentoxide or by warming aniline nitrate with acetic anhydride, this rearrangement would appear to play an integral part in the formation of the nitroanilines. When the para position is blocked as in 2,4-dichloro-1-nitroaminobenzene the rearrangement, following the unimolecular law, leads to the 2,4-dichloro-6-nitroaniline, corresponding to ortho substitution. But it is of some interest that 2,6-dibromo-1-nitroaminobenzene has been reported to yield a mixture of 2,6-dibromo-4-nitroaniline and 2,4-dibromo-6-nitroaniline, whereas direct nitration of 2,6-dibromoacetanilide yields only the *p*-nitro derivative (165). In commenting on these facts, Porter says that this rearrangement probably occurs regularly in the nitration of any aromatic amine. Furthermore, he says that both Armstrong and Bamberger have proposed the theory that all nucleus substitutions in aromatic amines are preceded by the formation of such addition products. In this respect it is significant, as in another example given by Porter, that the first step in the mercurization of aromatic amines has been shown to be the addition of mercuric chloride or mercuric acetate to the amino group, this being followed by a shift to the ortho or para position. That *p*-nitrodimethylaniline, which is too weak a base to form an amino-mercury salt, cannot be mercurized in the ring is offered as further evidence in favor of this mechanism.

Turning to the sulfonation of aniline, a reaction which is believed to proceed in a fashion strictly analogous to the nitration of aniline, further interesting evidence is available. Thus aniline sulfate is supposedly first formed, followed by a splitting-off of water to form phenylsulfamic acid. On heating, this yields principally the *p*- and some of the *o*-aminobenzenesulfonic acid (73). Porter states that the temperature of the reaction determines the quantity of each of these products and that at temperatures above 180°C. the para derivative is obtained exclusively. A very similar case is that of α-naphthylamine, which on sulfonation yields first a sulfamic acid, which is subsequently converted at higher temperatures to 1-naphthylamino-4-sulfonic acid (73). From these cases involving aniline it seems very probable that an addition compound is first formed by the reagent adding on to the original substituent, followed by a splitting-off of water to give a definite compound, and finally by a molecular rearrangement either to the para or the ortho position. It also seems possible that higher temperatures favor rearrangement to the para position at the expense of the ortho isomer. Whether formation of the para compound is preceded by rearrangement to the ortho position or whether it is formed directly cannot be definitely decided, although the experiment already mentioned concerning 2,6-dibromo-l-nitroaminobenzene, in which the ortho positions were both blocked by bromine atoms, might possibly mean that the ortho derivative must be formed first, for this isomer was definitely found among the products. Some support for this idea is lent by such analogous cases as the sulfonation of toluene and the sulfonation of benzoic acid, in which the ortho isomer appears to be an intermediate product.

Many other examples apparently indicating such a substitution reaction mechanism are also offered by Porter. Thus, diacetanilide rearranges on heating into the *o*- and *p*-acetylaminoacetophenone, although acetanilide fails to undergo such a process. *β*-Phenylhydroxylamine is converted into *p*-aminophenol when heated with sulfuric acid. That the *o*-aminophenol is formed too is also implied by Porter. The transformation of acetylchloroaminobenzene into *o*- and *p*-chloroacetanilide has also received Porter's attention. He presents the following facts with regard to this rearrangement: It is unimolecular and may be brought about by exposure to light. Hydrochloric and hydrobromic acids cause a rapid and quantitative conversion to the chloroacetanilides. Although a number of workers propose that the conversion is caused by intermediate formation of hypochlorous acid or other reagents, followed by direct chlorination, further information shows that such is not necessarily the case. Thus the reaction proceeds more rapidly in non-aqueous solvents such as benzene, glacial acetic acid, or absolute alcohol than in the presence of water. The rearrangement occurs in dry benzene solution in total absence of any electrolyte, merely on exposure to light. That the conversion is actually a molecular rearrangement seems probable, especially in view of the fact that dry crystals of acetylchloroaminobenzene when exposed to light gradually go over to *o*- and *p*-chloroacetanilide and that the same change can be brought about in a few minutes by heat alone.

The formation of *p*-toluidines from alkylaminobenzenes is also discussed by Porter. This reaction has been shown to occur between two groups in the single molecule; heating seems to be necessary; and no rearrangement to the ortho position is reported to occur. Similarly, methylene derivatives such as $PhNH—CH_2—NHPh$, when warmed with hydrochloric acid or an excess of the amine hydrochloride, undergo a rearrangement which results in the attachment of the methylene group to the para carbon atoms of the benzene nucleus. But if the para position is occupied, the migrating group goes to the ortho position. In addition to these examples, Porter also reports that triphenylmethylaniline when heated with half its weight of zinc chloride for 15 minutes at 160°C. is converted into *p*-aminotetraphenylmethane. He likewise refers to the case where, in an alcoholic or an aqueous solution of hydrogen chloride, nitrosoamines are transformed into *p*-nitrosoanilines. A final example of this class is the conversion of phenylhydrazine hydrochloride into *p*-phenylenediamine when heated to 200°C.

The numerous examples above certainly add credence to the particular mode of substitution reaction under consideration, at least with amino derivatives. But other types of benzene derivatives also provide similar evidence. The conversion of phenyl allyl ether into *o*-allylphenol, although it offers no strict analogy with any substitution reaction, is of interest (165). Porter also presents the conversion of sodium phenyl carbonate to sodium *o*-hydroxybenzoate when heated to 120–140°C. in an autoclave. Similarly potassium phenylsulfate is converted by heat into the salt of *p*-hydroxybenzenesulfonic acid. These examples are given by Porter, and he further indicates that the rearrangements go to the ortho position at lower temperatures and to the para position at higher temperatures. Another type of addition compound formation is provided by the work of Bourgeois and Abraham (29) in regard to the bromination of thio derivatives. If the transformation of benzoyl nitrate as previously described be recalled, still another type is added to the above evidence. Likewise attention should be called again to Reddelien's study concerning benzaldehyde and the author's work on the sulfonation of benzoic acid. That the sulfonation of phenol may be preceded by the formation of phenylsulfuric acid must also be remembered. With regard to the monohalogenated benzenes, there is the formation of phenyliodosochloride and its conversion to *p*-chloroiodobenzene (98).

Although a majority of these examples involve amino compounds, there is actually a fair variety in which such rearrangements occur. Indeed the nature of these rearrangements indicates that introduction to the side chain followed by rearrangement to the ring is at least a possible mechanism. Though the scheme cannot be applied to all cases of aromatic substitution, it nevertheless gives a clear meaning to that type of reaction designated as indirect. Of the other type of reaction, direct substitution, no more will be said than that it is apparently characterized by direct entry of the incoming substituent to its ultimate position.

In conclusion it is hoped that, even though little attention has been given to the theoretical side, this review of just a limited portion of the experimental evidence may serve to help toward a proper understanding of the problem.

The author desires herewith to express his most sincere appreciation of the encouraging and helpful advice of Professor E. Emmet Reid of The Johns Hopkins University.

REFERENCES

(1) Adkins: J. Am. Chem. Soc. **47**, 1419–26 (1925).
(2) Ainley and Challenger: J. Chem. Soc. **1930**, 2171–80.
(3) Andrich and LeBlanc: Chem. Zentr. **1916**, I, 606.
(4) Armstrong and Berry: Proc. Chem. Soc. **16**, 159 (1900).
(5) Arnall: J. Chem. Soc. **125**, 811–6 (1924).
(6) Arnall and Lewis: J. Soc. Chem. Ind. **48**, 159–60T (1929).
(7) Aronheim and Dietrich: Ber. **8**, 1401–5 (1875).
(8) Auger and Vary: Compt. rend. **173**, 239–40 (1921).
(9) Auwers: Ber. **35**, 456 (1902).
(10) Bacharach: J. Am. Chem. Soc. **49**, 1522–7 (1927).
(11) Baines: J. Chem. Soc. **121**, 2810–3 (1922).
(12) Baker, Cooper, and Ingold: J. Chem. Soc. **1928**, 426–31 (1928).
(13) Baker and Ingold: J. Chem. Soc. **1926**, 2462–75 (1926).
(14) Bamberger: Ber. **27**, 584–7 (1894).
(15) Bamberger: Ber. **27**, 671 (1894).
(16) Bamberger and Hindermann: Ber. **30**, 654–5 (1897).
(17) Bamberger and Kunz: Ber. **30**, 2274–7 (1897).
(18) Bamberger and Tschirner: Ber. **32**, 1882–903 (1899).
(19) Bancroft: J. Phys. Chem. **12**, 417–47 (1908).
(20) Beaumont and Haemmerle: Chem. Abstracts **23**, 1122 (1929).
(21) Beckurts and Otto: Ber. **11**, 2061–6 (1878).
(22) Beilstein and Geitner: Ann. **139**, 331–42 (1866).
(23) Beilstein and Kuhlberg: Ann. **155**, 1–29 (1870).
(24) Beilstein and Kurbatow: Ann. **182**, 102 (1876).
(25) Beilstein and Schlumm: Ann. **133**, 248 (1865).
(26) Blanksma: Rec. trav. chim. **21**, 282 (1902).
(27) Boedtker: Bull. soc. chim. [4] **3**, 726–9 (1908).
(28) Bornwater and Holleman: Rec. trav. chim. **31**, 236 (1912).
(29) Bourgeois and Abraham: Rec. trav. chim. **30**, 407–25 (1911).
(30) Bramley: J. Chem. Soc. **109**, 436 (1916).
(30a) Bruner and Vorbrodt: Chem. Zentr. **1909**, I, 1807–8.
(31) Bruns: Ber. **28**, 1954–5 (1895).
(32) Challenger, Higginbottom, and Huntington: J. Chem. Soc. **1930**, 26–34.
(33) Chandelon: Ber. **16**, 1749–53 (1883).
(34) Chattaway and Orton: J. Chem. Soc. **79**, 461–9 (1901).
(35) Claus and Buecher: Ber. **20**, 1623 (1887).
(36) Claus and Reh: Ann. **266**, 209 (1891).
(37) Cohen and Dakin: J. Chem. Soc. **75**, 893–6 (1899).
(38) Cohen and Dakin: J. Chem. Soc. **79**, 1111–34 (1901).
(39) Cohen, Dawson, and Crossland: J. Chem. Soc. **87**, 1034–7 (1905).
(40) Cohen, Dawson, etc.: J. Chem. Soc. **97**, 1623–36 (1910).

(41) Cohen and Hartley: J. Chem. Soc. **87,** 1360–7 (1905).
(42) Cooper and Ingold: J. Chem. Soc. **1927,** 836–41.
(43) Copisarow: J. Chem. Soc. **119,** 442–7 (1921).
(44) Coste and Parry: Ber. **29,** 788–92 (1896).
(45) Datta and Chatterjee: J. Am. Chem. Soc. **38,** 2545–52 (1916).
(46) Datta and Chatterjee: J. Am. Chem. Soc. **39,** 435–41 (1917).
(47) Datta and Chatterjee: J. Am. Chem. Soc. **41,** 292–5 (1919).
(48) Datta and Fernandes: J. Am. Chem. Soc. **36,** 1007–11 (1914).
(49) Davis, Worral, Drake, Helmkamp, and Young: J. Am. Chem. Soc. **43,** 594–607 (1921).
(50) Dimroth and Schmaedel: Ber. **40,** 2411 (1907).
(51) Dubois: Z. Chem. **1866,** 705–6.
(52) Dubois: Z. Chem. **1867,** 205–7.
(53) Dumreicher: Ber. **15,** 1866–70 (1882).
(54) Edinger and Goldberg: Ber. **33,** 2875–83 (1900).
(55) Edinger and Goldberg: Ber. **33,** 2883–85 (1900).
(56) Ekbon: Ber. **35,** 651–6 (1902).
(57) Elbs and Jaroslawzew: J. prakt. Chem. [2] **88,** 92–4 (1913).
(58) Elbs and Volk: J. prakt. Chem. [2] **99,** 269–75 (1919).
(59) Faust and Mueller: Ber. **5,** 777–9 (1872).
(60) Fichter and Glanzstein: Ber. **49,** 2473–87 (1916).
(61) Fittig: Z. Chem. **1871,** 449–50 (1871).
(62) Fittig and Ramsay: Ann. **169,** 242–61 (1873).
(63) Fluerscheim and Holmes: J. Chem. Soc. **1928,** 1607–16.
(64) Fluerscheim and Holmes: J. Chem. Soc. **1928,** 2230–42.
(65) Francis: Ber. **39,** 3798–804 (1906).
(66) Francis: Proc. Chem. Soc. **21,** 302–3 (1905).
(67) Francis, A. W.: Chem. Rev. **3,** 257–89 (1926).
(68) Fries: Ann. **346,** 128–59 (1906).
(69) Friswell: J. Soc. Chem. Ind. **27,** 258 (1908).
(70) Fritzche: J. prakt. Chem. [1] **73,** 296 (1858).
(71) Fuchs: Monatsh. **36,** 138 (1915).
(72) Garrick: Z. Chem. **1869,** 549–55.
(73) Gattermann: Die Praxis des organischen Chemikers, 21st edition, pp. 186–7. Berlin and Leipzig (1928).
(74) Gattermann: Die Praxis des organischen Chemikers, 21st edition, pp. 230–1. Berlin and Leipzig (1928).
(75) Gebauer-Fuelnegg and Reese: Monatsh. **50,** 231–4 (1928).
(76) Gebler: Chem. Abstracts **21,** 1450 (1927).
(77) Gibson, Duckham, and Fairbairn: J. Chem. Soc. **121,** 270–83 (1922).
(78) Gilliard, Monnet, and Cartier: Fortschritte der Theerfarbenfabrikation—Friedlaender **4,** 1261 (1894–97).
(79) Glinzer and Fittig: Ann. **136,** 301–3 (1865).
(80) Gluud and Kempf: J. Chem. Soc. **103,** 1530 (1913).
(81) Goldschmidt and Larsen: Z. physik. Chem. **48,** 424–34 (1904).
(82) Goldstein: Ber. **11,** 1943 (1878).
(83) Gomberg and Stone: J. Am. Chem. Soc. **38,** 1601 (1916).
(84) Goslich: Ber. **8,** 352–4 (1875); Ann. **180,** 93–108 (1875).
(85) Goss, Hanhart, and Ingold: J. Chem. Soc. **1927,** 250–61.
(86) Goss, Ingold, and Wilson: J. Chem. Soc. **1926,** 2440–62.

(87) Griess: Ber. **8**, 527 (1875); **10**, 1871 (1877).
(88) Haines and Adkins: J. Am. Chem. Soc. **47**, 1419–26 (1925).
(89) Hantzch and Mai: Ber. **28**, 978 (1895).
(90) Harding: J. Chem. Soc. **119**, 1261–6 (1921).
(91) Hasse: See Holleman, reference 98, p. 156.
(92) Hirtz: See Holleman, reference 98.
(93) Hoff: Ann. **311**, 101–2 (1900).
(94) Hoffman: Ann. **57**, 64–8 (1848).
(95) Holdermann: Ber. **39**, 1250–8 (1906).
(96) Holleman: Ber. **39**, 1715–6 (1906).
(97) Holleman: Chem. Rev. **1**, 187–230 (1924–25).
(98) Holleman: Die direkte Einfuehrung von Substituenten in den Benzolkern. Leipzig (1910).
(99) Holleman: Lehrbuch der organischen Chemie, 18th edition, p. 417. Leipzig (1927).
(100) Holleman: Rec. trav. chim. **18**, 267–91 (1899).
(101) Holleman: Rec. trav. chim. **19**, 188–203 (1900).
(102) Holleman: Rec. trav. chim. **32**, 134–9 (1913).
(103) Holleman: Rec. trav. chim. **33**, 33–4 (1914).
(104) Holleman and Caland: Ber. **44**, 2504–22 (1911).
(105) Holleman and de Bruyn: Rec. trav. chim. **19**, 79–106 (1900).
(106) Holleman and de Bruyn: Rec. trav. chim. **19**, 364–76 (1900).
(107) Holleman, Hartogs, and van der Linden: Ber. **44**, 704–28 (1911).
(108) Holleman and Hoeflake: Rec. trav. chim. **34**, 261–4 (1915).
(109) Holleman and Polak: Rec. trav. chim. **27**, 435–54 (1908).
(110) Holleman and Polak: Rec. trav. chim. **29**, 416–46 (1910).
(111) Holleman and Rinkes: Rec. trav. chim. **30**, 48–100 (1911).
(112) Holleman and van den Arend: Rec. trav. chim. **28**, 408–23 (1909).
(113) Holleman and van der Linden: Chem. Zentr. **1910**, II, 640–1 (1910).
(114) Holleman, Vermeulen, and de Muoy: Rec. trav. chim. **33**, 1–34 (1914).
(115) Hove: Chem. Abstracts **21**, 2256 (1927).
(116) Huebner: Ann. **208**, 299–300 (1881).
(117) Huebner and Brenken: Ber. **6**, 170–4 (1873).
(118) Huebner and Majert: Ber. **6**, 790–5 (1873).
(119) Hunnius: Ber. **10**, 2006–11 (1877).
(120) Ingold: J. Chem. Soc. **127**, 513–8 (1925).
(121) Istrati: Beilstein's Handbuch der organischen Chemie, 4th edition, **5**, 201 (1922).
(122) Jackson and Field: Am. Chem. J. **2**, 1–11 (1880).
(123) Jahresber. Chem. **1875**, 299–320.
(124) Jahresber. Chem. **1875**, 356.
(125) Jannasch and Huebner: Ann. **170**, 117–23 (1873).
(126) Kekulé: Ann. **137**, 169 (1866); Beilstein, 3rd edition, Vol. II, p. 80.
(127) Kekulé: see Holleman, reference 98, p. 65.
(128) Kekulé: Z. Chem. **1866**, 687–9.
(129) Kekulé: Z. Chem. **1867**, 199.
(130) Kidokoro: Chem. Abstracts **11**, 3027 (1917).
(131) Koerner and Paterno: Jahresber. Chem. **1872**, 587–8.
(132) Ladenberg: Ber. **8**, 536 (1875).
(133) Laubenheimer: Ber. **7**, 1765 (1874); **8**, 1621 (1875).

(134) Leeds: Ber. **14**, 482–92 (1881).
(135) Limpricht: Ann. **177**, 60–78 (1875).
(136) Limpricht: Ann. **186**, 134–48 (1877).
(137) Lossen: Chem. Zentr. **1903**, II, 1224.
(138) Lossen: Chem. Zentr. **1904**, II, 1486.
(139) Maarse: Rec. trav. chim. **33**, 207–38 (1914).
(140) Margueyrol and Loriette: Bull. soc. chim. [4] **25**, 370–1 (1919).
(141) Meldola and Streatfield: J. Chem. Soc. **73**, 681–90 (1898).
(142) Menke: Rec. trav. chim. **44**, 141–9 (1925).
(143) Merck in Darmstadt: Fortschritte der Theerfarbenfabrikation-Friedlaender, **3**, 845–6 (1890–94).
(144) Meyer and Noelting: Ber. **7**, 1308–14 (1874).
(145) Michael and Norton: Jahresber. Chem. **1878**, 451.
(146) Monnet, Reverdin, and Noelting: Ber. **12**, 443–5 (1879).
(147) Mouneyrat and Pouret: Bull. soc. chim. [3] **19**, 801–3 (1898).
(148) Mouneyrat and Pouret: Compt. rend. **127**, 1025–8 (1898).
(149) Nagidson and Kalishevski: Chem. Abstracts **22**, 4502 (1928).
(150) Natanson: Ber. **13**, 415–7 (1880).
(151) Neumann: Ann. **241**, 33–89 (1887).
(152) Noelting: Ber. **8**, 594–9 (1875).
(153) Noelting and Forel: Ber. **18**, 2672 (1885).
(154) Obermiller: Ber. **40**, 3623–47 (1907).
(155) Obermiller: J. prakt. Chem. [2] **89**, 70–86 (1914).
(156) Offerman: Ann. **280**, 5–6 (1894).
(157) Olsen and Goldstein: Ind. Eng. Chem. **16**, 66–71 (1924).
(158) Oppenheim: Ber. **3**, 736 (1870).
(159) Orton: Ber. **40**, 370–6 (1907).
(160) Otto: Ann. **143**, 100–17 (1867).
(161) Peltzer: Ann. **136**, 200 (1865).
(162) Pictet: Ber. **40**, 1163–6 (1907).
(163) Pictet and Karl: Bull. soc. chim. [4] **3**, 1114–26 (1908).
(164) Pictet and Khotinsky: Ber. **40**, 1163–6 (1907).
(165) Porter: Molecular Rearrangement, A. C. S. Monograph Series, No. 45. The Chemical Catalog Co., New York (1928).
(166) Post: Ber. **8**, 1547–9 (1875).
(167) Ray and Day: J. Chem. Soc. **117**, 1405–7 (1920).
(168) Reddelien: J. prakt. Chem. **91**, 213–44 (1915); Z. angew. Chem. **35**, 580 (1922).
(169) Reese: J. Am. Chem. Soc. **54**, 2009–17 (1932).
(170) Reilly, Creedon, and Drumm: J. Chem. Soc. **1929**, 641–4.
(171) Remsen: Ann. **178**, 275 (1875).
(172) Rosenstiehl: Ann. chim. phys. [4] **27**, 433–76 (1872).
(173) Rosenstiehl: Z. Chem. **1869**, 635.
(174) Salomonoff: see Holleman, reference 98, page 166.
(175) Schaarschmidt: Ber. **57**, 2065–72 (1924).
(176) Schaarschmidt and coworkers: Ber. **58**, 499–502 (1925).
(177) Scheufelen: Ann. **231**, 158 (1885).
(178) Schleuderberg: J. Phys. Chem. **12**, 598–611 (1908).
(179) Schramm: Ber. **18**, 606–9 (1885).
(180) Schultz and Ichenhauser: J. prakt. Chem. [2] **77**, 113–4 (1908).
(181) Seaman and Johnson: J. Am. Chem. Soc. **53**, 711–23 (1931).

(182) Seelig: Ann. **237**, 129–81 (1887).
(183) Senderens and Aboulenc: Compt. rend. **186**, 1497–9 (1928).
(184) Seyewitz and Biot: Compt. rend. **135**, 1120–2 (1902).
(185) Shoesmith and McGechen: J. Chem. Soc. **1930**, 2231–6.
(186) Silberrad: J. Chem. Soc. **127**, 1724–31 (1925).
(187) Silberrad: J. Chem. Soc. **127**, 2677–84 (1925).
(188) Skraup and Beifuss: Ber. **60B**, 1074–7 (1927).
(189) Spiegel and Hayman: Ber. **59**, 202–4 (1926).
(190) Stark: Ber. **43**, 670–4 (1910).
(191) Stewart: Recent Advances in Organic Chemistry, Vol. I. Longmans, Green and Co., London (1927).
(192) Sulkowski: Ber. **8**, 636–8 (1875).
(193) Thomas: Bull. soc. chim. [3] **19**, 459–62 (1898).
(194) Thomas: Bull. soc. chim. [3] **21**, 286–8 (1899).
(195) Thomas: Compt. rend. **126**, 1211–4 (1898).
(196) Thomas: Compt. rend. **128**, 1576–8 (1899).
(197) Thomas: Compt. rend. **144**, 32–4 (1907).
(198) Tishchenko: Chem. Abstracts **22**, 3397 (1928).
(199) Toehl and Eberhard: Ber. **26**, 2940–5 (1893).
(200) Van der Laan: Rec. trav. chim. **26**, 1–54 (1907).
(201) Van der Lee: Rec. trav. chim. **45**, 690 (1926).
(202) Varma and Kulkarni: J. Am. Chem. Soc. **47**, 143–7 (1925).
(203) Varma and Panicker: Chem. Abstracts **24**, 5740 (1930).
(204) Varnholt: J. prakt. Chem. [2] **36**, 17 (1887).
(205) Wahl, Normand, and Vermeylen: Chem. Abstracts **16**, 1937 (1922).
(206) Welter: Z. angew. Chem. **8**, 217–9 (1895).
(207) Weselsky: Ber. **8**, 98–100 (1875).
(208) Wheeler and McFarland: Am. Chem. J. **19**, 363–7 (1897).
(209) Wieland: Ber. **54**, 1776–84 (1921).
(210) Witt and Utermann: Ber. **39**, 3901–5 (1906).
(211) Zaki: J. Chem. Soc. **1928**, 983–9.

CLASSIFICATION OF REFERENCES

Benzoic acid

Halogenation: 25, 28, 35, 36, 47, 80, 98, 137, 161, 203, 208.
Nitration: 66, 87, 96, 98, 100, 132, 161, 192.
Sulfonation: 8, 50, 95, 98, 139, 156, 158, 167, 169, 171, 183.

Nitrobenzene

Halogenation: 24, 81, 126, 133, 177.
Nitration: 1, 95, 98, 105, 163.
Sulfonation: 56, 135, 155.

Benzenesulfonic acid

Halogenation: 61, 72, 136.
Nitration: 135, 155.
Sulfonation: 98, 110.

Toluene

Halogenation: 3, 7, 19, 22, 38, 39, 40, 45, 46, 48, 54, 55, 57, 60, 79, 109, 118, 122, 125, 145, 178, 179, 182, 184, 186, 187, 190, 195, 199, 200, 205.

Nitration: 23, 27, 49, 69, 77, 88, 95, 112, 114, 130, 134, 142, 146, 153, 159, 164, 172, 173, 206.
Sulfonation: 21, 62, 76, 78, 90, 104, 167.

Phenol

Halogenation: 11, 30, 33, 51, 52, 59, 83, 89, 91, 99, 111, 117, 124, 138, 141, 143, 188, 198, 204.
Nitration: 5, 9, 20, 65, 70, 74, 82, 98, 150, 162, 189, 207, 209.
Sulfonation: 98, 129, 140, 154, 157, 166, 174, 180.

Aniline

Halogenation: 34, 58, 68, 71, 94, 98, 128.
Nitration: 10, 14, 15, 31, 65, 93, 107, 116, 142, 162, 210.
Sulfonation: 4, 16, 17, 73, 98.

Halobenzenes

Halogenation: 37, 41, 43, 47, 48, 53, 98, 113, 121, 123, 127, 147, 148, 151, 193, 194, 195, 196, 197.
Nitration: 1, 44, 101, 102, 106, 149, 175, 176, 202.
Sulfonation: 21, 131, 144, 152, 160, 167.

SUPPLEMENTARY REFERENCES

Benzoic acid

Nitration: Griess (87), Holleman (98), Ladenburg (132), Peltzer (161), Sulkowski (192).
Sulfonation: Dimroth and Schmaedel (50), Holleman (98), Offerman (156), Oppenheim (158), Ray and Day (167), Remsen (171), Senderens and Aboulenc (183).

Toulene

Halogenation: Jannasch and Huebner (125).
Nitration: Beilstein and Kuhlberg (23), Rosentiehl (173).
Sulfonation: Beckurts and Otto (21), Fittig and Ramsay (62), Gilliard, Monnet, and Cartier (78).

Halobenzenes

Halogenation of Halobenzenes: Jahresber. Chem. (123).
Bromination of PhBr: Dumreicher (53).
Bromination of PhCl and PhI, heating with $FeBr_3$: Thomas (196).
Bromination of PhI in presence of iron: Hirtz (92).
Bromination of PhCl in presence of $AlCl_3$: Mouneyrat and Pouret (147).
Bromination of PhCl in presence of Al–Hg couple: Cohen and Dakin (37).
Chlorination of PhCl in presence of $AlCl_3$: Mouneyrat and Pouret (148).
Chlorination of PhCl, heating with $FeCl_3$: Thomas (195).
Chlorination of PhBr, heating with $FeCl_3$: Thomas (193).
Chlorination of PhI, heating with $FeCl_3$: Thomas (194).
Chlorination of PhBr and PhI in presence of and by TlCl: Thomas (197).
Chlorination of PhCl in presence of Al–Hg couple: Cohen and Hartley (41).
Iodination of PhI in presence of HIO_3 and H_2O: Kekulé (127).
Iodination of PhCl in presence of H_2SO_4: Istrati (121).
Iodination of PhCl in presence of HNO_3: Datta and Chatterjee (47).