On the Jacobsen Reaction. IV.[1] *Character and Reaction Mechanism*

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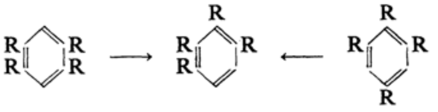
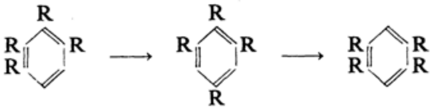
In the electrophilic substitution of highly-substituted aromatic compounds, the migration or replacement of substituents by the attacking groups has often been observed.[2-6] Although these phenomena have long been recognized, however, there have been few systematic studies on the scope of such anomalous substitution. The position at which substitution occurs is determined by the group already present in the aromatic ring and can usually be predicted from the rules governing aromatic substitution. As the compounds become more complex, however, it is difficult to predict the position precisely from the so-called " rules for orientation." This may be because the course of the reaction and the ease with which it takes place become much more influenced by such factors as the number, structure, and type of groups attached to the ring, as well as by the electronic and steric effects of these groups. Thus, the tendency towards an orthodox reaction, in which the replacement of hydrogen by an attacking group is in accordance with the rules of directive influence, is decreased while, at the same time, the reaction leading to the production of anomalous products becomes prominent.

The most typical of these anomalous reactions is the Jacobsen reaction.[7-10] This name has been given to the migration of an alkyl group or halogen atom of polysubstituted benzene derivatives containing only halogen atoms, only alkyl groups or a combination of the two, a migration which occurs when these substances are sulfonated or when their sulfonic acids are allowed to stand in contact with sulfuric acid. One of the most interesting features of this reaction is the migration of an alkyl group or halogen atom to the vicinal position. At first sight, this is in direct contrast to the orienting effects in the Friedel-Crafts reaction and has long been the object of much study.

Jacobsen reaction

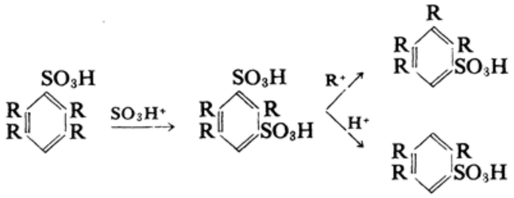


Friedel-Crafts reaction[11]



Although several mechanisms have been proposed for this reaction,[10,12-14] none of these proposals seem to be satisfactory. Some of them will, however, be cited here.

Arnold and Barnes[15] have proposed the following mechanism for the formation of the vicinal compound;



According to this theory, the migrating alkyl group is detached from the sulfonic acid molecule as a cation by the entrance of a second sulfonic acid group; this cation then replaces the more hindered sulfonic acid group

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1) Previous papers in this series: a) R. Goto and H. Suzuki, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 167 (1963); b) H. Suzuki and R. Goto, ibid., **84**, 284 (1963); c) R. Goto and H. Suzuki, ibid., **84**, 435 (1963).

2) G. F. Hennion and SF. de C. McLeese, *J. Am. Chem. Soc.*, **64**, 2421 (1942).

3) P. W. Robertson and H. V. A. Briscoe, *J. Chem. Soc.*, **101**, 1964 (1912).

4) D. V. Nightingale, *Chem. Revs.*, **40**, 117 (1947).

5) D. V. Nightingale and H. B. Hucker, *J. Org. Chem.*, **18**, 1529 (1953).

6) H. Hopf and A. K. Wick, *Helv. Chim. Acta*, **43**, 1473 (1960); ibid., **44**, 19 (1961).

7) L. I. Smith, "Organic Reactions 1," John Wiley & Sons, Inc., New York (1942), p. 370.

8) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley & Sons, Inc., New York (1944), p. 212.

9) C. M. Suter and A. W. Weston, "Organic Reactions 3," John Wiley & Sons, Inc., New York (1946).

10) C. L. Moyle and L. I. Smith, *J. Org. Chem.*, **2**, 112 (1937).

11) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold, New York (1941).

12) J. Herzig, *Monatsh.*, **2**, 192 (1881).

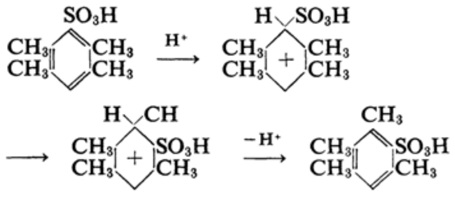
13) O. Jacobsen, *Ber.*, **19**, 1215 (1886).

14) G. Schroeter and S. Götzky, ibid., **60**, 2035 (1927).

15) R. T. Arnold and R. A. Barnes, *J. Am. Chem. Soc.*, **66**, 960 (1944).

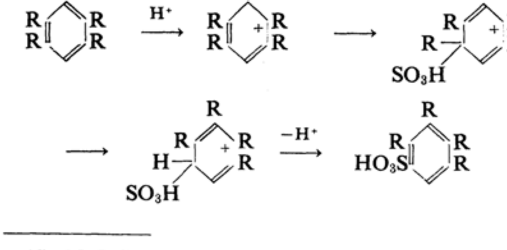
of the di-sulfonic acid. This mechanism is, however, not tenable in view of: (a) the failure to isolate the postulated intermediary di-sulfonic acid; (b) the fact that the migration of an alkyl group occurs, even under the mild conditions under which the formation of di-sulfonic acid is improbable; (c) the failure to explain many reactions involving the migration of halogen atoms, and (d) the fact that the conversion of the sulfonic acid group into amide or ester exerts an inhibitory effect on the reaction.

Dewar[16] has assumed the intramolecular migration of the sulfonic acid group; applied to durene, the reaction can be written as follows:



While a plausible explanation for some reactions of simple compounds, this mechanism fails when attempts are made to apply it to a variety of compounds which undergo the reaction. For example, since the sulfonic acid group always takes the less blocked position, the sulfonation of 5-substituted pseudocumene occurs preferrentially at the 3-position. Thus, one would, according to his theory, expect, 4-substituted hemimellitene to be the sole product from 5-substituted pseudocumene. This is not the case, however, as 5-ethylpseudocumene affords chiefly 3-ethylpseudocumene, whereas 5-isopropylpseudocumene gives no vicinal compound. Moreover, this mechanism is inconsistent with the fact that durene itself undergoes the Jacobsen reaction more readily than isodurene. His mechanism also cannot be applied to the halogen migration.

Fieser and Fieser[17] have explained the reaction on the basis of an allylic-type rearrangement of the substituent groups:



In above mechanism the sulfonic acid is first protonated to form the aronium ion, which undergoes the allylic migration of a sulfonic acid group and the reverse migration of a methyl group, followed by the expulsion of a proton, to form prehnitene sulfonic acid. This mechanism is untenable since it cannot be used satisfactorily to explain the formation of vicinal compounds from either *unsym*-tetraalkyl or pentaalkylbenzenes as well as most of the reaction involving the migration of a halogen atom.

Thus no mechanism has yet been found which will satisfactorily explain all the available data. This is probably because several mechanisms are responsible for the Jacobsen reaction. Many of the studies of the mechanism of the reaction so far have been concerned with the reactions involved in the formation of vicinal compounds. In addition to these somewhat peculiar reactions, however, there exist a number of reactions which should be classed as Jacobsen reactions in the sense that they involve the migration of an alkyl group or halogen atom in the course of sulfonation. Therefore, it is apparent that a single mechanism capable of accounting for all the variations of the Jacobsen reaction cannot be postulated on the basis of such simple assumptions as have been mentioned above.

In this paper, the author would like first to summarize all the results of his studies, together with those of some previous workers, of the Jacobsen reactions, and then, classifying them according to their reaction types into three groups, to propose a more reasonable mechanism consistent with all the data.

Experimental Procedure

The details of the experimental procedure and findings have been given in the previous papers of the series, I-III,[1] they will not be repeated here.

The Jacobsen Reaction.—*Polyalkylbenzenes.*—The general procedure was as follows: a mixture of hydrocarbon and sulfuric acid was magnetically stirred and gradually heated on a water bath. The color changed from yellow to red; it then deepened to reddish brown, and finally to black. The complete solution of the hydrocarbon was usually effected at 60~80°C. The mixture was kept at this temperature range for 4~6 hr. and then allowed to stand for a day or two at room temperature. The mixture was diluted somewhat with water, and all solids were removed by filtration. The filtrate was distilled with superheated steam, the distillate was extracted with ether, and the extract was washed with aqueous sodium hydroxide and dried over calcium chloride. Then the solvent was evaporated and the residual oily material was fractionated.

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[16] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford Press, London (1956).

[17] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," D. C. Heath and Company, Boston (1961), p. 665.

Polyalkylhalogenobenzenes and Polyhalogenobenzenes.—The standard procedure for conducting the experiments with these compounds was divided into two parts, depending upon the solubilities of the reaction products. In procedure I, the whole reaction mixture was poured onto ice and all solids were removed by filtration. The solid was washed, dried and subjected to chromatographic separation on an alumina column. To the acidic filtrate a saturated sodium chloride solution was added to precipitate the sodium sulfonate. The salt was filtered and converted to sulfonamide, which was then fractionally crystallized. Procedure II was the same as I except for the method of handling the filtrate. The sulfonic acid solution was hydrolyzed by passing superheated steam through the filtrate, and the distillate was subjected to fractional distillation.

The Identification of the Reaction Products.—*Polyalkylbenzenes*.—All the specimens obtained from the Jacobsen reactions were inspected by gas-chromatography and infrared spectroscopy and then identified by conversion to known polybromo or polynitro compounds. The structure proof that all the groups attached to the ring were located vicinally, was effected either by the oxidation with diluted nitric acid of a portion of the specimen to benzene polycarboxylic acid, or by the transformation of the specimen into a phenanthrophenazine derivative through the dinitro and diamino compounds, which proved that the two vacant positions were ortho to each other, that is, all four alkyl substituents were in vicinal positions.

Polyalkylhalogenobenzenes and Polyhalogenobenzenes.—The oils obtained from the hydrolysis of sulfonic acids were carefully fractionated, and each fraction was subjected to gas-chromatographic and infrared spectroscopic inspection. The vicinal location of all substituent groups was established by the conversion of a specimen to a phenanthrophenazine derivative by the same method as that used in I. Solid crystalline materials were, after chromatographic separation on an alumina column, recrystallized from ethanol or benzene; they were identified by mixed melting determination with an authentic specimen prepared by other methods.

Results and Discussion

All the Jacobsen reactions may be divided into two general types, intramolecular and intermolecular; in both cases there are transfers of an alkyl group and/or halogen atom.

Polyalkylbenzenes.—The compounds which yield "abnormal products" are limited almost exclusively to tetra or pentaalkylbenzenes containing tetramethylene rings and/or alkyl groups with a short, straight chain, such as methyl, ethyl and *n*-propyl, while those with alkyl groups of a branched structure, such as isopropyl and *t*-butyl, the elimination of these or other alkyl groups are the only reactions taking place. Mono, di and trialkylbenzenes merely yield sulfonic acids, which are quite stable towards sulfuric acid.[18]

The Jacobsen reaction embodies an electrophilic attack upon the ring of polysubstituted benzenes and is dependent upon increased electron density at the position of sulfonation. It is readily apparent that an electron-attracting group, such as the nitro or carboxyl group, would inhibit the reaction. The conversion of sulfonic acid group to sulfonamide or ester exerts an inhibitory influence on the migration of an alkyl group. Reagents also exert a definite effect over the course of the reaction; fuming sulfuric acid usually favors sulfonation, whereas common sulfuric acid often brings about the migration of alkyl groups. These, and other known facts, suggest that the reversibility of sulfonation is the factor of greatest importance in determining whether a Jacobsen reaction will take place or not.

The process of the Jacobsen reaction of polyalkylbenzenes may be divided into two stages; both stages must be gone through before any Jacobsen reaction can be expected to occur in the sulfonation of polyalkylbenzenes.

(a) The elimination of an alkyl group, which occurs during the sulfonation of polyalkylbenzene relatively resistant to sulfonation owing to its highly crowded structure. In most cases the combined effects of steric hindrance and the entrance of a powerful electron-attracting group are necessary to bring about the expulsion of the migrating group.

(b) The alkyl cation thus ejected migrates, according to its stability, intramolecularly (vicinal orientation) or intermolecularly (disproportionation). The formation of the vicinal compound occurs when the migrating alkyl group can readily take the vacant position meta to the entering acid group.

Thus, with polyalkylbenzenes containing isopropyl or a *t*-butyl group, the first stage *a* readily takes place to give a bulky cation, which is, however, incapable of participating in the next stage *b* of the reaction.[19] On the other hand, mono, di and trialkylbenzenes are simply sulfonated to give stable sulfonic acids, from which no alkyl group can be removed at all. Therefore, with these compounds no Jacobsen reaction proceeds. *sym*-Hydrindacene has a structure formally similar to those present in octahydroanthracene and durene, but it does not undergo the reaction when left standing with sulfuric acid. This may possibly be

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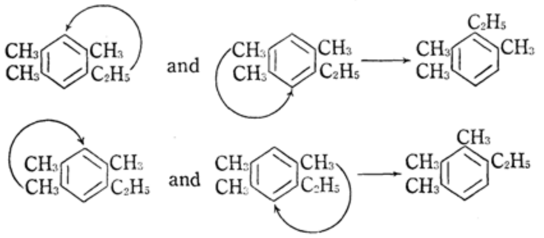
[18] With some di- and trialkylbenzenes containing bulky groups, such as isopropyl or *t*-butyl, the elimination of one of these is observed.

[19] Recently, an interesting reaction involving the intramolecular migration of *t*-butyl group has been reported by M. Menard, D. Awang and F. L. Chubb, *Can. J. Chem.*, **40**, 1738 (1962).

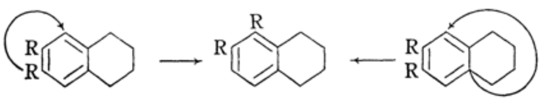
explained by the small hindering effects of five-membered rings.

In the Jacobsen reaction of tetraalkylbenzene, small amounts of trialkylbenzenes and hexaalkylbenzene were always formed. Trialkylbenzene fractions obtained from mixed tetraalkylbenzene were mixtures of several compounds. These facts indicate that there is a possibility of the formation of two or more vicinal isomers, depending on which alkyl group may shift towards the vacant position meta to the sulfonic acid group. For example, 5-ethylpseudocumene afforded two vicinal isomers, together with considerable amounts of prehnitene.[20]



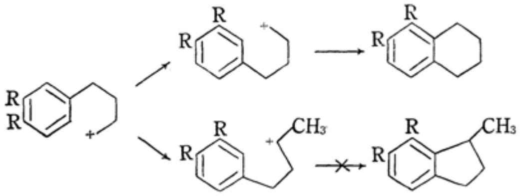
An experiment conducted upon a mixture of durene and *sym*-tetraethylbenzene led to a complex mixture of polyalkylbenzenes, in which the main products were also prehnitene and *vic*-tetraethylbenzene. This fact indicates that the migration of an alkyl group to the vicinal position proceeds intramolecularly. There is apparently an inverse correlation between the ease with which a compound undergoes the Jacobsen reaction and the ease with which the compound can be sulfonated. Thus, when durene and isodurene were subjected to the action of sulfuric acid under the same conditions, it was noted that the time required for the complete migration of the methyl group was much less with durene than with isodurene.

The conversion of 6, 7-dialkyltetralins to vicinal compounds can theoretically proceed by two different routes: the alkyl group may migrate from the 6 (or 7) position to the 8 (or 5), and the tetramethylene ring may open and then close in the ortho position to the alkyl group.



The evidence that the main reaction takes place through the latter course may be briefly summarized as follows: (a) the reaction products contained only small amounts of monoalkyltetralins; (b) octahydroanthracene, in comparison to *sym*-tetraalkylbenzene, was much more readily converted to the vicinal compound under the same conditions; (c) when 5, 7- and 6, 7-dimethyltetralin were subjected to the same conditions of the Jacobsen reaction, the former gave only a small amount of an oily product which could not be identified, whereas the latter readily converted into the vicinal compound.

Although the opening of a ring, followed by the migration of an intermediate with a cationic terminal carbon atom, would involve the simultaneous isomerization of the group to the more stable secondary carbonium ion, no hydrindene derivative was detected in the reaction products from dialkyltetralins. This may be explained both by the well-known preference for the formation of a six-membered rather than a five-membered ring in cyclization, and by the tendency for a bulky cation to avoid a highly blocked position. Dialkyltetralins containing a isopropyl group were always converted into the compounds in which the isopropyl group was eliminated.



The relatively high yields of *vic*-dialkyltetralins compared to those of *vic*-tetraalkylbenzenes are attributed to the fact that one end of the long chain cation is attached to the ring and so cannot leave the molecule freely. Therefore, although *sym*-tetra-*n*-butylbenzene, with which an analogous process might be expected to occur, has not yet been studied, the formation of a vicinal compound can hardly be expected.

Reaction products from mixed polyalkylbenzenes are usually complex mixtures and require extensive purification. Furthermore, the yields are low, and the probable structure inferred from analogy should be investigated by independent methods. Thus, the Jacobsen reaction cannot be considered as a general synthetic method for *vic*-tetraalkylbenzenes.

Polyalkylhalogenobenzenes and Polyhalogenobenzenes.—An extensive study of the reaction of polyalkylhalogenobenzenes has shown, as can be predicted on theoretical grounds, that increasing the number of alkyl groups attached to the benzene ring favors both the migration

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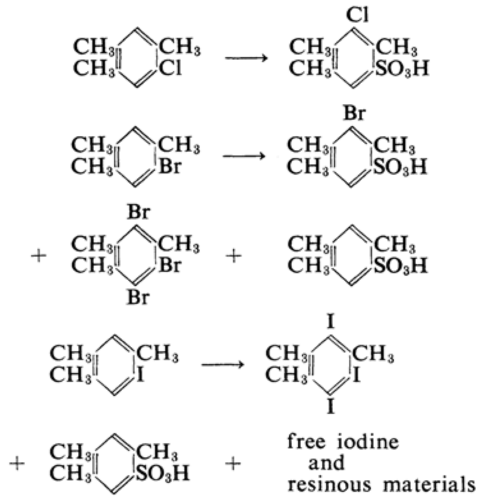
20) The isolation of neither of these isomers was successful. Although all possible isomeric products were undoutedly formed in the reaction of mixed polyalkylbenzene, their presence had been demonstrated or inferred only by a combination of gas-chromatography and infrared spectroscopy because of the experimental difficulties involved in separation.

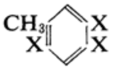
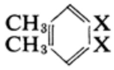
of the halogen atom and the decomposition of the compound to tarry materials. Thus, there exists a certain limited scope within which the reaction can proceed smoothly. For example, monochloroxylenes are merely sulfonated, while monoiodoxylenes afford polyiodoxylenes in high yields; with monochlorotetramethylbenzenes the migration of the methyl group is observed, whereas with monoiodotetramethylbenzenes, the reaction proceeds too readily, yielding intractable resinous materials.

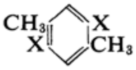
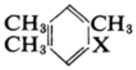
The iodine atom is most readily, and the chlorine atom is least easily, replaced by the sulfonic acid group; therefore, the disproportionation is most prevalent with iodine compounds, whereas the formation of vicinal compounds is found with chlorine compounds. Bromine compounds occupies an intermediate place with respect to ease of replacement; hence, they show both disproportionation and intramolecular migration simultaneously. The three reactions which follow illustrate this statement well:



The iodine cation is unable to re-enter the molecule because of its bulkiness and so is set free as elementary iodine.

The behavior of a number of *sym*-polyhalogenobenzenes and *sym*-polyalkylhalogenobenzenes towards sulfuric acid is summarized in the following table:

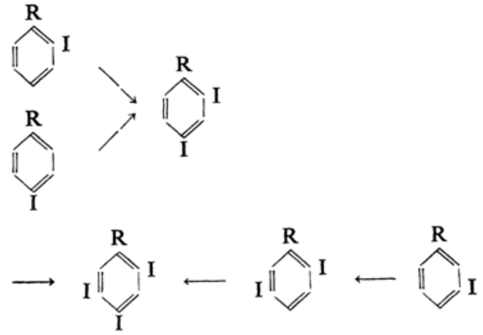
X			
Cl			(+)
Br	−	−	+
I	−	−	−

X			
Cl	+	(+)	+
Br	+−	(+)	+−
I	−	−	−

where sign + denotes the formation of the vicinal compound and sign −, disproportionation. The parentheses mean that the reaction occurs only under drastic conditions.

With polyhalogenobenzenes, the Jacobsen reaction is confined almost entirely to polybromo and polyiodobenzenes. A few special cases involving chlorine migration have been found, but for the most part the chlorine atom does not undergo the migration. It appears that the halogen atom always migrates intermolecularly if any reaction occurs at all, and all the available evidence indicates that the ease of migration in these compounds is in the order of I>Br>Cl. As the ring-bonded fluorine atom is unable to form a cation, it, of course, cannot take part in the migration.

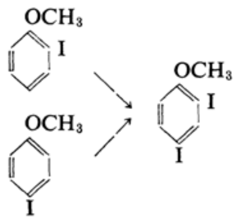
In order to determine the effect of various substituents upon the ease, course and limits of the reaction, the action of sulfuric acid upon a number of halogenobenzene derivatives was studied. Electron-attracting groups, such as the nitro, carboxyl and carbonyl, hindered the reaction so greatly that it usually failed to take place when any of these were attached to the ring. On the other hand, an accumulation of electron-releasing groups, such as hydroxy and alkoxy, facilitated the reaction so much that it was often difficult to prevent the compounds from decomposing to tarry materials. The presence of bulky groups, such as isopropyl and *t*-butyl, on the aromatic ring also interfered with the reaction. The importance of the steric factor was revealed by an examination of the products from monoiodoalkylbenzenes; with the methyl and ethyl groups, the migration products were obtained in high yields, whereas with the isopropyl and *t*-butyl groups, the reaction was that leading to the formation of resinous materials, with no definite product.

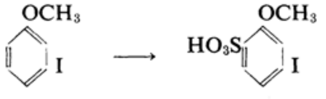


R=Methyl or ethyl

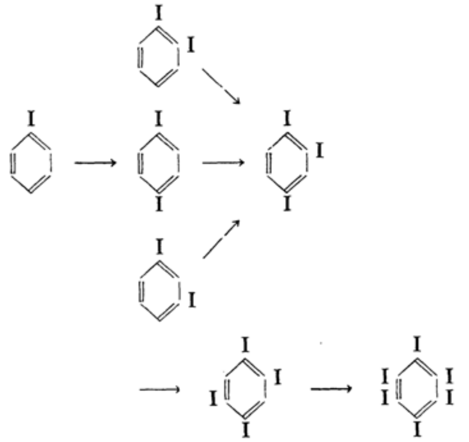
No attack of halogen atom upon the alkyl group was observed.

In some cases, slight changes in the structure of the compound may cause great differences in the ease of the migration of the halogen atom. For example, *o*- and *p*-iodoanisol readily gives polyiodo compounds, but *m*-isomer is simply sulfonated to give a stable 6-sulfonic acid.

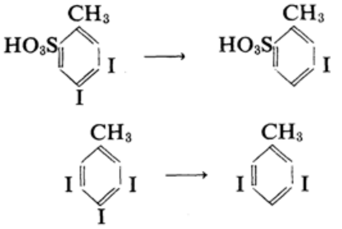




The reaction usually proceeds as the progressive halogenation of the parent compound, and a certain isomer is always formed in preference to others. For example,



When there exist more than one halogen atom capable of migration, the preferential replacement occurs with those present at the positions that have a higher electron density or a greater steric hindrance.

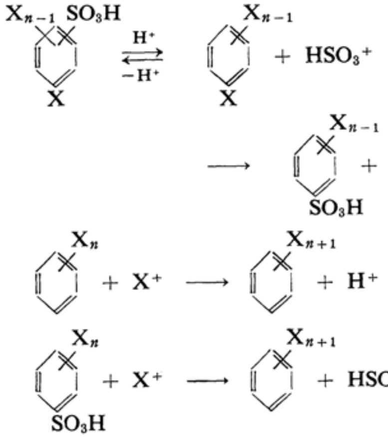


The reaction is considered of much value for the direct synthesis of some polyiodo compounds.[21]

Mechanism.—All the Jacobsen reactions so far observed can be divided into three groups according to their reaction types: *the first*, shown by a compound relatively resistant to sulfonation because of its highly crowded structure, involves an anomalous sulfonation leading to the elimination of an alkyl group or a halogen atom, followed by its migration; *the second*, in which the normal sulfonation of a compound constitutes the initial phase of the reaction, is most often encountered with these compounds which are readily sulfonated to form a stable sulfonic acid (the migration of substituent groups on the ring gradually occurs intra- or intermolecularly, depending on their structures and experimental conditions); *the third* is shown by some polyiodo compounds, in which no sulfonation can be expected at all because of their highly crowded structures and reduced reactivities (the protonation of the compound, followed by the expulsion of the iodine cation, must constitute the initial phase of this reaction).

In the following discussion, for each individual group of reactions the author has attempted to formulate a mechanism with which to explain satisfactorily the experimental findings so far obtained on the Jacobsen reaction.

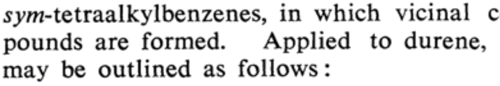
(I) The first group involves compounds relatively difficult to sulfonate and may be represented by the following generalized scheme:



(a)

(b)

This is a two-stage reaction initiated by the electrophilic attack of a sulfonic acid group, which will, of course, seek a position with high electron density and small steric hindrance. The alkyl group or halogen cation which is eliminated during sulfonation will react with the parent compound according to Eq. a, or with the sulfonic acid according to Eq. b. The most typical reactions of this group are those observed in the sulfonation of *sym*-tetraalkylbenzenes, in which vicinal compounds are formed. Applied to durene, this may be outlined as follows:



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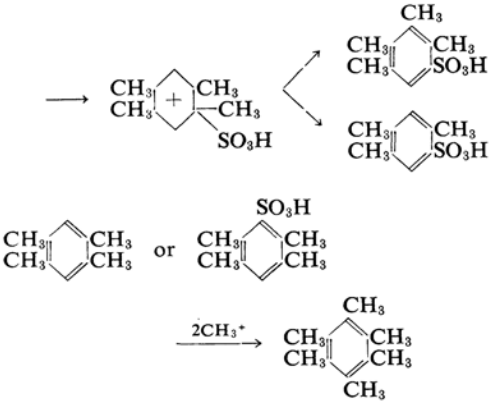
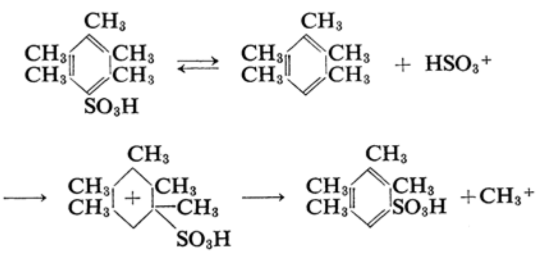
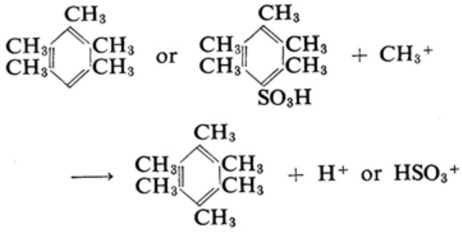
[21] H. Suzuki and R. Goto, This Bulletin, 36, 389 (1963).



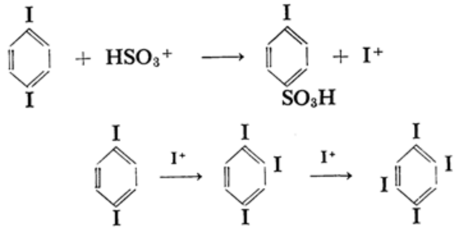
The formation of the vicinal compound may be interpreted as follows: a partially positive methyl group may be ejected from durene by the attack of a sulfonic acid group, but, never becoming completely free, it may form a π-complex with the ring and then pass to the vacant position meta to the sulfonic acid group. The remarkable color changes involved in the initial phase of the reaction support the theory that the reaction proceeds through the intermediary complex described above. The ability of several migrating groups to take this vacant position, giving vicinal compounds, is influenced to a large extent by steric requirements. This can readily be visualized by a series of 5-substituted pseudocumenes: the combined inductive and mesomeric effects of methyl groups give rise to a high electron density at the 5-position of pseudocumene derivatives and hence facilitate the electrophilic attack at this position by a sulfonic acid group, which expels a substituent group there as a cation. When the cationic group ejected is reactive and is sterically small enough, there a vicinal orientation is always observed. This is the case with 5-methyl, 5-ethyl, 5-chloro and 5-bromopseudocumene. If larger groups are involved in the reaction, the elimination of these groups is the only reaction that proceeds. These are found, for example, with 5-isopropyl and 5-iodopseudocumene.

The reactions of dialkyltetralin and pentaalkylbenzene may also be incorporated into this group. For example, with pentamethylbenzene:



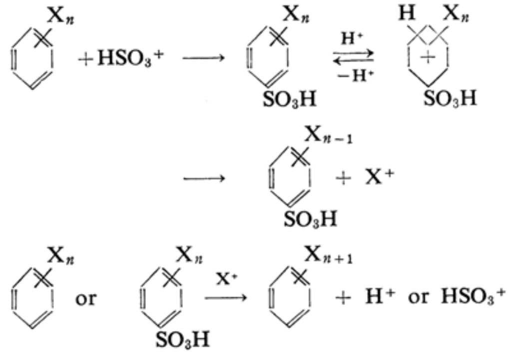


Next, let us consider compounds with only a few substituent groups. It has long been known that the sulfonation of *p*-diiodobenzene is always accompanied by disproportionation, thus giving *p*-iodobenzene sulfonic acid and mixtures of polyiodobenzenes. This process is also represented by an analogous two-stage mechanism, in which the following processes take place:



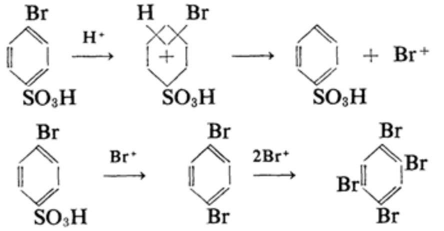
When some polyalkylbenzenes containing *t*-butyl groups are allowed to stand in contact with sulfuric acid, the elimination of the *t*-butyl group is observed to some extent. In these cases, however, the extreme aversion of the *t*-butyl group to the entry in a position ortho to the alkyl groups in the ring inhibits the further alkylation of the parent hydrocarbons; thus, no reaction analogous to the Jacobsen proceeds.

(II) The second group includes the reactions which are most often encountered with compounds readily subject to the action of sulfuric acid. As has been mentioned above, the ease of sulfonation is inversely related to that of migration; hence, the compounds of this group need more time for the completion of the reaction. It is best represented by the following generalized scheme:

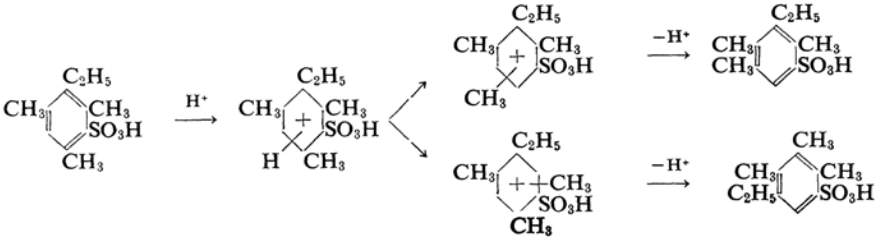


The reaction scheme above is interpreted at follows: sulfonic acid is first protonated to form an intermediate complex, from which the group present at the position of higher electron density and larger steric hindrance is ejected. The alkyl group or halogen atom thus expelled may migrate, according to its stability, intramolecularly to form vicinal compounds or intermolecularly to yield disproportionation products.

The formation of polybromobenzenes from monobromobenzene is one example:

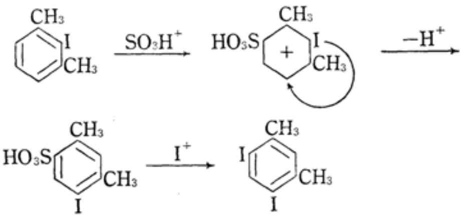


There are two possible routes by which a vicinal compound can be formed from a nonvicinal compound: one is that just described in group I, the other belongs to group II. For example, *unsym*-tetraalykylbenzenes are necessarily sulfonated ortho to both alkyl groups unless one of them is displaced by the entering sulfonic acid group. Thus, there arises a great steric hindrance which forces the migration of one of the alkyl groups so as to reduce the blocking action on the sulfonic acid group. Applied to ethylmesitylene, this may be outlined as follows:



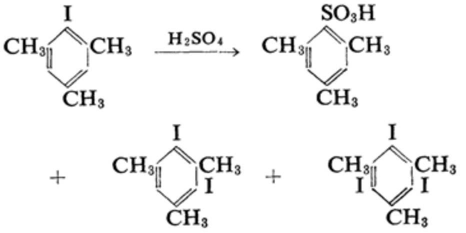
The vicinal orientation found with *unsym*-tetraalkylbenzene sulfonic acid is attributed to the buttressing effect of the alkyl group meta to the sulfonic acid group, because *sym*-trialkylbenzenes in which no buttressing effect of meta alkyl group is present can never show the Jacobsen reaction.

Another interesting example was found in the reaction of 2-iodo-*m*-xylene and 2, 3-diiodotoluene (cf. a future communication), where was formed not the expected 2, 4-diiodo-*m*-xylene nor 2, 3, 6-triiodotoluene, but the symmetrically-substituted 4, 6-diiodo-*m*-xylene and 2, 4, 5-triiodotoluene. These must have been formed as a result of initial sulfonation at the 6-position, followed by the intramolecular shift of the iodine atom from the hindered position 2 to the 4.[22]



These results further support the concept that the entry of a bulky group at the meta position has a great influence on the stability of the substituent group sterically hindered by two ortho substituents.

The sulfonation of iodomesitylene might be another example where no reaction proceeds without accompanying the disproportionation of the iodine atom;[23]



These two types of reaction routes, I and II, however, must be regarded as extremes; a number of the reactions may possibly take place through a course which could be regarded as a combination of the two. Which type of reaction predominates depends on the steric requirements of the compound subjected to the Jacobsen reaction. With highly crowded compounds, the reaction scheme I, involving direct displacement, seems important, whereas with less crowded compounds the reaction scheme II predominates.

(III) The third group is quite different from the two mentioned above; here sulfuric acid appears to act only as a protic solvent. Some polyiodo compounds with highly crowded structures, with which no sulfonation can be

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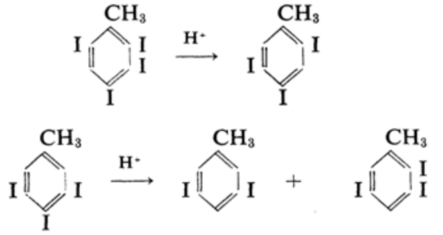
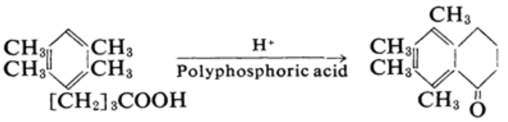
[22] As *m*-xylene sulfonic acid and iodine afford no iodinated compound under the same conditions, the intermolecular migration of iodine atom is less probable.

[23] A. Tohl and R. Eckel, *Ber.*, **26**, 1099 (1893).

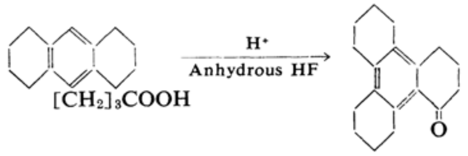
expected to occur, undergo this type of reaction under drastic conditions. For example:



These can not be classed as true Jacobsen reactions, however, because no sulfonation is involved in the above reactions. There are, however, many interesting observations in the literature on the migration of an alkyl group or halogen atom, analogous to the Jacobsen reaction, where neither sulfonation nor a sulfonic acid group is concerned. The following are some examples:

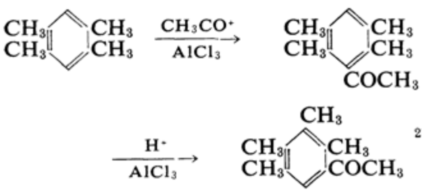


24)

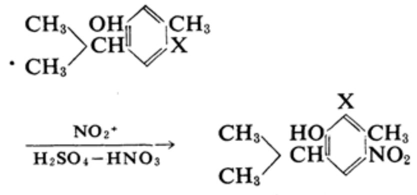


25)

26)



27)



28)

X=Cl or Br

All cases contain intra- and/or intermolecular migration in the presence of an acidic medium, of an alkyl group or of a halogen atom, involving the vicinal orientation of these groups. If we consider that the nitro, carbonyl or acetyl group plays the same role as that of the sulfonic acid group in the Jacobsen reaction, then we may suppose that the above reactions are Jacobsen types and may indeed take place by analogous processes.

For the purpose of classifying these anomalous reactions, it seems convenient to give the term "Jacobsen Reaction" a much wider meaning, that is, to extend the definition to the general cases of anomalous electrophilic substitution, in which there is observed an intra- or intermolecular migration of substituent groups expelled by the entry of electrophilic attacking groups under the very influence of acidic solvents. Therefore, the term "Jacobsen Reaction" will no longer mean only abnormal sulfonation in a narrow sense, but a variety of anomalous electrophilic substitutions of a similar nature which are at present not systematized and are included in other categories.

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