The Anomalous Behavior of Some 2, 6-Disubstituted Iodobenzenes in the Jacobsen Reaction[1]

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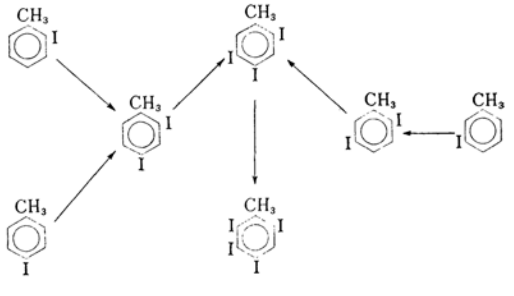
Aromatic iodo compounds containing electron-releasing groups in the nucleus readily undergo disproportionation in the presence of sulfuric acid to give polyiodo compounds.[2] This is the Jacobsen reaction. The reaction proceeds like a progressive iodination of the starting material, an entering iodine atom always taking the position of higher electron density and smaller steric hindrance, in accordance with the orientation rule of the usual electrophilic substitution. An example is the conversion of iodotoluenes to polyiodotoluenes:



As has been reported in previous papers of this series,[2] however, some 2, 6-disubstituted iodobenzenes, such as 2-iodo-*m*-xylene, 2, 3-diiodotoluene, and 1, 2, 3-triiodobenzene, exhibit anomalous behavior in the reaction, affording none of the expected vicinal (or asymmetrical) compounds, but only symmetrically-substituted products; that is, the

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[1] The Reaction of Polysubstituted Aromatics. VI; this series of studies hereafter will be called by this title. Part V: This Bulletin, **37**, 1858 (1964).

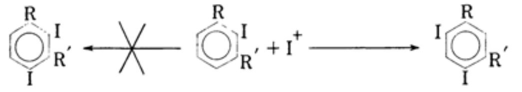
[2] R. Goto and H. Suzuki, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, **84**, 167 (1963); H. Suzuki and R. Goto, ibid., **84**, 284 (1963); H. Suzuki and R. Goto, This Bulletin, **36**, 389 (1963).

TABLE I. ACTION OF SULFURIC ACID ON 2-IODO-*m*-XYLENE

Expt. No.	2-Iodo-*m*-xylene g.	Sulfuric acid g.		Reaction temp. °C	Reaction time hr.	Product g.	Main component
1	2.3	6.0		20—23	3	0.7	4,6-Diiodo-*m*-xylene Tetraiodo-*m*-xylene
2	2.3	1.0		20—23	1	1.6	2- and 4-Iodo-*m*-xylene
3	2.3	0.2		20—23	4	1.9	2- and 4-Iodo-*m*-xylene
4	2.3	1.0		20—23	3.5	1.1	2- and 4-Iodo-*m*-xylene 2,4- and 4,6-diiodo-*m*-xylene
5	2.3	6.0		20—22	0.6	0.9	4,6- and 2,4-diiodo-*m*-xylene 4-Iodo-*m*-xylene
6	2.3	6.0	Water 1.2	20—22	1	2.1	Only 2-iodo-*m*-xylene
7	2.3	1.0	Mesitylene 2.4	20—22	0.3	3.4	2-Iodo-*m*-xylene Mesitylene Iodomesitylene
8	2.3		PPA 7.0	ca. 140—150	2.5	1.9	2- and 4-Iodo-*m*-xylene

PPA = Polyphosphoric acid

iodine atom located in the position 2 in the original compound migrates to the position 4 in the final product, as is shown in the following scheme:



In the present paper, the authors wish to report the results of their mechanistic study of this novel reaction. We used only 2-iodo-*m*-xylene as the reagent because of its ease of synthesis. To get more precise knowledge about the reaction, we also prepared four isomeric diiodo-*m*-xylenes and subjected them to the several conditions of the Jacobsen reaction; the results of these experiments will, however, be described in a succeeding paper. The reaction products were identified by an inspection of their infrared spectra and gas chromatogram.

Experimental

Procedure. — Weighed 2-iodo-*m*-xylene and sulfuric acid (or PPA) were placed in a small, stoppered flask and then stirred magnetically at a given temperature for a definite time. Then the mixture was diluted with water, and the precipitated solid or oily matter was separated by extraction and purified through an alumina column, using petroleum ether as the eluant. The solid or oily matter which remained after the evaporation of the solvent was then subjected to infrared spectroscopic or gas chromatographic inspection. The reaction conditions and the products are summarized in Table I.

Materials. — 2-Iodo- and 4-iodo-*m*-xylene were prepared from the corresponding *m*-xylidines (Tokyo Kasei products, G. R. grade) by the ordinary procedure: 2-iodo-*m*-xylene[3] (b. p. 100—101°C/12 mmHg), 4-iodo-*m*-xylene[4] (b. p. 108—109°C/12 mmHg). The synthesis of four isomeric diiodo-*m*-xylenes will be reported in the succeeding paper.

Results and Discussion

In the presence of an excess of sulfuric acid, the disproportionation of 2-iodo-*m*-xylene was completed so fast that in order to find out any possible intermediates it was necessary to carry out the reactions in the system containing an insufficient amount of sulfuric acid. As one molecule of *m*-xylene-4-sulfonic acid was inevitably formed for every intermolecular migration of an iodine atom, the disproportionation was considerably suppressed and the isomerization became prominent.[5] As may be seen from Fig. 2a and Fig. 3a, at an early stage of the reaction only a slight formation of diiodo-*m*-xylenes was found on the gas chromatogram, while on the infrared spectrogram the absorption bands characteristic of 2-iodo-*m*-xylene (698 and 767 cm^{-1}) were already much weakened and the absorption bands due to 4-iodo-*m*-xylene (805 and 872 cm^{-1}) were considerably strengthened. Even in the presence of a slight amount of sulfuric acid, 2-iodo-*m*-xylene gradually isomerized to the 4-iodo isomer during a prolonged reaction time. These facts clearly establish the prior isomerization of 2-iodo-*m*-xylene to the 4-iodo isomer.

Figure 3b indicates that two diiodo-*m*-xylenes were formed at an early stage of the reaction,

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[3] S. F. Birch, R. A. Dean, T. A. Tidler and R. A. Lowry, *J. Am. Chem. Soc.*, **71**, 1362 (1949).

[4] A. Klages and C. Liecke, *J. prakt. Chem.*, **61**, 307 (1900).

[5] 4-Iodo-*m*-xylene sulfonic acid is in part hydrolyzed to give 4-iodo-*m*-xylene and sulfuric acid, whereas *m*-xylene-4-sulfonic acid is very stable under ordinary conditions.

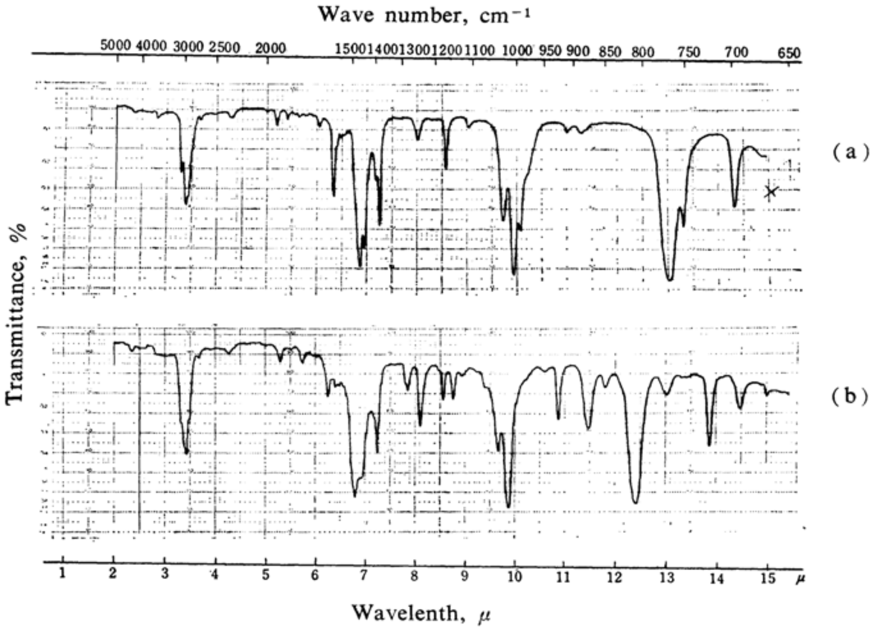


Fig. 1. Infrared spectra of iodo-*m*-xylenes.

(a) 2-Iodo-*m*-xylene
(b) 4-Iodo-*m*-xylene

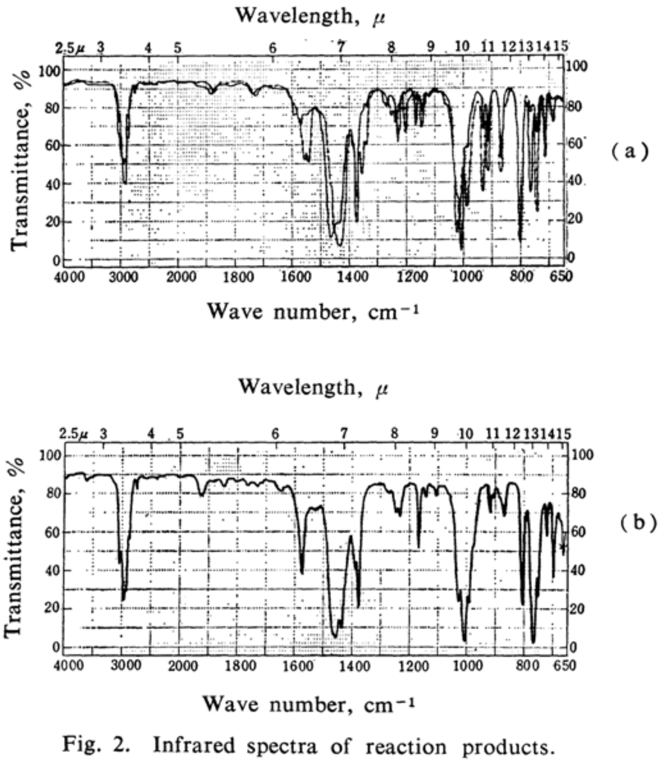


Fig. 2. Infrared spectra of reaction products.

(a) Full line Exp. No. 4
Dotted line Exp. No. 5
(b) Exp. No. 8

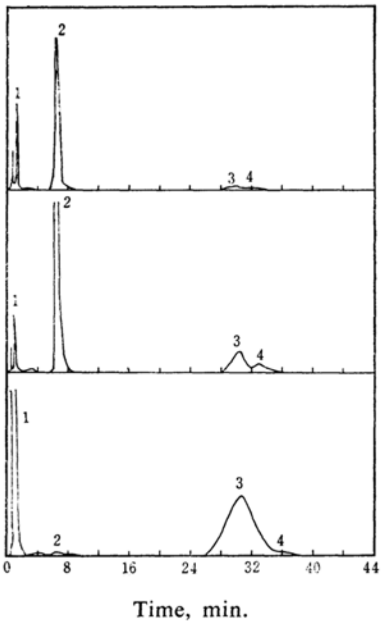


Fig. 3. Gas chromatogram of reaction products.
(a) Exp. No. 3 (b) Exp. No. 5 (c) Exp. No. 1
Peak 1 Solvent (benzene or petroleum ether)
2 2- or 4-Iodo-*m*-xylene
3 4,6-Diiodo-*m*-xylene
4 2,4-Diiodo-*m*-xylene
Stationary phase: Apiezon grease L, 3 m.
Carrier gas: Hydrogen
Column temperature: 245—246°C

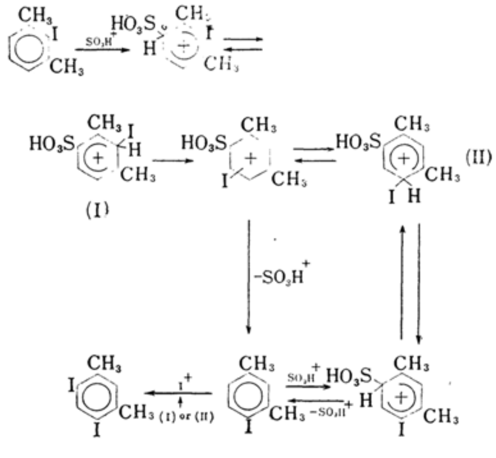
but one of them was gradually diminished during the usual Jacobsen reaction, which was carried out with a large excess of sulfuric acid. This minor precursor was identified as 2,4-diiodo-*m*-xylene. As will be described in the succeeding paper, however, 2,4-diiodo-*m*-xylene is comparatively stable towards the action of sulfuric acid and does not isomerize so readily to 4,6-diiodo-*m*-xylene under these conditions. Therefore, this compound cannot be considered to be a major intermediate.

In the crossed Jacobsen reaction of *m*-xylene-4-sulfonic acid with *p*-iodocumene (this compound readily liberates the iodinium cation in sulfuric acid), a considerable amount of elementary iodine was liberated, and the iodinated *m*-xylenesulfonic acid could not be isolated from the reaction mixture. Thus, it is reasonable not to postulate the complete detachment of the migrating iodine atom during the isomerization, because the iodinium cation formed under those conditions cannot be so active as to iodinate the *m*-xylene-4-sulfonic acid successfully. Little liberation of elementary iodine or sulfur dioxide during the reaction also supports this view.

An effort to isolate 2-iodo-*m*-xylene sulfonic acid from the reaction mixture was fruitless; *m*-xylene-4-sulfonic acid was always obtained, together with small amounts of 4-iodo-*m*-xylene-6-sulfonic acid. This may be interpreted as indicating that the migration of the iodine atom from the hindered (=2) to the less hindered position (=4) occurs prior to the completion of the sulfonation. If the reaction was carried out with an excess of mesitylene, the iodine atom was readily transferred to give iodomesitylene. This fact indicates that the iodine atom migrates to the position of higher electron density, because mesitylene is supposed to be much more basic than either 2- or 4-iodo-*m*-xylene. Characteristic color changes which always accompany the halogen migration were also observed during the reaction, and the color disappeared upon the addition of water.

In this connection, another interesting phenomenon was observed in the similar isomerization of 2-iodo-*m*-xylene caused by polyphosphoric acid (PPA) of a high temperature (Fig. 2b). Here, however, only an intramolecular migration of the iodine atom was observed, and the reaction needed more severe conditions and a much longer time in order to be completed.

From the results described above, we may conclude that the reaction proceeds mainly through the prior isomerization of 2-iodo-*m*-xylene to the 4-isomer, followed by the usual disproportionation; this process may be formulated as follows:



2-Iodo-*m*-xylene reacts reversibly with sulfuric acid to form a σ-complex, a benzenonium intermediate (I), in which the iodine atom, blocked on both sides by two ortho methyl groups, is jammed so hard by the entry of a bulky sulfo group that it is crowded out and migrates through π and σ-complex transition states to the position of the next highest electron density. If it settles down at the position 4 of the same molecule or replaces the sulfo group at the position 6, the isomerization occurs; if another molecule attacks the intermediate I or II nucleophilically and if the iodine is transferred, a disproportionation results. The easy transfer of the iodine atom generally found in the crossed Jacobsen reaction of some aromatic iodo compounds with highly alkylated benzenes[6] may also be explained consistently by this mechanistic scheme, assuming that the benzenonium intermediate formed by the entry of the sulfo group is attacked by the highly basic polyalkylbenzenes. The differences in the ease of migration between the reaction caused by sulfuric acid and that brought about with PPA is best interpreted as follows: in PPA 2-iodo-*m*-xylene is first protonated to form a benzenonium intermediate in which the iodine atom is less hindered than in a corresponding sulfonic acid intermediate (I) and thus migrates at a slower rate intramolecularly to the position 4.

This anomalous Jacobsen reaction draws our attention for the very interesting reason that the migrating group is not that one which is replaced directly by the attacking group (this type of replacement is the most general one encountered in the anomalous electrophilc substitution of aromatic compounds), but is one which is present at a position (meta) distant from the place where the actual reaction occurs. Further evidence to support the above mechanism will be reported in the succeeding paper.

Summary

Some 2, 6-disubstituted iodobenzenes undergo an anomalous Jacobsen reaction and so afford none of the expected vicinal, but only symmetrical diiodo products. This anomaly has been investigated using 2-iodo-*m*-xylene as the reagent. The reaction has been found to proceed mainly through the rapid isomerization of 2-iodo-*m*-xylene to the 4-iodo isomer, followed by the normal disproportionation to 4, 6-diiodo-*m*-xylene. A possible mechanism has also been proposed on the basis of the results obtained.

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[6] H. Suzuki, T. Sugiyama and R. Goto, This Bulletin, 37, 1858 (1964).