[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

THE ACCELERATIVE *ORTHO* EFFECT. III. THE ORIENTATIONS IN THE MERCURATIONS OF VARIOUS AROMATIC COMPOUNDS

YOSHIRO OGATA AND MASARU TSUCHIDA

Received July 12, 1955

In our previous reports (2) a peculiarity was noted that in the mercuration of nitrobenzene a considerable amount of *ortho* mercuric compound was obtained and the phenomenon was explained by calculating coulombic interactions between atomic charges in the transition state of the reaction (1). It is the purpose of the present work to investigate the orientation in the mercuration of some other aromatic compounds and to interpret the results obtained in the light of electrostatic interaction at the transition state previously reported (1). The mercuration was carried out with or without solvent. In general, glacial acetic acid was used as the solvent except with phenyltrimethylammonium nitrate where dilute nitric acid was employed. The mercuric compounds thus produced, in the form of arylmercuric acetates or nitrates, were precipitated with sodium or calcium chloride as arylmercuric chlorides and then were converted into aryl bromides by treating with bromine. The isomeric composition of the product was determined by cautious fractional crystallizations.

It was found that the reaction of benzamide with mercuric acetate occurred almost exclusively at the *ortho* position, and that benzophenone and methyl benzoate were mercurated mainly at the *ortho* and some at the *meta*, but that no *para*-substituted product was isolated. These three compounds are known to be *meta*-orienting in the usual electrophilic substitution. The mercuration of fluorenone occurred at the 1-position, *ortho* to the carbonyl group, in spite of the fact that ordinary electrophilic reagents attack the 2-position (3). The mercuration of phenyltrimethylammonium nitrate gave exclusively the *meta* product, just like the orientation in the usual electrophilic substitution (4). Phenylacetic acid and methyl phenylacetate both afforded mainly *para* mercurated products. Isolation of the mercuration product of anthraquinone or acenaphthenequinone was unsuccessful in our hands. In acetic acid as a solvent benzoic acid was found to be mercurated principally at the *meta*, less at the *ortho* and none at the *para* position, while Dimroth (5) obtained exclusively the *ortho*-mercurated benzoic acid by heating its mercuric salt.

Table I shows the coulombic interaction energies at the transition state of mercuration. In Table II, comparison is made between the experimental results and the predicted orientations from these electrostatic interactions of the atomic charges at the activated complexes. The method of calculation has been described in Parts I (1) and II (2). It is assumed that the carbonyl oxygen atom is situated on the plane of the benzene ring and in the nearest position to the mercury atom with —C═O angle of 120°.

The experimental results are almost in accord with the prediction. The exceptions are those for phenylacetic acid and methyl benzoate, the discrepancy perhaps being attributed to inadequate application of Price's atomic charges to these cases; in fact, according to his calculation, the nitration of phenylacetic acid would occur at the *meta* position which does not accord with the experimental fact. Recently, it was reported that azoxybenzene (6), benzanthrone (7), diphenyl sulfone (8), and quinoline N-oxide (9), gave products mercurated at the *ortho*, Bz-1, *ortho*, and 8-positions, respectively. These facts will be accounted for by the same assumption. Although many authors have discussed the relation between reactivity of aromatic compounds and the electron density at the position of attack, it seems that little attention has been paid to the electron density of the attacking species. In so far as the characteristics of the attacking reagents are taken into account, this paper will give a unique aspect.

Other probable explanation for these *ortho* orientations will be discussed briefly below.

If the ground state resonance is preserved in the transition state in the follow-

TABLE I

INTERATOMIC ELECTROSTATIC INTERACTION ENERGIES AT THE TRANSITION STATES FOR MERCURATION (kg. cal./mole)

(*Cf.* Part I and II)

	ΔE_o	$\Delta E_o'$	$\Delta E_o + \Delta E_o'$	ΔE_m	$\Delta E_m'$	$\Delta E_m + \Delta E_m'$	ΔE_p	$\Delta E_p'$	$\Delta E_p + \Delta E_p'$
Benzamide	5.32	−11.03	−5.7	0.55	−6.70	−6.2	−1.52	−11.03	−12.6
Benzophenone	10.70	−4.07	6.6	4.22	0.02	4.2	2.01	−4.07	−2.1
Fluorenone	10.70	−4.07	6.6	4.22	0.02	4.2	2.01	−4.07	−2.1
Benzoic acid F[a]	25.83	−12.88	12.9	0.69	−6.67	−6.0	−0.14	−12.88	−13.0
Benzoic acid Hg[b]	−24.0	−30.1	−54.1	−8.4	−23.0	−31.4	−91.1	−30.1	−121.2
Methyl benzoate	1.31	−15.26	−13.9	−1.17	−8.52	−9.7	−1.17	−15.26	−16.4
Phenylacetic acid Hg[b]	0.83	−6.96	−6.1	−2.01	−5.68	−7.7	−4.15	−6.96	−11.1
Phenyltrimethylammonium nitrate	−94.5	−123.5	−218.0	−69.5	−118.6	−188.1	−65.5	−123.5	−189.0

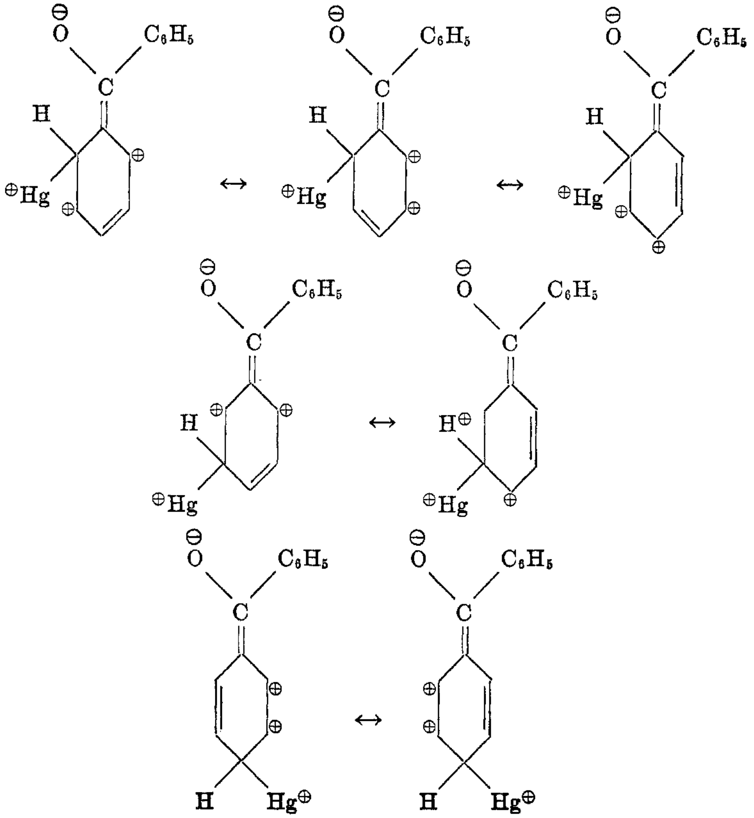
[a] Free acid, corresponding to the mercuration with insufficient mercuric reagent.
[b] Mercuric salt, corresponding to the mercuration with excess mercuric reagent.

TABLE II

COMPARISON OF THE CALCULATED ORIENTATION FROM ELECTROSTATIC INTERACTIONS WITH THE OBSERVED RESULTS

	Calc'd	Obsv'd
Benzamide	$o > m > p$	$o \gg m > p$
Benzophenone	$o > m > p$	$o \gg m > p$
Fluorenone	$o > m > p$	$o \gg m, p$
Benzoic acid F	$o > m > p$	$o \gg m, p$
Benzoic acid Hg	$m > o > p$	$m \gg o$
Methyl benzoate	$m > o > p$	$o > m \gg p$
Phenylacetic acid Hg	$o > m > p$	$p \gg o, m$
Phenyltrimethylammonium ion	$m > p > o$	$m \gg p, o$

ing manner, then the greater similar-charge separation will favor the *ortho* attack more than the *para* attack, but the *meta* substitution should be more favorable than the *ortho* substitution because two charge-separated forms are possible for the *meta* substitution; the experimental results are often not in accord with this prediction. Furthermore, this explanation does not account for the difference in the orientation between monovalent and divalent attacking cations, *e.g.*, the very small *ortho* orientation in nitration and the comparatively large *ortho* orientation in mercuration.



The steric inhibition of resonance with the bulky attacking agent, mercuric ion, which surely accelerates the *ortho* substitution does not seem to account for the fact that a rigid and planar 9-fluorenone molecule is also mercurated at the *ortho* position.

An explanation that the mercuric ion at first attacks a negative pole of the substituent and then rearranges to the *ortho* position seems to coincide with our idea, since the transition state for the reaction should be the rearrangement step in which the Kekulé form resonance of the benzene ring is lost.

This electrostatic explanation, however, appears not to be applicable to the active benzene derivatives substituted with the *ortho-para* directing groups, since, in these cases, the electrostatic attraction between the substituent and the reagent takes so little part in comparison with a large activating effect of the substituent. Brown and his co-workers (10) have recently reported a relationship between the orientation and the electrophilic activity of each reagent including some data on the mercuration of mono- and poly-alkylbenzenes. They have not referred to the benzene derivatives with *meta*-orienting groups, but it seems necessary to consider the interaction between the substituent and the reagent at least with these compounds. In fact, the preferential *ortho* substitution which often approaches 100% is unexplicable in Brown's theory.

EXPERIMENTAL

All materials used were carefully purified either by recrystallization when they were solid or distillation when liquid. To avoid selective loss of one of the isomers in recrystallization, the filtrate was collected and was concentrated in a vacuum, extracted with ether, and the resulting crops again were analyzed. Each experiment was repeated three times, the average yield being recorded. Procedures for the mercuration are described below.

Benzamide. (*a*). A mixture of benzamide (3 g.), mercuric acetate (5 g.), and glacial acetic acid (30 ml.) was refluxed for 6 hours, and the product was poured with stirring into an aqueous solution (100 ml.) of saturated sodium chloride and the resulted flocculent precipitate was filtered. After drying, there was obtained a white powder of the mercuric compound (2.1 g). To this compound suspended in chloroform was added a solution of bromine-potassium bromide, and the solution was shaken vigorously until dissolution of mercuric bromide was complete. The chloroform layer was washed with an aqueous sodium sulfite and then with water. After removal of the solvent, crude bromobenzamides (0.7 g.) were obtained, which when recrystallized once from chloroform gave *o*-bromobenzamide (0.5 g.) m.p. 147.0°, and showed no depression of m.p. upon admixture with the authentic material. Neither the *meta* nor the *para* isomer was isolated.

(*b*). Benzamide (20 g.) and mercuric acetate (15 g.) were gently refluxed for 6 hours. The product was poured into a methanolic solution of calcium chloride (*ca.* 10%) and the arylmercuric chloride was precipitated. The filtered precipitate (15 g.) was washed with ether and was converted into bromobenzamide in the usual way, yielding *o*-bromobenzamide (5.0 g.), m.p. 147.0°, as the sole product.

Benzophenone. (*a*). According to Dimroth's method (5), benzophenone was mercurated without a solvent. The resulting bromobenzophenones were proven to contain *ca.* 95% of the *ortho* and 5% of the *meta* isomer. The structures of these products were confirmed by mixture melting point determinations. The authentic materials were obtained from corresponding bromobenzoyl chlorides by the Friedel-Crafts reaction with benzene.

(*b*). Benzophenone (10 g.) and mercuric acetate (7 g.) were dissolved in glacial acetic acid (50 ml.) and were heated for 6 hours at 98°. The mercuration was found to occur 85% at the *ortho* and 15% at the *meta* position. No *para* isomer was found.

Fluorenone. (*a*). A mixture of fluorenone (15 g.), m.p. 85.5°, mercuric acetate (15 g.), and glacial acetic acid (50 ml.) was refluxed for 10 hours and the product was poured into a methanolic solution (150 ml.) of calcium chloride (*ca.* 10%). This precipitate was filtered, washed with dilute methanol and dried, yielding a yellow powder (8.2 g.) of the mercuric compound. After treating as usual with bromine, there was obtained a crude product (3.1 g.), which on recrystallization from acetic acid gave 1-bromofluorenone (2.4 g.), m.p. 138°, and a small amount of a mixture of brominated fluorenones. On further recrystallization from an aqueous mixture of acetic acid and isopropyl alcohol, the m.p. rose to 139° (literature m.p. of 1-bromofluorenone, 138°).

Anal. Calc'd for $C_{13}H_7BrO$: C, 60.26; H, 2.72; Br, 30.84.
Found: C, 60.48; H, 2.74; Br, 30.71.

The mixture m.p. with authentic 2-bromofluorenone (m.p. 144°), prepared from 2-nitrofluorene (11) *via* reduction, Sandmeyer reaction, and oxidation, showed a depression. The m.ps. of the other mono bromofluorenones are: *3*-, 162°; *4*-, 127°. Hence they differ largely from the melting point of 1-bromofluorenone.

(*b*). Fluorenone (20 g.) and mercuric acetate (10 g.) were gently refluxed for 2.5 hours and the reaction product was worked up as before. It gave 5.4 g. of a crude product which, after only one recrystallization from acetic acid, gave 1-bromofluorenone, m.p. 138°, (3.5 g.).

Anthraquinone. In glacial acetic acid as the solvent mercuration of anthraquinone was attempted under various conditions, but it was unsuccessful. In nitric acid with mercuric nitrate, the mercuration was surpassed by nitration, which produced polynitro anthraquinones.

Acenaphthenequinone. No mercuration occurs in either acetic or nitric acid as the solvent. In the latter solvent, 3-nitronaphthalic acid anhydride, m.p. 249°, was isolated as a sole product.

Benzoic acid. A mixture of benzoic acid (10 g.) and mercuric acetate (10 g.) in glacial acetic acid (60 ml.) was refluxed for 10 hours and the product was poured into an aqueous solution of sodium chloride. After filtration and washing with benzene, 11 g. of the mercuric compound was obtained which gave 4 g. of crude bromobenzoic acids by the bromination process. The acid was further converted to the bromobenzamides and these were submitted to careful fractional crystallization from benzene. It was found that the isomer ratio of *ortho* to *meta* was 1:4. No *para* compound was detected spectrophotometrically. The *ortho* and *meta* compounds thus obtained did not show melting point depressions when admixed with authentic materials.

Methyl benzoate. A mixture of methyl benzoate (20 g.) and mercuric acetate (15 g.) was gently refluxed for 5 hours and was poured into a methanolic solution (100 ml.) of calcium chloride. The product was filtered, and washed with benzene, then being converted into the methyl bromobenzoates which weighed 8 g. A further conversion of the product with phosphorus pentachloride and then with ammonia into the bromobenzamides gave 6 g. of crude product, which after careful recrystallization from benzene yielded 4.1 g. of *o*-bromobenzamide together with 1.5 g. of *m*-bromobenzamide. These two products show no depression of melting points on admixture with authentic materials. No *para* compound was isolated.

Phenylacetic acid. A mixture of phenylacetic acid (10 g.) m.p. 76.5°, mercuric acetate (7 g.), and 60 ml. of acetic acid was heated with stirring at 98° for 12 hours. The product was poured into an aqueous solution of sodium chloride, and the precipitate was filtered, washed with benzene, and dried. The yield was 4.0 g. The mercuric compound was converted into the bromo acid (0.8 g.), and then was submitted to oxidation with a slightly alkaline solution of potassium permanganate. The acid which resulted proved to be *p*-bromobenzoic acid on recrystallization from dilute acetic acid. Furthermore, in order to confirm it, another portion of the oxidation product was converted into *p*-bromobenzamide, m.p. 189.5° and mixture m.p. 189.5°, the product containing neither the *ortho* nor the *meta* isomer.

Methyl phenylacetate. A mixture of methyl phenylacetate (10 g.) and mercuric acetate (15 g.) was gently refluxed for 7 hours, poured into an aqueous solution of calcium chloride, and filtered. The mercuric compound weighed 7.0 g. After bromination, and hydrolysis with aqueous alkali, the product (2.2 g.) was oxidized as before to obtain crude bromobenzoic acid (1.8 g.), which on recrystallization gave 0.8 g. of *p*-bromobenzoic acid, m.p. 255° and mixture m.p. 254°. There was no indication of the presence of the other isomers.

Phenyltrimethylammonium nitrate. Phenyltrimethylammonium nitrate (12) (3 g.), dissolved in a mixture containing conc'd nitric acid (6 ml., *sp. gr.* 1.41), water (35 ml.), and mercuric oxide (6 g.), was heated at 95° for 20 hours. The reaction product was poured into an aqueous solution of sodium chloride, and the resulting fine needles of mercuric salt (6.0 g.) were precipitated. The precipitate was brominated, yielding bromophenyltrimethylammonium tribomide which deposited on the bottom and then was heated at 70° while air was bubbled through to expel an excess of bromine. In order to eliminate the mercuric salt, hydrogen sulfide was passed into the mixture and it was filtered. Addition of potassium iodide (10 g.) to the filtrate gave 2.1 g. of bromophenyltrimethylammonium iodide as a crystalline precipitate. Structure of the portion mercurated and then brominated was confirmed by the dry distillation of the iodide under reduced pressure. The distillate (1.3 g.) was converted into its picrate, m.p. 136°, which showed no depression of m.p. on admixture of the authentic picrate of *m*-bromodimethylaniline. No trace of the *o*- or *p*-isomer was detected. The use of more concentrated nitric acid (over twice that in the above case) as the solvent in the mercuration gave the *m*-nitrophenyltrimethylammonium salt.

SUMMARY

The orientation in the mercuration of some aromatic compounds has been studied and found to be *ortho* with benzamide, *ortho* and some *meta* with benzophenone, the 1-position with fluorenone, *meta* and less *ortho* with benzoic acid, *ortho* and less *meta* with methyl benzoate, *para* with phenylacetic acid and methyl phenylacetate, and *meta* with phenyltrimethylammonium nitrate. These results seem best to be explicable in terms of the electrostatic interaction between the atomic charges at the transition state. The mercuration of anthraquinone and acenaphthenequinone has been unsuccessful.

YOSHIDA, KYOTO, JAPAN.

REFERENCES

(1) Part I, OGATA AND TSUCHIDA, *J. Org. Chem.*, **20**, 1631 (1955).

(2) PART II, OGATA AND TSUCHIDA, *J. Org. Chem.*, **20**, 1637 (1955).

(3) For the example, see BEILSTEIN'S *Handbuch der Organischen Chemie*, Vol. VII, Hauptw., p. 464.

(4) FERGUSON, *Chem. Revs.*, **50**, 48 (1952).

(5) DIMROTH, *Ber.*, **35**, 2852 (1902).

(6) UKAI AND ITO, *J. Pharm. Soc. Japan*, **73**, 821 (1953).

(7) BERNARDI, *Gazz. chim. ital.*, **67**, 380 (1937) [*Chem. Abstr.*, **32**, 1260 (1938)].

(8) UKAI, YAMAMOTO, HIRANO, AND YOTSUZUKA, *Pharm. Bull. Japan.*, **3**, 105 (1955).

(9) UKAI, YAMAMOTO, AND HIRANO, *J. Pharm. Soc. Japan*, **73**, 823 (1953).

(10) BROWN AND MCGARY, *J. Am. Chem. Soc.*, **77**, 2300, 2306, 2310 (1955).

(11) *Org. Syntheses*, Coll. Vol., II, 447 (1948).

(12) VORLÄNDER AND SIEBERT, *Ber.*, **52**, 284 (1948).