Iodination and Iodo-compounds. Part IV.[1] The Effect of Substituents and Solvent Composition on the Rate of Aromatic Iodination by Means of the Tri-iodine Cation

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The rate and products of the reaction between each of a range of deactivated substituted benzenes and the tri-iodine cation, in sulphuric acid solution, have been investigated. The rate constants may be correlated by the electrophilic substituent constants σ^+ giving a value for the reaction constant $\rho = -6{\cdot}4$. The kinetic isotope effect for the iodination of benzoic acid was found to be $k_H/k_D = 2$. Further details of the solvent effect are reported.

THE rates of chlorination[2] and bromination[3] of substituted benzenes have been shown to be correlated by the electrophilic substituent constants σ^+ and reaction constants have been determined for these reactions under various conditions. Similar data have been lacking for iodination reactions, however, because of the low reactivity of the previously investigated iodinating agents. Previous work of ours[4] has shown that sulphuric acid solutions of the tri-iodine cation I_3^+ (Masson's reagent[5]) react with nitrobenzene and benzoic acid by a process which is first order in each reactant. The present paper reports an extension of this work to a wider range of compounds allowing a value of the reaction constant ρ to be determined and further details of the solvent effect to be studied.

RESULTS AND DISCUSSION

The Order of Reaction.—For all the substrates investigated the reaction was found to be of the second order, first order in Masson's reagent and in the substrate. (The possible competing first-order reaction suggested earlier[4] was not confirmed; the apparent deviation from second-order kinetics is due to interference by the products of the reaction in circumstances when the substrate is not present in an excess.) No significant variation in the rate constant with the initial concentration of the substrate was observed. For example Table 1 shows the uniformity of the rate constants for the iodination of 4-chlorobenzoic acid in 98·5% sulphuric acid at 25° over a 6-fold variation in the initial substrate concentration (in each case the initial concentration of Masson's reagent was *ca.* $0{\cdot}25 \times 10^{-3}$ mol kg^{-1}).

TABLE 1

Rate constants for iodination of 4-chlorobenzoic acid (98·5% H_2SO_4; 25°)

10^3[ArH]/mol kg^{-1}	2·22	2·68	5·22	5·82	7·37	13·5
k_2/kg mol^{-1} s^{-1}	0·28	0·27	0·29	0·21	0·27	0·27

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The Effect of Substituents on the Rate of Iodination.—The rate constants were measured for the iodination of a number of substituted benzenes at 43° in 98·5% sulphuric acid, as shown in Table 2, which also lists the position of entry of the first iodine atom and the sum of the electrophilic substituent constants at this reaction site.[2]

TABLE 2

Observed rate constants for iodination by means of Masson's reagent (43°)

Substrate	k_2/kg mol^{-1} s^{-1}	Position of substitution	$\Sigma\sigma^+$
Benzoic acid	13·2 (obs.)	3	0·32
Benzoic acid	$2·7 \times 10^3$ (corr.)		
2-Nitrotoluene	60	4	0·36
Benzotrifluoride	12·1	3	0·52
4-Chlorobenzoic acid	3·0	3	
2-Fluoronitrobenzene	2·7	5	0·60
2-Chloro-6-nitrotoluene	2·6	4	0·76
2-Chloronitrobenzene	1·2	5	0·78
Nitrobenzene	1·1	3	0·67
3-Chloronitrobenzene	0·052	4	
4-Chloronitrobenzene	0·042	3	
2,6-Dinitrotoluene	0·016	4	1·03
3-Nitrobenzotrifluoride	0·0012	5	1·19

Since in the compounds under consideration substitution occurred largely at a single site the observed rate constants were assumed to approximate to the partial rate constants at the reaction site when constructing the Hammett plot. In the case of benzoic acid a correction was made to allow for the degree of protonation of the substrate. The number of available deactivated monosubstituted benzenes was limited and so the results for some disubstituted (and one trisubstituted) benzenes were included in the correlation assuming the validity of the additivity principle. Although this principle has been shown to be of limited accuracy in some cases [3,6] nevertheless a satisfactory correlation was obtained. From these results the reaction constant was calculated as $-6·4 \pm 0·6$, by the least squares method. The linear correlation coefficient r is 0·95.

Few investigations of the direct substitution of very deactivated compounds have been carried out; de la Mare and Hilton have studied the bromination of benzoic acid and nitrobenzene,[3] the results for which were consistent with those for the more reactive substrates which were included in their Hammett plot.

The great difference in the reactivities of the tri-iodine cation and molecular iodine [7] is reflected in their very different selectivities towards aromatic compounds, as indicated by the ρ values. A similar trend has been found for bromination by means of a positive species (thought to be H_2OBr^+ [3]) as compared with the reaction of molecular bromine, and also for chlorination by means of $AgCl_2^+$, as compared with the reaction of molecular chlorine.[8,9]

The order of reactivity of the chloronitrobenzenes is o-Cl > NO_2 > m-Cl > p-Cl, which is the same as for nitration.[10] The three compounds which cannot be included in the Hammett plot due to chlorine being *ortho* to the reaction site yield a value of *ca.* 0·2 for the apparent σ^+ for an *ortho*-chlorine atom. This compares with a published value of 0·26.[11]

The Kinetic Isotope Effect.—We have reported [4] that the kinetic isotope effect for the iodination of nitrobenzene by means of Masson's reagent is $k_H/k_D = 3·4 \pm 0·6$; we now report the result for benzoic acid. Trial experiments showed no significant exchange of deuterium between pentadeuteriobenzoic acid and the sulphuric acid solvent over a period longer than a kinetic run, so it was possible to measure the rate constant for the iodination of the deuterio-compound by the same method and under the same conditions as for benzoic acid.[4] The rate constant in 98·5% sulphuric acid at 25° was found to be $k_D = 1·02 \pm 0·03$ kg mol^{-1} s^{-1} (average of five experiments). The value for benzoic acid is $k_H = 2·1 \pm 0·07$ kg mol^{-1} s^{-1}. The kinetic isotope effect $k_H/k_D = 2·1 \pm 0·1$ is sufficiently large for it to be considered a primary isotope effect, and thus to indicate the breaking of a carbon–hydrogen bond in the transition state.

Reactions with a small negative ρ value usually do not show a kinetic isotope effect [7] but the present case is not a unique exception (*cf.* mercuriation [2]). Some features of iodination which might be expected to lead to the observation of a kinetic isotope effect have been noted by Zollinger.[12] These include the comparatively weak carbon–iodine bond and the low acidifying effect of the iodine atom on the carbon–hydrogen bond which is to be broken. The present results are also consistent with the discussion [13] of the kinetic isotope effect in terms of the 'relative leaving abilities' of the two electrophilic groups in the intermediate, here the iodine atom and the proton.

Effect of Solvent Composition on Rate of Iodination.—The behaviour of the other substrates examined is similar to that reported for nitrobenzene and benzoic acid;[4] in each case the rate of iodination by means of Masson's reagent increases as the proportion of water in the solvent is increased over the range investigated.

Two substrates were selected for further examination: 2-chloronitrobenzene, as an example of a compound which, under the reaction conditions, is almost unprotonated, and 4-chlorobenzoic acid, as an example of a compound which is extensively protonated. The results for the reactions at 25° are given in Tables **3** and **4**.

There is a reasonably linear relationship between the rate of iodination of 2-chloronitrobenzene and the molal concentration of water in the solvent (r calculated by the least squares method is 0·93). Since water is almost completely protonated within this range of sulphuric

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acid concentrations, the concentration of the hydrogen sulphate ion, which is the main basic species in this solvent system, may be taken as equal to the concentration of water. The rate constant does not extrapolate to zero at zero concentration of hydrogen sulphate ion. These results are consistent with the catalysis of the reaction by hydrogen sulphate ion, and also, to a smaller extent, by sulphuric acid molecules; similar results were obtained in the case of nitrobenzene.[4]

TABLE 3

Rate constants for iodination of 2-chloronitrobenzene (25°)

k_2/kg mol^{-1} s^{-1}	0·21	0·38	0·33	0·41	0·62	0·60	0·65	0·88	0·92
H_2SO_4 (%)	98·5	95·7	95·4	94·6	93·3	92·3	91·2	89·7	89·2

TABLE 4

Rate constants for iodination of 4-chlorobenzoic acid (25°)

k_2/kg mol^{-1} s^{-1}	0·27	0·68	0·89	1·55	1·8	2·1	2·8	2·9
H_2SO_4 (%)	98·5	96·5	95·6	95·0	94·5	94·0	93·8	93·7

Due to variations in the degree of its protonation with the solvent composition, a linear relationship is not found between the rate of iodination of 4-chlorobenzoic acid and the hydrogen sulphate ion concentration. A correction can be made for the protonation (1). The equilibrium constant may be written in terms of the acidity function (2).[14] The proportion of unprotonated substrate present in solution is then given by equation (3).

$$\mathrm{ArH} + \mathrm{H^+} \rightleftharpoons \mathrm{ArH_2^+} \qquad (1)$$

$$K_b = [\mathrm{ArH_2^+}]/H_0[\mathrm{ArH}] \qquad (2)$$

$$[\mathrm{ArH}]/[\mathrm{ArH}] + [\mathrm{ArH_2^+}]) = 1/(K_bH_0 + 1) \qquad (3)$$

If it is assumed that the extrapolated value for the rate constant at zero hydrogen sulphate ion concentration (k_0) represents the reaction catalysed by sulphuric acid molecules, and also that the concentration of the latter remains approximately constant over the range of solvent composition used, the corrected rate constant for the iodination of the free substrate, catalysed by the hydrogen sulphate ion alone is given by equation (4). A plot of the corrected rate constants against the hydrogen sulphate ion concentration is shown in the Figure. An approximately straight line (r 0·96) which passes through the origin is obtained. Similar results were also obtained for benzoic acid.[4]

$$k'_{\mathrm{corr.}} = (k_{\mathrm{obs}} - k_0)(K_bH_0) + 1) \qquad (4)$$

Linear correlations have been found to exist between the rate of nitration in sulphuric acid solution and the hydrogen sulphate ion concentration for a wide range of substrates.[15-20] The magnitude of these effects is also similar to those reported here for the iodinations.

Base catalysis appears to be ruled out, in the case of nitration, by the rarity with which kinetic isotope effects are observed.[21] There is also evidence that some solutes which do not act as bases in sulphuric acid can catalyse nitration.[20] At present there is no entirely satisfactory general explanation of the form and magnitude of these effects.

The investigation of the kinetics of electrophilic aromatic substitution reactions in sulphuric acid solution other than nitration may contribute towards the further clarification of this problem. It would appear unlikely that the solvent effects for the iodinations are mainly caused by 'environmental factors', however, particularly in view of the observed kinetic isotope effects.

The Effects of the Solvent Composition on the Tri-iodine Cation.—The spectra of solutions made by adding weighed drops of a stock solution of Masson's reagent to sulphuric acids of various compositions were observed. The initial spectra of the solutions in the more acidic solvents down to 88% H_2SO_4 were characteristic of the tri-iodine cation. As the proportion of water in the solvent was increased, the **293** nm peak decreased in magnitude, however, and the **463** nm peak shifted towards the **500** nm peak characteristic of molecular iodine. On adding drops of a stock solution of Masson's reagent to 80·5 or 84% sulphuric acid the characteristic brown colour immediately changed to pink and the spectrum of the solution showed only molecular iodine to be present. In the case of solutions in 98·5 and 95% H_2SO_4 there was little change in the spectrum over a period of three days, whereas the spectrum of the solution in 88% sulphuric acid after this period showed the presence of a large proportion of molecular iodine. Even in the latter solvent there was very little change over the period of time occupied by a kinetic run.

In the present work solutions in sulphuric acids of compositions less than 89% were not used in the kinetic experiments.

Preparative Iodination.—Each substrate used in the kinetic work was also iodinated on a preparative scale by means of Masson's reagent in order to be sure that iodination does takes place and also to identify the major product so that the main position of substitution was known. The conditions were chosen to be as similar as possible to those under which the kinetic experiments were carried out, rather than those which might give the optimum yield. The main position of substitution was in nearly all cases that expected from the usual directive effects of the substituents present. An interesting

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exception was 3-chloronitrobenzene, which gave 3-chloro-4-iodonitrobenzene. This appears to be a further example of the reluctance of cationic iodine to substitute *ortho* to a nitro-group.[1]

Although the development of the preparative applications of Masson's reagent was not within the scope of the present work, the results of the preparative iodinations indicate that it is an effective iodinating agent able to give good yields with a range of highly deactivated substrates.

Identification of the Products.—The ^{1}H n.m.r. spectra of the crude products in general indicated one product together, in most cases, with some unchanged starting material. (In the case of 2-nitrotoluene an appreciable amount of a second product was indicated; here the minor product was separated but in other cases only the major product was examined.)

TABLE 5

Preparative conditions for the iodination reactions

Code	Substrate	I_2 (g)	KIO_3 (g)	Mole ratio I_3^+ : ArH	Time	Temp.
1	4-Chlorobenzoic acid	45·4	5·50	4	5 days	Room
2	4-Chloronitrobenzene	45·2	5·46	4	5 days	Room
3	2-Chloronitrobenzene	11·3	1·38	1	1 h	Room
4	3-Chloronitrobenzene	11·3	1·38	1	1 week	0°
5	2-Nitrotoluene	13·0	1·57	1	45 min	Room
6	2,6-Dinitrotoluene	14·6	1·77	1·5	5 days	Room
7	2-Fluoronitrobenzene	12·7	1·53	1	1 day	Room
8	Benzotrifluoride	12·2	1·47	1	1 day	0°
9	3-Nitrobenzotrifluoride	37·2	4·40	4	1 week	80—90°
10	2-Chloro-6-nitrotoluene	10·4	1·25	1	6 h	Room

TABLE 6

Products of the iodination reactions

Code	Product	Wt. of crude product (g)	Method of purification	Yield (%)
1	4-Chloro-3,5-di-iodobenzoic acid	9·2	Cryst. ethanol	71
2	4-Chloro-3,5-di-iodonitrobenzene	10·1	† Chromat. ether	62
3	2-Chloro-5-iodonitrobenzene	8·0	† Chromat. petrol 60—80°	51
4	3-Chloro-4-iodonitrobenzene	7·2	Cryst. petrol 60—80°	42
5a	4-Iodo-2-nitrotoluene	7·4	† Chromat. petrol 60—80°	56
5b	2-Iodo-6-nitrotoluene		† Chromat. petrol 60—80°	16
6	4-Iodo-2,6-dinitrotoluene	7·9	Cryst. methanol	49
7	2-Fluoro-5-iodonitrobenzene	7·5	† Chromat. petrol 60—80°	63
8	3-Iodobenzotrifluoride	7·4		
9	3-Iodo-5-nitrobenzotrifluoride	6·3	† Chromat. petrol 40—60°	22
10	2-Chloro-4-iodo-6-nitrotoluene	6·5	† Chromat. petrol 60—80°	49

† In all cases the stationary phase was Peter Spence Grade H alumina; petrol = light petroleum of b.p. stated.

After separation and purification the products were identified from their ^{1}H n.m.r. spectra, microanalyses, and m.p. The products from the iodination of 3-nitrobenzotrifluoride and 2-chloro-6-nitrotoluene have not previously been reported.

EXPERIMENTAL

Instrumentation.—Details are given in Parts II[4] and III.[1]

Kinetics Experiments.—The method was described in Part II.[4]

Hydrogen Exchange in [$^2H_5$]*Benzoic Acid.*—A solution of pentadeuteriobenzoic acid in sulphuric acid (0·1 mol kg^{-1}) was kept for 4 days at room temperature. The solution was poured on ice and the acid was filtered off and dried. A solution of the resulting solid in carbon tetrachloride was found to have no observable ^{1}H n.m.r. spectrum, whereas a solution of benzoic acid of 5% the concentration gave a clear spectrum with the same instrumental settings.

Iodination Reactions.—General preparative method. The substrate (5 g) was dissolved in AnalaR sulphuric acid (50 g). Quantities of iodine and potassium iodate, calculated to give the required ratio of tri-iodine cation to substrate, were added to a separate portion of sulphuric acid (50 g) and stirred or shaken in a closed system until dissolved. The two solutions were then mixed and stirred. After reaction the mixture was poured on crushed ice and the subsequent procedure was similar to that described in Part III.[1] The preparative conditions for each of the substrates are summarised in Table 5 and the products and the method of their purification in Table 6.

Identification of the products. (1) 4-Chloro-3,5-di-iodobenzoic acid [Found: *M*, 401 (by titration with standard sodium hydroxide solution). Calc. for $C_7H_3ClI_2O_2$: *M*, 408·5] had m.p. 316° (lit.,[22] 309—312°) τ (Me_2SO) 1·62 (s). (2) 4-Chloro-3,5-di-iodonitrobenzene (Found: C, 17·7; H, 0·6; N, 3·6; Cl, 8·7; I, 61·9. Calc. for $C_6H_2ClI_2NO_2$: C, 17·6; H, 0·5; N, 3·4; Cl, 8·7; I, 62·0%) had m.p. 113—114° (lit.,[23] 110°), τ (Me_2SO) 1·35 (s). (3) 2-Chloro-5-iodonitrobenzene (Found: C, 25·6; H, 1·2; Cl, 12·4; N, 4·8; I, 44·8. Calc. for $C_6H_3ClINO_2$: C, 25·4; H, 1·1; Cl, 12·5; N, 4·9; I, 44·8%) had m.p. 73—74° (lit.,[24] 74°), τ (CCl_4) 1·86 (d, *J* 2·5 Hz, 6-H), 2·20 (dd, $J_{4,6}$ 2·5, $J_{3,4}$ 9·0 Hz, 4-H), and 2·73 (d, *J* 9·0 Hz, 3-H). (4) 3-Chloro-4-iodonitrobenzene (Found: C, 25·6; H, 1·1; Cl, 12·4; N, 4·8; I, 44·5%) had m.p. 100—101° (lit.,[23] 103°), τ (CCl_4) 1·73 (d, *J* 2·5 Hz,

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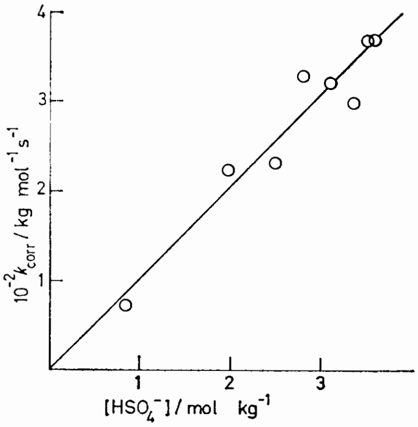

Variation of 'corrected rate constant' with hydrogen sulphate ion concentration for the iodination of 4-chlorobenzoic acid

2-H), 1·90 (d, J 8·5 Hz, 5-H), H_3 and 2·21 (dd, $J_{2,6}$ 2·5, $J_{5,6}$ 8·5 Hz, 6-H). (5a) 4-Iodo-2-nitrotoluene (Found: C, 32·0; H, 2·5; N, 5·3; I, 48·3. Calc. for $C_7H_6INO_2$: C, 31·9; H, 2·6; N, 5·4; I, 47·9%) had m.p. 59° (lit.,[25] 60·5°), τ (CCl_4) 1·73 (d, J 2·0 Hz, 3-H), 2·20 (dd, $J_{3,5}$ 2·0, $J_{5,6}$ 8·0 Hz, 5-H), 2·92 (d, J 8·0 Hz, 6-H), and 7·43 (s, Me). (5b) 2-Iodo-6-nitrotoluene had m.p. 33—34° (lit.,[26] 36°), τ (CCl_4) 1·95 (dd, H-3), 2·30 (dd, 5-H), 2·97 (dd, 4-H), and 7·41 (s, Me) ($J_{3,5}$ 2·5, $J_{3,4}$ 7·5, and $J_{4,5}$ 8·0 Hz). (6) 4-Iodo-2,6-dinitrotoluene (Found: C, 27·4; H, 1·6; N, 8·9; I, 41·0. Calc. for $C_7H_5IN_2O_4$: C, 27·3; H, 1·6; N, 9·1; I, 41·2%) had m.p. 89—90° (lit.,[1] 91°), τ (CCl_4) 1·76 (s) and 7·50 (s, Me). (7) 2-Fluoro-5-iodonitrobenzene (Found: C, 27·1; H, 1·1; F, 7·2; N, 5·1; I, 47·4. Calc. for $C_6H_3FINO_2$: C, 27·1; H, 1·1; F, 7·1; N, 5·3; I, 47·7%) had m.p. 34° (lit.,[27] 35·5°), τ (CCl_4) 2·90 (dd, H-3), 2·07 (qd, H-4), and 1·65 (dd, H-6) ($J_{3,4}$ 8·8, $J_{3,F}$ 10·0 Hz, $J_{4,6}$ 2·5, $J_{4,F}$ 4·0, and $J_{6,F}$ 6·7 Hz). (8) 3-Iodobenzotrifluoride had ^1H n.m.r. and i.r. spectra identical with those of an authentic specimen. (9) 3-*Nitro*-5-*iodobenzotrifluoride* (Found: C, 26·4; H, 1·1; F, 18·2; N, 4·3; I, 40·3. $C_7H_3FINO_2$ requires C, 26·5; H, 0·9; F, 17·9; N, 4·4; I, 40·1%) had m.p. 24—26°, τ (CCl_4) 1·20 (q), 1·47 (q), and 1·68 (q). (10) 2-*Chloro*-4-*iodo*-6-*nitrotoluene* (Found: C, 28·4; H, 1·8; Cl, 11·9; N, 4·6; I, 42·5. $C_7H_5ClINO_2$ requires C, 28·2; H, 1·7; Cl, 11·9; N, 4·7; I, 42·7%) had m.p. 56—57°, τ (CCl_4) 2·03 (d, J 2 Hz), 2·08 (d, J 2 Hz), and 7·53 (s, Me).

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